

Surgical management of early stage cervical cancer: Ten years experience from one Greek health region

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Summary

Purpose of investigation: Cervical cancer is the second most common malignancy in women, in both incidence and mortality. In the present study, we report our results of treating 93 consecutive patients with early invasive cervical cancers (Stages I-IIA).

Methods: The patients of this study comprised all women recognized with stage I-IIA cervical cancer during 1991-2000. Patients with stage IA1 cervical cancer without lymphovascular space involvement underwent either conservative management by means of large loop conization or simple hysterectomy. The remaining patients underwent radical hysterectomy and lymphadenectomy or radiation therapy. Mean (\pm SD) duration of follow-up was 6 (\pm 1.7) years.

Results: The mean (\pm SD) age of patients with stage I-IIA cervical cancer was 41.3 (\pm 9.1) year. Thirty-five patients with stage IA1 disease were managed conservatively with loop excision and 19 patients subsequently became pregnant. Fifty-two patients with stage IA2, IB and IIA cervical carcinoma underwent radical hysterectomy and lymphadenectomy.

Conclusion: Young women with stage IA1 cervical carcinoma wishing future fertility who undergo loop excision have a 100% cure rate. Women with stage IA2, IB, and IIA cervical cancer should undergo radical hysterectomy and lymphadenectomy or radiation therapy.

Key words: Cervical cancer; Microinvasion; Loop conization; Fertility; Radical hysterectomy; Lymphadenectomy.

Introduction

Cervical cancer is the second most common malignancy in women, in both incidence and mortality, with more than 471,000 new cases diagnosed each year worldwide [1]. The most important determinant of prognosis in patients with cervical cancer is the clinical stage. Over the past 50 years, there has been a sharp decline in the incidence and mortality from cervical cancer. This decline has been related mainly to the mass utilization of the Papanicolaou smear for cervical cancer screening. However, the mean age of all grades of preinvasive cervical lesions, including grade III intra-epithelial neoplasia, has declined during the last decade [2]. This could possibly be due to earlier identification through screening, different social behavior or earlier and heavier exposure to risk factors for cervical carcinogenesis, such as human papillomavirus (HPV) infection. Similarly, the mean age of both micro- and frankly invasive cervical cancer is also declining with studies showing the mean age at diagnosis being in the early 30s and 40s, respectively [2, 3]. Therefore, it is not unusual for the clinician to deal with a diagnosis of microinvasive cervical cancer (FIGO, stage IA) [4, 5]. In the last decade a number of advances have occurred in the treatment of cervical cancer. These advances have resulted in a variety of benefits including improved survival, improved quality of life and preservation of fertility in selected patients with stage IA1 disease [6]. The current FIGO definition divides stage IA (microinvasive cervical

cancer) into two categories. Stage IA1: "measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm. Stage IA2: "measured invasion of stroma greater than 3 mm and no greater than 5 mm in depth and no wider than 7 mm" [5].

The standard surgical approach to stage IA2, IB, and IIA cervical cancer consists of radical hysterectomy, lower peri-aortic lymphadenectomy, and complete bilateral pelvic lymphadenectomy [7]. Although there is general consensus that either surgery or radiation therapy produces equivalent cure rates, radical hysterectomy is often selected as primary therapy, based on a shorter treatment course, opportunity for ovarian preservation and better post-treatment vaginal function [7]. For women with advanced-stage disease treatment includes radiotherapy along with chemotherapy.

This article reports our results of treating 93 consecutive patients with early invasive cervical cancers (Stages I-IIA) at the Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Ioannina University Hospital (Ioannina, Greece).

Material and Methods

The patients in this study comprised all women diagnosed during 1991-2000 with early stage cervical cancer (Stages I-IIA).

