

# Microinvasive squamous carcinoma of the cervix: treatment modalities

FERNANDO MOTA

Serviço De Ginecologia, Hospitais da Universidade de Coimbra, Coimbra, Portugal

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Patients with FIGO stage IA1 squamous cell carcinoma of the cervix can be treated conservatively with simple hysterectomy or, if young and desiring to preserve their fertility, with conization only, provided surgical margins are free of dysplasia or invasive disease. When the surgical margins are involved a repeat conization should be performed. Patients with FIGO stage IA2 or stage IA1 carcinoma with extensive lymph vascular space invasion benefit from a modified radical hysterectomy with pelvic lymph node dissection. If preservation of fertility is an issue, then conization with extraperitoneal or laparoscopic pelvic lymphadenectomy can be performed. Alternatively, radical trachelectomy with pelvic lymphadenectomy may be a safer procedure. Individualization of therapy based on an exhaustive pathological evaluation of an adequate cone biopsy specimen is of paramount importance for treatment planning and disease control.

*Key words:* cervix; microinvasive squamous cell carcinoma; treatment

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In 1994 FIGO (International Federation of Gynecology and Obstetrics) defined microinvasive squamous cell carcinoma of the uterine cervix as a microscopic lesion that invaded below the basement membrane to a maximum depth of 5 mm and with an horizontal spread not exceeding 7 mm. The diagnosis should be based on pathological examination of a cone biopsy including the entire lesion to assess correctly the depth and linear extent of invasion. These microcarcinomas were further subdivided into two categories/stages: IA1 defined as a tumor that invaded to a depth of 3 mm or less, whereas

stage IA2 referred to tumors invading to a depth greater than 3 mm and up to 5 mm. In both stages, the horizontal spread should not exceed 7 mm, otherwise the tumor should be assigned to stage IB. The depth of stromal invasion should be measured from the base of the epithelium, either squamous or glandular, from which it originates to the deepest point of invasion. In this classification lymph vascular space invasion (LVSI) was not included as part of the definition, but FIGO recommended that it should be recorded as it may affect treatment decisions in the future.

The incidence of microinvasive cervical carcinoma is steadily increasing, afflicts women predominantly in their forties and fifties, and approximately 60–70% of patients have stage IA1 disease.

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#### Abbreviations:

CIN: cervical intraepithelial neoplasia; ESI: early stromal invasion; FIGO: International Federation of Gynecology and Obstetrics; HPV: human papillomavirus; LVSI: lymph vascular space invasion

#### Concept of 'early stromal invasion'

The purpose of defining microinvasive cervical carcinoma is to identify a group of patients who

are not at risk of lymph node metastases or tumor recurrence and who therefore may be treated conservatively. Some authorities (1) consider that 'early stromal invasion' (ESI) is a unique and distinct histological entity but it is not included in FIGO classification. Early stromal invasion is characterized by the presence of microscopic epithelial neoplastic buds, which emanate from the base of a carcinoma *in situ* (CIN 3, high-grade squamous intraepithelial lesion). This invasive focus consists of well-differentiated cells with an abundant pink-staining cytoplasm, and hyperchromatic nuclei, and are surrounded by an inflammatory cell infiltrate predominantly comprised of lymphocytes.

These early invasive lesions without measurable volume are not viewed as a separate entity by FIGO classification and are lumped in with all stage IA1 tumors. In fact, among a total of 429 women with invasion of less than 3 mm 80% had ESI (2), which will dilute the group and improve treatment results. Moreover, there are differences in terms of vascular involvement, recurrences, and survival between ESI and lesions invading between 1 and 3 mm. This may result from the fact that lymph vascular spaces are rare and extremely small in the stroma adjacent to the basement membrane. In an extensive review of the literature, Ostor (3) reported that among 1409 women with ESI there were no lymph node metastasis and only four cases were documented with tumor recurrence (0.3%) (Table I). Hence, the small foci of ESI apparently have no clinical significance and therefore can be treated just like *in situ* disease, provided the surgical margins are clear. It should be noted, however, that extension into the endocervical canal and glandular involvement are greater than in CIN. Consequently, ESI requires subsequent hysterectomy more often than CIN.

