The Clinical Outcome of Patients with Microinvasive Cervical Carcinoma

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1. Introduction

Cervical cancer, the second most common cancer in women, develops through well-defined precursor lesions with potential to progress to invasive disease if not properly detected and eradicated. In cervical carcinogenesis, human papillomavirus (HPV) plays an important causal role. Besides the evidental causal role in cervical carcinogenesis, HPV is an important prognostic factor for disease progression as well (Syrjänen, 2000). Early invasive carcinoma is an intermediate state in the development of invasive carcinoma from a cervical intraepithelial neoplasia. According to clinical experience, the early stage of invasion has much better prognosis when compared to an advanced invasive cancer. This warrants the recognition of microinvasive carcinoma (MIC) as a separate entity among cervical cancer that is not visible at inspection, and therefore only diagnosed by histological examination of a biopsy specimen that contains the complete lesion (Wright et al., 1994).

Mestwerdt was the first to notice that cervical cancers with less than 5 mm of invasion behave less malignant and therefore could be treated by less radical surgery. He named these tumours "Mikrokarcinom". Mestwerdt also introduced tumour depth of 5 mm as a parameter of the management of cervical carcinoma and suggested a less radical surgery for such cases. Subsequent authors proposed different maximal depths as the upper limit of an invasive growth (Mestwerdt, 1947). Following Mestwerdt's publication and before the most recent FIGO definition of stage IA cervical cancer in the 1994, an intense discussion has continued concerning the definition of microinvasion, terminology and treatment modalities as related to disease outcome, e.g. lymph node metastasis, reccurence and cancer death (Creasman, 1995). The latest FIGO definition of stage IA1 cervical cancer is defined as cervical carcinoma confined to the uterus with stromal invasion less than 3.0 mm and stage IA2 cervical cancer with stromal invasion more than 3.0 mm but not more than 5.0 mm, with limited horizontal spread beyond 7.0 mm (World Health Organization, 2006). Because of the effective use of screening, an increasing number of women are being diagnosed with cervical cancer in an early stage of the disease. However, many of these cases occur in younger women, for whom the preservation of fertility is desirable. More conservative methods have emerged as alternative treatment modalities for these women, as they may allow for future fertility, without having a considerable adverse effect on cure rates.

The objective of this review is to discuss the management of patients with microinvasive cervical cancer and present the Ljubljana experience on management of FIGO stage IA (both IA1 and IA2) cervical cancer.

2. Management of stage IA cervical carcinoma

Lesions of the microinvasive type present a paradox in that they breach the basement membrane yet are rarely associated with metastasis. Traditionally the presence of stromal invasion predetermines a belief that metastasis is imminent and radical surgery obligatory. There is now considerable debate on the necessity for obligate radicality by radical hysterectomy and lymphadenectomy or radical irradiation such that conservative management, simple hysterectomy or even therapeutic cone biopsy, are alternatives in most cases. Individualization of treatment to reduce therapy-associated early and late morbidity is the most current trend in cervical cancer surgery. Despite advances over the past 3 decades in decreasing the morbidity of treatment, the cure rate associated with radical surgery (approximately 90%) has not changed appreciably. The limited risk of parametrial and nodes involvement in case of MIC unbalances the morbidity of radical hysterectomy and pelvic node removal.

Figure 1 shows the treatment options for microinvasive carcinoma of the cervix, based on the latest guidelines within the ESGO community and prepared by ESGO Educational Committee (ESGO, 2010).

Conization as definitive therapy should be reserved for patients who desire fertility preservation. The candidates for this procedure would be those patients with FIGO stage IA1 disease (less than or equal to 3 mm stromal invasion). The selection criteria for this conservative approach to definitive therapy should include squamous histology, negative conization margin, and adequate pathologic processing of the tissue specimen. The patient needs to be compliant with a follow-up regimen. In patients with 3 mm or less depth of stromal invasion who do not desire fertility preservation, a simple extrafascial hysterectomy can be performed.

Patients with FIGO stage IA2 cervical carcinoma can be treated with modified radical hysterectomy and pelvic and para-aortic lymph node dissection. Selection of such patients for a modified radical hysterectomy include squamous histology with negative conization margins following adequate pathologic processing of tissue.

Patients with positive cone margins should be treated as if they had frankly invasive disease and undergo a radical hysterectomy with pelvic and para-aortic lymph node dissection.

The patients who are nonsurgical candidates or individuals not opting for surgical management should be treated with primary radiation therapy.

The use of adjuvant radiation therapy in lymph node positive patients has been controversial. A recent studies indicates that postoperative radiotherapy in node positive cervix cancer significantly improves pelvic control, disease-free survival, and overall survival.

Stage IA1, LVSI negative:	
	Conization if preservation of fertility is desired or Simple (extrafascial, type A) hysterectomy with or without salpingoophorectomy
Stage IA1 with extensive LVSI and Stage IA2:	
	Conization or radical trachelectomy if preservation of fertility is desired or Modified radical hysterectomy (type B) and Pelvic lymphadenectomy
Stage IA1 or IA2 nonsurgical candidates:	
	Primary radiation therapy.