Abnormal cytological findings in pap smears and/or vaginal bleeding were the most common presenting symptoms and findings. The referral policy for colposcopy was either persistent abnormal cervical cytologic findings suggesting low-grade squamous intraepithelial lesion (IgSIL) for 3-12 months, or immediate colposcopic evaluation following a single smear

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suggesting high-grade lesion (hgSIL) or possible invasion. Cytologic features suggesting possible microinvasion have been described in previous studies [8]. Colposcopic features suspicious of microinvasion included atypical vessels and dense acetowhite epithelium with or without ulceration. The management was either surveillance by means of cytology and colposcopy, in cases where both suggested low-grade lesions (mainly in nulliparous women or those wishing future fertility), or large loop excision of the transformation zone, in cases with completed family or findings suggesting high-grade SIL. The large loop excision was either shallow excision of the transformation zone or a conization, according to standard colposcopic practice. All large loop conizations were performed on an outpatient basis by the same experienced colposcopist (E.P.) with a Valley-Lab Force 2 Unit (USA) and Ultra Fine Diathermy Loops (Rocket of London, UK). The intention was always to excise the whole lesion together with a 2-3 mm lateral margin of normal looking epithelium. Diathermy ball cauterization to the cervical crater following the excision was avoided at the new, immediately post-conization, external os. This was performed with the intention of keeping the squamo-columnar junction visible, which might otherwise have disappeared within the canal. Histological diagnosis of microinvasion was made in the cone biopsy specimens. Depth of invasion was measured in a standard fashion estimating the distance from the basement membrane to the most deeply invasive area of cancer. Lateral spread, when it was present, was also measured. One senior pathologist (N.A.) reviewed all of the cases.

Staging procedures included physical examination, routine chemistries, colposcopy, endocervical curettage, cystoscopy, intravenous urography, sigmoidoscopy, X-ray examination of the chest and skeleton, and CT abdomen/pelvis with contrast.

Patients with stage IA1 cervical cancer without lymphovascular space involvement underwent either conservative management by means of large loop conization followed by intensive cytologic and colposcopic surveillance or simple hysterectomy, according to their wishes. Patients with stages IA2, IB, and IIA underwent radical hysterectomy and lymphadenectomy or radiation therapy. During radical hysterectomy, paraaortic lymph nodes routinely were excised and submitted for frozen section before proceeding with the radical hysterectomy. If the paraaortic lymph nodes were involved, the procedure was abandoned in favor of radiation and chemotherapy.

Mean (\pm SD) duration of postoperative follow-up was 6 (\pm 1.7) years.

Results

During the study period, a total of 121 patients with cervical cancer were identified. Staging and age at diagnosis are presented in Table 1. Ninety-three patients had stage I-IIA cervical cancer, whereas 28 patients had stage IIB-IV cervical cancer. Most of the patients had stage IA (39.5%) and IB (25%) lesions (Table 1). The mean (\pm standard deviation, SD) age for stages I-IIA was 41.3 (\pm 9.1) years whereas for stages IIB-IV was 52.5 (\pm 7.1) years.

Stage IA Cervical Carcinoma

A histologic diagnosis of stage IA cervical carcinoma in a large loop conization cervical specimen was made in 48 women. In two cases the lesion was an adenocarcinoma, in one case there was coexisting invasion in both squamous and glandular epithelium, and the other 45

Table 1. — Distribution of patients according to stage of disease of cervical cancer.

Stage	Patients	
	No (%)	Age (years), mean \pm SD
IA	48 (39.5%)	36.6 \pm 7.9
IB	30 (25.0%)	43.5 \pm 8.2
IIA	15 (12.5%)	43.9 \pm 11.2
IIB	14 (11.5%)	50.7 \pm 9.3
III	11 (9.0%)	52.0 \pm 4.1
IV	3 (2.5%)	55.0 \pm 7.9

cases were squamous lesions. The mean (\pm SD) age of the patients was 36.6 (\pm 7.9) years.

The referral cytology was persistent mild dyskaryotic changes for 15 months in one case, moderate dyskaryotic in 13 cases, severe dyskaryotic in 28 cases (in two of which severe glandular atypia was reported), and in six cases the cytologic features suggested possible invasion. Colposcopy was satisfactory in 39 cases, with a colposcopic impression of high-grade lesion in 19 cases and suspected microinvasion in 20 cases. In the remaining nine cases, colposcopy was unsatisfactory. None had had colposcopic features suggesting low-grade SIL.