### Stage IA1 cervical carcinoma

In the above-mentioned literature review, Ostor (3) reported that among 2274 women with squamous lesions and stromal invasion of less than

Table I. Percentage of lymph node metastases, recurrences and death among 5681 patients with microinvasive carcinoma of the cervix

Stromal invasion	Patients, <i>n</i>	+nodes	Recurrences	Death
ESI	1409	0	0.3	0.07
<1 mm	2274	0.1	0.4	0.1
1–3 mm	1324	0.4	1.7	0.5
3.1–5 mm	674	2.1	3.7	1.9

ESI = early stromal invasion.

+nodes = lymph node metastases.

1 mm, there were three cases of lymph node metastases (0.1%) and eight cases in which tumor recurrence developed (0.4%). In contrast, among 1324 squamous lesions invading between 1 and 3 mm, there were five cases with lymph node metastases (0.4%) and 23 cases with invasive recurrence (1.7%) (Table I). Most of these patients were treated conservatively.

Lymph vascular space invasion (LVSI) is uncommon in stage IA1 disease, with Ostor (3) reporting an incidence of 15%. It is known that LVSI increases with increasing depth of invasion (4) (Table II). As tumors invade more deeply into the stroma, the incidence of LVSI increases from 4.4% with lesions infiltrating less than 1 mm to approximately 20% in stage IA2 disease. It also appears that patients most at risk of lymph node metastases and recurrences are those with LVSI, particularly with extensive involvement (4) (Tables III and IV). These data show that as the depth of stromal invasion increases, so does the risk for nodal metastases and recurrences. Both nodal disease and tumor recurrence are also intimately correlated to LVSI. Others have corroborated these observations (2,5,6). Therefore, it

Table II. Incidence of lymph vascular space involvement by depth of stromal invasion in microinvasive carcinoma of the cervix

Depth of invasion	Patients, <i>n</i>	+LVSI
<1 mm	548	24 (4.4%)
1–3 mm	596	98 (16.4%)
3.1–5 mm	350	69 (19.7%)

+LVSI = presence of lymph vascular space invasion.

Table III. Frequency (%) of lymph node metastases by depth of stromal invasion and lymph vascular space involvement in microinvasive carcinoma of the cervix

LVSI ( <i>n</i> = 581)	Depth of invasion	
	≤ 3 mm	3.1–5 mm
Negative ( <i>n</i> = 479)	0.8%	8.3%
Positive ( <i>n</i> = 102)	8.2%	7.5%

LVSI = lymph vascular space invasion.

Table IV. Risk of recurrence (%) by depth of stromal invasion and lymph vascular space involvement in microinvasive carcinoma of the cervix

LVSI ( <i>n</i> = 748)	Depth of invasion	
	≤ 3 mm	3.1–5 mm
Negative ( <i>n</i> = 601)	0.6%	1.7%
Positive ( <i>n</i> = 147)	3.1%	15.7%

LVSI = lymph vascular space invasion.

seems prudent to treat patients exhibiting such adverse parameters more aggressively.

Some authors consider confluent tumor growth and poor cell differentiation as risk factors for nodal metastases and recurrence. However, the specificity of both variables is low, and they may not represent independent prognostic factors (7–9). This means that pattern of invasion and tumor grade, on their own, should not change treatment planning, but should be recorded and alert to the clinical significance of a particular lesion.

On the contrary, the status of the margins of the conization specimen should be carefully evaluated, as they are a significant predictor of residual invasion (4,9–11). Roman et al. (11) reported on 87 women with microinvasive carcinoma on conization specimens and followed by either repeat conization or hysterectomy. Significant predictors of residual invasion included status of the internal margin (residual invasion present in 22% of women with an involved margin vs. 3% with a negative margin;  $p < 0.03$ ) and the combined status of the internal margin and postconization endocervical curettage (residual invasion in 4% of patients if both negative, 13% if one positive, and 33% if both positive;  $p < 0.015$ ). They concluded that ‘if either the internal margin or the postconization endocervical curettage contains dysplasia or carcinoma, the risk of residual invasion is high and warrants repeat conization before definitive treatment planning’. However, it should be stressed that the status of the postconization endocervical curettage alone was not statistically significant to predict residual invasion. Hence, many clinicians do not perform routinely such a procedure.

