Abstract. Aim: To assess the efficacy and safety of conservative surgical approach for microinvasive cervical cancer with regards to cone margins status and lymph vascular space invasion (LVSI). Patients and Methods: This was a multicentre retrospective cohort study of 153 women diagnosed with microinvasive cervical cancer over a 10 years period (1993-2003). Results: In conservatively-treated women (n=80), neither cancer mortality nor disease relapse after 184.5±20.5 months of follow-up was detected. Residual disease in women who underwent secondary surgery was significantly related to positive margins on the primary cone excision (p=0.005) while no correlation with LVSI emerged. Conclusion: Conization can represent the definitive treatment for stage IA1, if surgical margins are cancer-free, independently of LVSI. A conservative surgical approach could also be considered in women with IA2 cervical cancer when preservation of fertility is strongly requested. A close long-term surveillance should be scheduled for conservatively-treated women.

In the last decades, both the relative proportion and absolute incidence of microinvasive cervical cancer have increased ten times in developed Countries, mainly in young women aged less than 40 years (1). Furthermore, we have seen a continuous trend of delayed childbearing, which results in an increased proportion of women diagnosed with a cervical cancer before their first pregnancy. Even if the prognosis of microinvasive cervical cancer is favorable, as reported by several studies (2-5), this diagnosis actually represents a difficult management dilemma, specifically in young women who desire to preserve their childbearing potential.

Different approaches have been employed to treat microinvasive cervical cancer, and controversies still exist on the surgical procedure that should be considered for the optimal management of the disease (6-13). Traditional surgical therapy for cervical cancer includes hysterectomy, with loss of childbearing potential. However, in the last years, a trend towards a conservative surgical approach has emerged, as preservation of fertility is desirable in young women, and radical procedures are associated with higher morbidity and mortality rates (14). Actually, both conization and simple hysterectomy are considered to be effective treatments for stage IA1 tumors. Conization is considered an acceptable management of stage IA1 cervical cancer, if the margin of the cone excision is clear and the lymph vascular space invasion (LVSI) has not occurred. If fertility preservation is desired, conization is satisfactory if all margins are clear (15). Radical hysterectomy with bilateral pelvic lymphadenectomy is the standard treatment of stage IA2 tumor. For this group of patients, a fertility preserving option is radical trachelectomy, which includes resection of the entire cervix and surrounding parametria, preceded by a laparoscopic bilateral pelvic lymphadenectomy (16). It is obvious that a close long-term surveillance should be...
scheduled for conservatively-treated women and, in the absence of specific guidelines, a 10-year follow-up should suffice for stage IA disease (1).

The aim of the present study was to describe the management and long-term outcome of women with microinvasive cervical cancer in four Gynecological Oncology Units in Northern Italy. The safety of a fertility-sparing surgical approach, with regard to prognostic factors such as the cone margins status and the LVSI was evaluated. The study was supported by the Italian Society of Colposcopy and Cervico-Vaginal Pathology (SICPCV).

Patients and Methods

Patients and surgical approaches. This was a multicentre retrospective cohort study of 153 women diagnosed with microinvasive cervical cancer over a 10-year period (1993-2003) in four Gynecologic Oncology Units in Northern Italy. Demographic data, surgical and pathological data as well as follow-up information were acquired by medical charts review. Among demographic data, age, menopause status and parity were evaluated. Surgical data included type of conization technique (cold knife conization, laser conization and large loop excision of the transformation zone; LLETZ) and type of hysterectomy (simple or radical, abdominal or vaginal approach). Pathologic records were reviewed regarding depth of invasion, horizontal extension of the tumor and the presence of LVSI. For patients who were managed by conization, the parameters of the cone specimens included also the status of surgical margins.

In patients who underwent secondary surgery, both specimens were analyzed to determine the total depth of invasion and horizontal extension. All cases were retrospectively staged according the 2009 International Federation of Gynecology and Obstetrics (FIGO) revised nomenclature: microinvasive carcinoma of the uterine cervix (FIGO stage IA) is defined as an invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm. Stage IA1 cervical cancer has a measured stromal invasion of ≤3 mm in depth and extension of ≤7 mm while stage IA2 cervical cancer has a measured stromal invasion of >3 mm and not >5 mm with an extension of not >7 mm (17).

All patients were followed-up every 3 months for the first year, every 6 months up to the second year and yearly thereafter. Follow-up included pelvic examination, Pap smear and colposcopy. Disease recurrence was defined as a histological diagnosis of Cervical Intra-epithelial Neoplasia of Grade 3 (CIN3) or more.

Statistical analysis. Statistical analysis was performed with the MedCalc database (MedCalc Software, Ostend, Belgium), assisted by the use of the Student’s t-test, \( \chi^2 \) testing and the Fisher’s exact test, as appropriate for categorical or continuous variables. A \( p \)-value <0.05 was considered statistically significant.

Results

During the study period, a total of 153 women with microinvasive cervical cancer, according to the FIGO classification staged as IA1 and IA2, were identified. The mean age was 44±12 years (range=25-78 years); 42 women (27.5%) were menopausal and 83 (54.2%) were <45 years old. Mean parity was 1.3±1.4. Diagnosis of microinvasive cervical carcinoma was made on tissue sample obtained with cervical conization in 132 cases; the remaining 21 cases were diagnosed after a non-conservative surgical approach without previous conization. In particular, immediate hysterectomy was more frequently performed on women aged ≥45 years compared to younger women (Table I).