The conizations were performed using a standard technique [9]. Histopathology showed depth of invasion between 3 and 5 mm (FIGO IA2) in seven cases and less than 3 mm in the remaining 41 cases (FIGO IA1). Space involvement was present in four cases. All seven patients with stage IA2 disease underwent radical hysterectomy. In one of these cases, there were metastatic deposits in the pelvic lymph nodes. None had residual invasive disease in the cervix. Three patients with stage IA1 but with space involvement also underwent radical hysterectomy with no residual or metastatic disease. Three further patients with stage IA1 underwent simple hysterectomy according to their wishes following a full explanation of the situation. None had residual or metastatic disease. Overall 13 women had a hysterectomy. The remaining 35 cases were managed conservatively with loop excision. All of these women have completed at least 36 months of follow-up (median 52 months). The follow-up protocol consisted of colposcopy and cytology every four months during the first two years and every six months thereafter for ten years. In no case has there been any cytologic or colposcopic evidence of residual or reoccurring disease. Five-year survival was 100% for stage IA cervical carcinoma.

Following conservative treatment 19 women have become pregnant. One underwent termination of pregnancy and another had a miscarriage at nine weeks' gestation. The remaining 17 women had full-term pregnancies and three have delivered twice since conization.

Stage IB and IIA Cervical Carcinoma

A diagnosis of Stage IB and IIA cervical carcinoma was made in 45 women. In four cases the lesion was an adenocarcinoma, in one case the lesion was an adeno-squamous carcinoma, and the other 40 cases were squa-

mous carcinomas. The mean (\pm SD) age of the patients with stage IB and IIA cervical carcinoma was 43.5 (\pm 8.2) years and 43.9 (\pm 11.2) years, respectively.

All the patients underwent radical hysterectomy and lymphadenectomy, apart from 2 women; one suffered from recent myocardial infarction and the other suffered from diabetic kidney disease. These two patients underwent radiation therapy.

Metastatic deposits in pelvic lymph nodes were found in three out of 30 patients (10%) with stage IB disease, and in 3 out of 15 patients (20%) with stage IIA disease. Metastatic deposits in paraaortic lymph nodes were found in one patient with stage IIA disease. Residual invasive disease was found in one patient with stage IB and in three patients with stage IIA disease (Table 2). During surgery, median blood loss was 950 ml. No patient developed fistula. There were no deaths during the early postoperative period. All the patients received routine subcutaneous heparin and antibiotic prophylaxis. Following surgery, during the first eight years of the study, patients with positive lymph nodes and/or positive surgical margins and/or microscopic involvement of the parametrium underwent adjuvant radiation therapy, whereas during the last two years these patients underwent adjuvant concurrent cisplatin-based chemotherapy and radiation therapy [10].

During the follow-up period, two patients with stage IB and four patients with stage IIA disease died. The 5-year survival for stage IB and IIA cervical carcinoma was 93.3% and 73.3%, respectively.

Table 1. — Incidence of extrauterine disease in 52 patients with stage IA2-IIA cervical carcinomas treated at the Department of Obstetrics and Gynecology at Ioannina University Hospital from 1991 to 2000.

	Stage IA2 (n = 7)	Stage IB (n = 30)	Stage IIA (n = 15)
(+) pelvic nodes	1	3	3
(+) paraaortic nodes	0	0	1
(+) surgical margins	0	1	3

Discussion

In the treatment of cancer the essential principle should be the eradication of the disease, thus ensuring maximum survival. Cervical cancer remains a major health problem worldwide, despite advances in screening. The overall 5-year survival rate ranges from over 93% for patients with stage I disease to 13% for those with stage IV disease [1].

The diagnosis of stage IA1 cervical squamous cell carcinoma should be based on cone biopsy. Systematic pathologic evaluation of the cone specimen is necessary. Where early invasion is identified, serial sections may be necessary to determine the extent of maximal depth of invasion, lateral involvement, and the presence of lymph vascular invasion. If squamous lesions are less than 3 mm in depth, the risk of having positive pelvic lymph nodes

is less than 1% [11]. If lesions are 3 to 5 mm in depth, the risk of having positive lymph nodes rises to 7.4% [11]. Young women wishing future fertility with cervical cancer stage IA1 can be managed solely using large loop conization [6]. Although lymphovascular involvement is generally considered to be an adverse prognostic factor in cervical cancer, the prognostic significance of lymphovascular involvement in stage IA1 is uncertain. Thus, patients need to be adequately informed regarding the balance between a desire to retain fertility, when this is an issue, and the very low rate of residual disease or metastatic deposits associated with conservative management [11].