Considering the above-mentioned data, a conization with clear surgical margins and no LVSI is considered an adequate treatment for patients with stage IA1 squamous cell carcinoma of the cervix (Fig. 1). Nevertheless, patients must return for regular follow-up examinations including cytology, colposcopy and probably also oncogenic HPV DNA testing, as this test may predict persistence of residual disease or tumor recurrence. Conization is the treatment of choice for young patients wishing to preserve their fertility. Loop excision has gained wide acceptance and is replacing cold-knife and laser conization. However, in large cervical lesions some authors (12) prefer to perform a cold-knife conization rather than a loop excision because the completeness of the procedure is higher, and the rate of tissue transection and misorientation is lower for the cold-knife method.

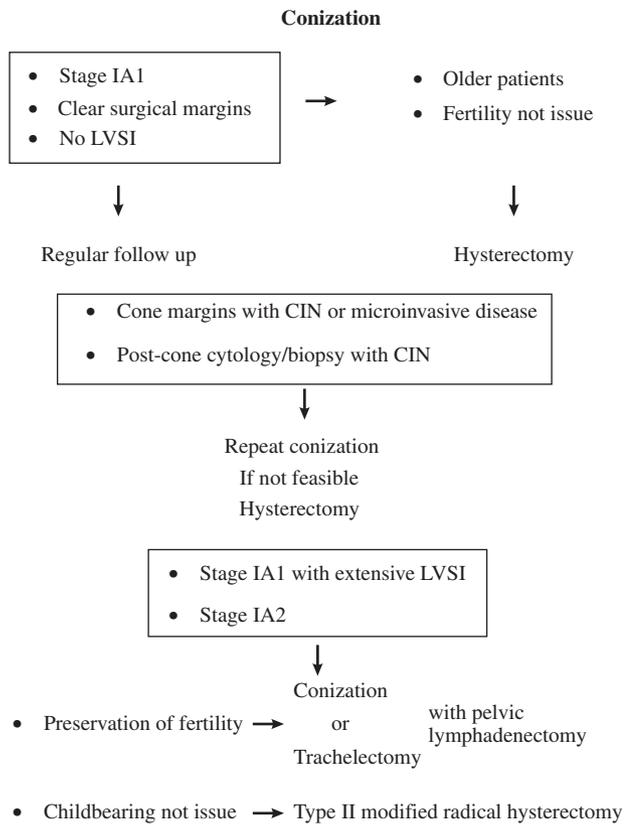


Fig. 1. Algorithm depicting the therapeutic strategy for microinvasive squamous cell carcinoma of the uterine cervix.

If future childbearing is not required, simple hysterectomy may be considered. Vaginal hysterectomy is preferable because the cervix is excised under direct visual control, whereas at abdominal hysterectomy the lesion may be cut through. This may explain the lower recurrence rates after vaginal hysterectomy in comparison with the abdominal approach. When colposcopic examination shows no evidence of extension of the tumor onto the vaginal fornices, a vaginal cuff does not need to be removed. Recurrences in the vaginal vault usually result from the presence of involvement of adjacent vaginal mucosa. This could be prevented with a careful colposcopic examination before surgery. If the vaginal fornices are involved, a partial vaginectomy will be performed, preferably vaginally.

Whenever the cone margins or the postconization endocervical curettage contain CIN or microinvasive carcinoma, or the postcone endocervical cytology, on regular follow up, reveals dysplasia, a repeat conization should be performed provided there is still sufficient cervical tissue remaining, which is often the case. A thorough pathologic examination of the surgical specimen is important to rule out microinvasive residual disease or even to disclose a frank carcinoma. If residual disease is

diagnosed, either a CIN lesion or microinvasive tumor foci, a simple hysterectomy should be offered to the patient. Women with stage IB tumors will benefit from additional therapy according to established protocols.