Fig. 1. Treatment options for MIC: accurate pathologic evaluation and negative cone margins for 2009 FIGO staging.

Reports describing primary radiotherapy for microinvasive cervical cancer are limited and generally include patients who have medical contraindications to surgery. As opposed to patients with larger volume invasive disease , brachytherapy is often the sole, or major, component of radiation used. Brachytherapy alone is an effective treatment for nonsurgical candidates with microinvasive cervical carcinoma. The incidence of lymph node metastasis and regional relapse following brachytherapy, is very low for small-volume invasive cervical carcinoma, particularly in those with maximal depth of stromal invasion less than 5 mm (Greer et al., 1990).

Recommended follow-up for patients with MIC after completed therapy is every 3 months during the first year, then every 6 months up to 5 years and annually afterwards. Investigations in addition to gynaecological examination, including cytology and colposcopy, should be performed depending on symptoms, local findings and general condition of the patient (ESGO, 2010).

3. The Ljubljana experience on management of stage IA cervical carcinoma and the clinical outcome of our patients

The Ljubljana experience on management of stage IA (both IA1 and IA2) cervical cancer consists of accumulated experience during several observation periods. During the period of 1960-1972, the surgical treatment in our institution followed the principle that cancer is cancer, therefore radical treatment is justified. During that period, 290 cases of stage IA cervical carcinoma were treated, the great majority by vaginal radical hysterectomy and abdominal radical hysterectomy with lymphadenectomy. Positive lymph nodes were found in none of these cases (Kovačič et al., 1989).

Our accumulated experience on the minimal risk of metastatic spread and reccurence, improved understanding of the development of early stages of cervical carcinoma, and the increasing frequency of young women wishing to preserve fertility were the reasons for the increased use of conservative treatment. A conservative surgical approach for MIC, FIGO stage IA was adopted when a scoring system was implemented in 1979, based on the evaluation of morphological criteria and exact estimation of the tumor size (Rainer, 1978). This scoring system has been used since 1979 as the basis for selecting treatment for all patients with stage IA cervical carcinoma. Table 1 shows the Rainer's scoring system.

The present scoring system was established when there was no definitive international consensus on the classification of MIC. The definition was vague and the criteria for identification varied. The applied score enabled uniform estimation of all histological criteria in every case and was effective in making decisions about the treatment modalities in individual cases. To obtain an unbiased estimation of the tumor size and its various histological parameters, 70 cases of MIC were subjected to stereological analysis (Eržen et al., 1995). The results of this analysis were used to define the criteria for the scoring system. The depth of stromal invasion, mitotic activity, pattern of invasion, host defence reaction and lymph-vascular space invasion (LVSI) were evaluated and scored. The patient's age and her wish to preserve fertility were also taken into consideration.

During the first observation period (1960 – 1972), the cases with the depth of infiltration more than 3 mm were classified as stage IB. If the clinical data including the patient's general condition and the surgeon's competence were not taken into consideration, the following total scores were used as the criteria of selection for the different treatment modalities.

Between 1989 and 1993 conization was the definitive treatment for patients with a score of 7 points or less, simple vaginal or abdominal hysterectomy was performed in those who scored 8 to 12 points, and radical hysterectomy with lymphadenectomy was suggested in patients with more than 12 points, using the Rainer's scoring system. According to this scoring system which was further modified in 1994 for MIC stage IA2, radical hysterectomy was no longer indicated. Until 1997 lymphadenectomy was performed only in patients with LVSI, and thereafter in all of the patients with MIC IA2.

During the observation period from 1973 to 2009 the rate of conisation with/without pelvic lymphadenectomy as the sole mode of treatment of MIC, FIGO stage IA has increased continuously and was the definitive treatment for almost 75% of all our

Morphological criteria		Points
I. Cellular type	- large cell type	1
	- keratinizing type	2
	- small cell type	2
II. Mitotic activity (per high power field)	- 5 -10 mitoses	1
	- more than 10 mitoses	2
III. Type of invasion	- pushing borders, singular buds	1
	- dropping off type	5
	- reticular or confluent type	7
IV. Defence reaction	- poor	1
V. Capillary-like space invasion	- present	10
VI. Depth of invasion	- less than 3 mm	2
	- 3 to 5 mm	4
	- more than 5 mm	8

Table 1. Scoring of the morphological criteria of MIC

patients. If resection margins were not disease-free or lateral clearance was not adequate, the suggested treatment was hysterectomy to avoid late recurrence. However the frequency of Wertheim radical hysterectomy and simple hysterectomy have declined accordingly. The Wertheim radical hysterectomy was performed only in 9,0 % of the cases, mostly due to incorrect preoperative diagnosis of invasive carcinoma, based on scanty biopsy material. The pelvic lymphadenectomy was performed in 11,2% of the cases, in these cases LVSI was present and the pelvic nodes were invariably free of cancer. The frequency of lymph node metastases in stage IA2 cervical cancer is reported to range from 0% to 9,7%. LVSI seems to play an important role in the risk of lymph node metastases in stage IA2 cervical cancer. The recent published article from Rogers LJ et al.

suggests that the latest studies adhering to the FIGO definitions showed a 0,5% incidence of lymph node metastases in stage IA2 cervical carcinomas, which is not as high as was previously believed. The very low rate of positive lymph nodes in correctly staged IA2 cases therefore cannot justify the inclusion of lymphadenectomy as part of standardised care for these patients (Eržen et al, 2001).