In the present study, we report our results of treating 93 consecutive patients with early invasive cervical cancers (Stages I-IIA) at the Department of Obstetrics and Gynecology of Ioannina University Hospital. Thirty-five patients with stage IA1 disease were managed conservatively with loop excision and 19 patients subsequently became pregnant. Fifty-two patients with stage IA2, IB, and IIA cervical cancer without medical contraindications underwent radical hysterectomy. The mean (\pm SD) age for stages I-IIA was 41.3 (\pm 9.1) years. This indicates that cervical cancer is a disease of young women. Cervical cancer has a tendency to spread to the pelvic and paraaortic lymph nodes. The overall incidence rates of pelvic and paraaortic nodal metastasis was 13.4% and 1.9% respectively. The incidence of lymphatic metastasis increased with stage; the rates of stage IIA were doubled those of stage IB. The overall 5-year survival rate was 100%, 93.3%, and 73.3% for stages IA, IB, and IIA respectively. The survival rate was comparable with the reported range of most studies [1].

Because of our policy of not performing radical hysterectomy in patients with gross paraaortic disease, the 1.9% incidence rate of paraaortic positivity represents micrometastasis. This finding confirmed the need for paraaortic lymphadenectomy to detect occult metastasis in this area [1].

Several studies have identified a poor prognosis for patients who undergo radical hysterectomy and have nodal involvement [12, 13, 14]. Of note, a recent intent-to-treat-analysis of stage IB and IIA cervical cancer in the United States revealed that there is a survival advantage for women with surgical intent-to-treat and tumors of 4 cm or less, independent of adjuvant therapy or age [15].

Over the last decade, specific clinical and pathological factors have been identified which are predictive of increased local recurrent and lymphatic metastasis. Primary tumor features that are predictive of nodal metastases include angiolymphatic space invasion, parametrial extension, clinical size lesion, depth of cervical stromal penetration, and histological grade [16]. In the absence of histologically demonstrated nodal metastases, tumor-related variables linked with an increased risk of recurrence include close vaginal margins, parametrial infiltration, tumor size, depth of invasion, angiolymphatic space involvement, adenocarcinoma cell type, histologic grade, and extensive stromal inflammatory cell infiltrate in the primary tumor [17, 18].

Following radical hysterectomy and lymphadenectomy, in patients with selected high-risk factors, such as positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium, postoperative radiation therapy has been the standard of care [1]. However, a recent phase III randomized trial revealed that, in these patients the addition of concurrent cisplatin-based chemotherapy to radiation therapy significantly improves progression-free and overall survival [10].

Our study shows that young women with stage IA1 cervical carcinoma wishing future fertility who undergo large loop conization have a 100% cure rate and a normal subsequent pregnancy outcome. Women with stage IA2, IB, and IIA disease should undergo radical hysterectomy and lymphadenectomy or radiation therapy. Following surgery, in patients with histologically documented extracervical disease (those with pelvic nodal involvement, positive margins, or parametrial extension), the current standard of care is adjuvant concurrent pelvic radiation and cisplatin-based chemotherapy [10]. For node-negative patients with risk factors (large tumors, depth of stromal infiltration, and lymphovascular space involvement) adjuvant pelvic radiation provides clear therapeutic benefit [16].

Conclusion

Cervical cancer remains a major health problem, being the second most common malignancy in both incidence and mortality worldwide. Screening with the Pap smear is the best currently available method of reducing the incidence and mortality of cervical cancer. Microinvasive squamous carcinoma with 3 mm or less of invasion and 7 mm or less of lateral spread (stage IA1) can be managed conservatively in cases where preservation of fertility is an issue, by large loop conization [6]. The choice of therapy should be influenced by the patient's desire to maintain fertility. However, due to estimates of nodal involvement of 4% to 10%, the recommended treatment for patients with stage IA2 disease continued to be radical hysterectomy with bilateral lymphadenectomy or radiation therapy [11].

Up to 85% of patients with other stage I (IA2 and IB) and stage IIA are cured [1]. For these patients, treatment with radical surgery or radiation is equally effective. In early-stage high-risk patients with cervical cancer, following surgery, the current standard of care is combined pelvic radiation and cisplatin-based chemotherapy [10].

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