It is of paramount importance to identify the subset of patients whose stage IA1 microinvasive tumors are at high risk of recurrence and therefore need to be treated more aggressively. Among the variables that can predict such adverse behavior, LVSI, especially when extensive, is the most important. Others (2) take also into account the poor differentiation of the carcinoma, which is debatable. In these circumstances, stage IA1 tumors with extensive LVSI should benefit from a modified radical hysterectomy with pelvic lymphadenectomy and with parametrial preservation, as parametrial invasion is extremely rare in microinvasive disease (5,13). If childbearing is desired, it is possible to perform a cone biopsy with extraperitoneal or laparoscopic pelvic lymphadenectomy. Alternatively, a safer option in the presence of extensive LVSI may be to perform a radical trachelectomy and pelvic lymph node dissection (Fig. 1).

### Stage IA2 cervical carcinoma

In a review of the literature, Ostor (3) reported on 674 patients with microinvasive squamous cell carcinomas with a depth of invasion between 3 and 5 mm, and a width of not more than 7 mm. The incidence of lymph node metastases was 2.1%, invasive recurrence occurred in 25 cases (3.7%), with 13 patients (1.9%) dying of their disease (Table I). Many of these patients, 33 per cent, were treated radically. Hence, these tumors are less aggressive than frank carcinomas but carry a greater risk of pelvic lymph node metastases, recurrences and death from disease in comparison with their stage IA1 counterparts.

It is generally agreed that the recommended treatment for stage IA2 squamous cell carcinoma of the cervix is a type II modified radical hysterectomy with pelvic lymph node dissection. However, this procedure definitely represents overtreatment for many patients, when more discriminative prognostic parameters have yet to be identified to prevent it. In young patients or when childbearing is desired, treatment options are similar to those previously described for stage IA1 lesions: conization with extraperitoneal or laparoscopic pelvic lymphadenectomy. Radical trachelectomy with pelvic lymphadenectomy (14) is a safer procedure when there is LVSI, and may also be indicated when a repeat conization is not possible in the presence of surgical margins with CIN or microinvasive disease (Fig. 1).

Finally, if nodal disease is not present no further treatment is required. Conversely, if lymph node metastases are identified pelvic irradiation might be recommended. Microinvasive squamous cell carcinoma in medically unfit patients with contraindications to surgery can be treated effectively with intracavitary irradiation.

### Concluding remarks

At least theoretically, patients with microinvasive cervical carcinoma adequately studied and correctly treated should have survival rates ranging from 98 to 100%. However, the last annual report (FIGO's Annual report, vol. 23, 1998) documented a 5-year overall survival rate of 95.1% for stage IA1 disease ( $n=518$  patients) and a similar rate of 94.9% for stage IA2 ( $n=384$ ). Efforts have to be made worldwide to improve these results, which must be studied in detail in order to corroborate the adequacy of the 1994 FIGO definition of microinvasive cervical carcinoma or to change it.

It is of paramount importance to perform a thorough pathological evaluation of an adequate surgical cone to analyze tumor dimensions, margins, LVSI and eventually cell differentiation and tumor confluence. It is also essential that there is close cooperation between the gynecologist and the pathologist, so that the best treatment modality is offered to the patient with microinvasive cervical disease.

I would like to emphasize that treatment should be individualized based on an integrated assessment of multiple factors. Some of these are related to the patient, such as age, childbearing desire, compliance to regular follow up and cancerphobia. Other factors include pathological parameters that should be considered, especially tumor dimensions, status of the cone margins and lymph vascular space invasion (Table V). Furthermore, it is hoped that in the near future

Table V. Selection criteria for individualization of therapy in microinvasive carcinoma of the cervix

Patient
age
childbearing desire
compliance to regular follow up
cancerphobia
Tumor
dimensions
cone margins
lymph vascular space invasion

more discriminative molecular/genetic prognostic markers that can assist in treatment planning may be identified.

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*Address for correspondence:*  
 Fernando Mota  
 Serviço De Ginecologia  
 Hospitais da Universidade de Coimbra  
 3049 Coimbra  
 Portugal  
 e-mail: fmota@huc.min-saude.pt