Overall, 143 women (93.5%) were diagnosed with stage IA1 cervical cancer and 10 women (6.5%) with stage IA2 cancer. Stromal infiltration was ≤1 mm in 101 cases (66%), ranged between 2 and 3 mm in 42 women (27.5%) and between 3 and 5 mm in 10 (6.5%) cases. One hundred and forty-five (94.8%) were squamous carcinomas, 7 (4.6%) were adenocarcinomas whilst only one was adenosquamous carcinoma (0.6%). The median horizontal extension of cancer was 3 mm (range=2-7 mm); LVSI was reported in 5 cases (3.3%).

Among the 132 women who underwent conization as primary surgery, 123 (93.2%) had disease at stage IA1 and 9 (6.8%) at stage IA2. Sixty-two stage IA1 women had conization as definitive surgery, because of free surgical margins and no LVSI; 61 underwent secondary surgery. Only 1 out of 9 stage IA2 carcinomas had conization as definitive surgery.

Overall, 80 women (52.3%) were definitively treated with a conservative surgical approach during the study period, considering 63 women who underwent cervical conization as primary surgery, 16 women who had re-conization as secondary surgical treatment and one woman who underwent trachelectomy as a secondary approach. Pathological characteristics of primary cone excision and secondary surgical treatment of 69 women who underwent secondary surgery are reported in Table II. The mean interval to secondary surgery was 8±2.3 weeks while residual disease was found in 9 cases. All cases with residual disease had a diagnosis of stage IA1 at primary conization; the diagnosis...
of stage IA1 was confirmed in 8 out of 9 patients with residual disease, while 1 was re-staged IA2.

The management of stage IA1 and IA2 cervical cancers, with regard to the histological features of the primary cone excision, is reported in Table III. Table IV reported the correlation between the histological features of the primary cone excision and the risk of residual disease at secondary surgery.

After primary conization, 12 women had positive cone margins and 5 of them (41.7%) reported residual disease at secondary surgery. The rate of residual disease at secondary surgery in women with negative cone margins was 7%. No residual disease at secondary surgery in women with LVSIs was reported and all cases of residual disease were LVSIs-negative at primary surgery.

Residual disease was significantly related to positive surgical margins (41.7% vs. 7%, p=0.005) but not with LVSIs on the cone excision (0% vs. 14.1%, p=0.83).

In our series, surgical treatment progressively became more conservative. In the period between 1998-2003, 84 women were diagnosed with microinvasive cervical carcinoma; conization was the primary treatment in 79 patients (94%) while only 5 women had immediate hysterectomy. In the previous years, 69 women were diagnosed with microinvasive cervical carcinoma and conization was the primary treatment in 53 of them (76.8%): the rate of conservative surgery was significantly higher in the last years (94% vs. 76.8%, p=0.005). A ten-year follow-up was complete for each woman and no recurrence was found after a mean follow-up of 184.5±20.5 months.
Discussion

This survey describes the surgical approach of microinvasive cervical cancer in four Gynecological Oncology Units in Northern Italy, during the period between 1993-2003. During the last decades, the incidence of microinvasive cervical cancer is increasing, mainly in young women aged less than 40 years and a high number of women are diagnosed with a cervical cancer before their first pregnancy. Different approaches are employed to treat microinvasive cervical cancer but a trend towards a conservative surgical approach has emerged, as preservation of fertility is desirable in young women and many studies reported the safety and efficacy of a fertility-sparing surgery, particularly in women with stage IA1 cervical cancer (4, 15). However data are conflicting and other Authors have reported different results. Recently Rasaglisioni et al. (23) as most of the previous published studies suggest that LVS1 does not represent an independent prognostic factor in women with microinvasive cervical carcinoma. However data are conflicting and other Authors have reported different results. Recently Rasaglisioni et al. (23) as most of the previous published studies suggest that LVS1 does not represent an independent prognostic factor in women with microinvasive cervical carcinoma. However, in case of clear surgical margins and positive LVS1, the possibility of a pelvic lymph node sampling should be discussed with the patient.

Even if the outcome of microinvasive cervical cancer is favorable, a close long-term surveillance should be scheduled for conservatively-treated women. One of the strengths of the present study is the long follow up period. The absence of recurrence or disease-related deaths in our cases after a mean follow-up of 184.5 months, once again confirms the efficacy and safety of conservative fertility-sparing surgery in women with microinvasive cervical cancer.

Previous studies reported a risk of recurrence of less than 2% and a risk of death of only 0.1% in women with stage IA1 cervical cancer (12, 26). Burghardt et al. (26) analyzed a cohort of 344 patients with stage IA1 cervical cancer and noted only one (0.3%) recurrence that was diagnosed 12 years after treatment with conization. In a cohort of 494 patients with microinvasive cervical cancer treated by conization, Winter (27) noted four cancer-related deaths in patients with microinvasive disease after a mean follow-up of 14 years, without significant differences between stage IA1 and IA2.

In conclusion, our study suggests that fertility-conserving surgery is efficacious and safe in women with IA1 cervical cancer with unaffected cone margins and independent of LVS1. A conservative surgical approach could also be considered in women with IA2 cervical cancer when preservation of fertility is strongly requested. It is the Authors’ opinion that a close long-term surveillance should be scheduled for conservatively-treated women, and, in the absence of specific guidelines, at least 10 years of follow-up are required.

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