The first abdominal radical trachelectomy in our Department was performed by Professor Novak in 1954, but it did not become part of the standardized protocol; it was performed only in a few cases. In 2008 radical trachelectomy (abdominal and laparoscopic) was re-introduced and has been a treatment tool in our Department since.

The Rainer's scoring system has been used at the Department since 1979 as the basis for selecting the treatment option for all patients with stage IA cervical carcinoma, but has generally not gained acceptance. When all the unfavorable prognostic factors are discussed and excluded by the tumor board the treatment of patients with IA MIC wishing to preserve fertility is individualized (Smrkolj et al., 2012).

4. Conclusion

We suggest that treatment of MIC IA can be less radical, particularly for young women who want to preserve their fertility and anatomical integrity, especially if LVSI is absent. The treatment of stage IA should be based on the evaluation of prognostic factors in addition to an adequate assessment of the tumour size. Both parameters should be accurately evaluated by examination of numerous or serial step sections of cervical cones. Individualisation of treatment in patients wishing to preserve fertility should be done when all the unfavourable prognostic factors are excluded. Standardisation of the microscopic examination of the cervix is highly recommended. Cone margins should be carefully examined and proven disease-free. Cases with incorrect clinical estimation of the tumour size, associated with histological diagnosis of invasive carcinoma in punch biopsy, may still result in over-treatment when stage IA is found in cervical specimen after radical hysterectomy. Preoperative high resolution magnetic resonance imaging with an endovaginal coil or preoperative 3D-ultrasound perhaps could identify such patients with small tumour volume and might avoid unnecessary radical operation. According to our experience, follow-up of the patients after conization by regular pelvic examination, cytology and colposcopy is mandatory at least every six months for two years, and yearly thereafter.

Correct diagnosis and adequate treatment of early invasive cervical carcinoma, stage IA, should take into account the existing information of the prognostic factors. This is essential to individualise the treatment to avoid unnecessary risks, as well as over- or under-treatment. Such prognostic factors include: adequate estimation of the tumour size, lymphatic vessel invasion, type of confluence of the invasion, mitotic activity, host defence reaction and accurate examination of the surgical margins. Unfortunately, the existing FIGO staging systems disregard some other important prognostic factors in early cervical carcinoma such as capillary-like space invasion, type of invasion and mitotic activity. The most frequently reported factors increasing the risk for lymph node metastasis, reccurence and cancer death are: depth and pattern of stromal invasion, involvement of lymphatic and vascular space, tumour volume and state of the resection margins. In addition to the above

listed major prognostic factors, the outcome of early invasive carcinoma of the uterine cervix could also be significantly affected by: subjectivity of microscopical examination and estimation of histological parameters in differential diagnosis, adequate sampling and technical preparation of all cervical biopsy specimen, particularly adequate handling and sampling of the cones and hysterectomy specimens.

Each of these factors should be considered thoroughly when the prognosis of the disease is assessed, not just from the standpoint of eradicating the cancer, but also to avoid unnecessary over-treatment and with respect to the functional integrity of the patients wishing to preserve fertility. In the near future, the diagnostic procedure should also benefit from immunohistochemical and molecular methods used to predict the behaviour of all tumours classified as microinvasive carcinoma that reccur and progress to frankly invasive carcinomas.

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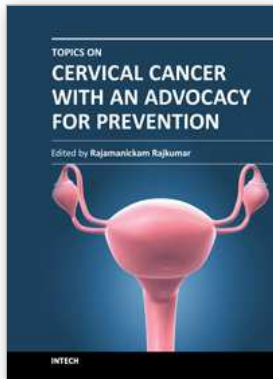
Topics on Cervical Cancer With an Advocacy for Prevention

Edited by Dr. R. Rajamanickam

Cervical Cancer is one of the leading cancers among women, especially in developing countries. Prevention and control are the most important public health strategies. Empowerment of women, education, "earlier" screening by affordable technologies like visual inspection, and treatment of precancers by cryotherapy/ LEEP are the most promising interventions to reduce the burden of cervical cancer.Dr Rajamanickam Rajkumar had the privilege of establishing a rural population based cancer registry in South India in 1996, as well as planning and implementing a large scale screening program for cervical cancer in 2000. The program was able to show a reduction in the incidence rate of cervical cancer by 25%, and reduction in mortality rate by 35%. This was the greatest inspiration for him to work on cerrvical cancer prevention, and he edited this book to inspire others to initiate such programs in developing countries. InTech - Open Access Publisher plays a major role in this crusade against cancer, and the authors have contributed to it very well.

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