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REVIEW ARTICLE

Modern treatment of invasive carcinoma of the uterine cervix

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Summary

Treatment of invasive cervical carcinoma is determined by the clinical disease stage. Microinvasive carcinoma of the uterine cervix, due to its limited metastatic potential, is usually curable with non-radical treatment. There are no standard approaches to the treatment of stage Ib-IIa carcinoma of the uterine cervix. Both radical surgery and radical radiotherapy are utilized with similar efficacy but with different associated morbidity and complications. Stage Ib1 was commonly treated with radical hysterectomy plus pelvic lymphadenectomy. Laparoscopically-assisted radical vaginal hysterectomy demonstrated similar efficacy and recurrence rates for this disease stage. In cases where fertility is to be preserved, radical vaginal trachelectomy is a valid option for small cervical cancers. Among the papers dealing with bulky cervical disease (stages Ib-IIa) a great deal of disagreement is evident. Some oncologic centres prefer primary surgery with postoperative radiotherapy, with or without chemotherapy, while others prefer primary chemoradiotherapy. Moreover, as a possible alternative, neoadjuvant chemotherapy followed by radical surgery is recommended for stage Ib2 disease. Simultaneous chemoradiation is being introduced as a new standard for advanced cancer, since it has been clearly demonstrated that it can prolong disease-free and overall survival. The treatment of recurrent carcinoma depends on the type of previous treatment, site and extent of recurrent disease, and on the disease-free period and general health of the patient. In conclusion, the decision on the treatment approach for invasive carcinoma of the uterine cervix should be individualized, based on numerous factors, such as disease stage, general health of the patient, cancer-related factors, in order to choose the best approach with minimal complications.

Key words: invasive carcinoma, modern, treatment, uterine cervix

Treatment of invasive carcinoma of the uterine cervix

Treatment of invasive carcinoma of the uterine cervix is conditioned by the clinical disease stage. The FIGO (International Federation of Gynecology and Obstetrics) staging system is still being utilized and is based on the anatomic extent of the disease and clinical evaluation, and cannot be altered with subsequent surgical findings [1].

In patients with cervical carcinoma verified by biopsy of the cervix, cone-biopsy or endocervical curettage, staging procedures are required, involving colposcopy, vaginal and rectal examination, cystoscopy and rectosigmoidoscopy in order to assess disease spread to the adjacent structures, such as parametria, bladder or rectum. Suspicion of bladder and/or rectal involvement should be histologically proven. It is recommended that these tests should be done under general anesthesia. Computerized tomography (CT) scanning and magnetic resonance imaging (MRI) are usually used to detect/confirm lymphadenopathy and involvement of the parametria. Positron emission tomography (PET) scanning is the best method to exclude small nodal disease, especially in the paraaortal region, where external radiation may carry survival advantage. It has been proven that PET is significantly superior to CT or MRI (sensitivity 90 vs. 60%) in the detection of metastatic lesions [2]. These diagnostic tests have not been included into the FIGO staging, but they should be utilized when required. Moreover, intravenous pyelography (IVP) is an option for the clinical stages of cervical cancer above Ib2.

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There is much dispute about whether cervical cancer should be surgically staged, since the FIGO staging seems unsafe, especially for advanced disease. This system also ignores one of the most relevant prognostic indicators – lymph node metastases. However, peritoneal laparotomy has not been proven as the most acceptable method for surgical staging. Laparoscopic extraperitoneal approach is being increasingly used as a new technique in the diagnosis of lymph node metastases. Some studies have tried to compare clinical with surgical staging and could not demonstrate survival advantage of surgical staging compared to clinical staging with extraperitoneal approach [3], while some others have indicated the usefulness of laparoscopic surgical staging for Ib2-III stage patients [4].

FIGO staging of invasive cervical carcinoma in patients from the University Clinic of Gynecology and Obstetrics Nis is shown in Table 1.

Stage Ia – microinvasive carcinoma of the uterine cervix

Microinvasive carcinoma of the uterine cervix (stage Ia) is an early stage of invasive carcinoma, with limited metastatic potential and curable with non-radical methods. The need for the definition of this stage has been motivated by the wish to preserve fertility and to prevent possible complications of radical treatment. The diagnosis of Ia stage of cervical squamous carcinoma should be based on conization, utilizing surgical techniques which do not have as a consequence cauterization of the margins. The treatment of microinvasive carcinoma should be planned in cooperation with an experienced pathologist, since histologic parameters are used to determine the extent of surgery and to establish the need for possible treatment of regional lymph nodes (the risk of nodal involvement is low here). The highest risk of nodal metastases, as well as for pelvic recurrence, is found in women with confirmed tumor emboli in the lymphatic and vascular space [5]. Each patient with microinvasive carcinoma should be evaluated individually. If there is no distant spread, simple but complete excision should be enough. Extended surgery is performed when there is a considerable probability of spread (Table 2).

Table 1. Number of patients treated for invasive carcinoma of the uterine cervix in the period 2003-2007 in the University Clinic of Obstetrics and Gynecology, Nis

Stage	*Number of patients*	*%*
Stage I	411	52.9
Stage II	199	25.5
Stage III	134	17.2
Stage IV	34	4.3
Total	778	99.9

Stage Ia1 carcinoma of the uterine cervix

A number of studies have suggested that FIGO stage Ia1 cervical carcinoma, defined as minimal microscopic invasion < 3 mm deep and < 7 mm wide, should be treated conservatively [6]. Treatment options for stage Ia1 cervical cancer in the absence of lymphovascular invasion are conization for women who want to preserve their reproductive potential, with the assumption that complete excision is possible, or simple hysterectomy for women who do not want to preserve their fertility. Surgical margins have to be "clean" in therapeutic conization. If the invasive lesion has been

Table 2. Treatment of invasive carcinoma of the uterine cervix in the University Clinic of Obstetrics and Gynecology, Nis

Stage	*No (%)*	*Co*	*Amp*	*Hyst. cl*	*No (%) WM*	*RT*	*CT/RT*	*Pal. ther*
IA-1	55 (7.1)	38 (6.9)	8 (14.5)	9 (16.3)	–	–	–	–
IA-2	20 (2.6)	–	4 (20.0)	6 (30.0)	10 (50.0)	–	–	–
IB-1	264 (33.9)	–	2 (0.7)	4 (1.5)	258 (97.7)	160 (60.0)	–	–
IB-2	72 (9.2)	–	–	4 (5.5)	68 (94.4)	30 (41.0)	–	–
IIA	59 (7.6)	–	–	2 (3.3)	57 (96.6)	26 (44.0)	–	–
IIB	140 (17.9)	–	–	–	–	102 (72.8)	38 (27.1)	–
IIIA	36 (4.6)	–	–	–	–	20 (55.5)	16 (44.4)	–
IIIB	98 (12.6)	–	–	–	–	80 (81.6)	18 (18.3)	–
IVA	22 (2.8)	–	–	–	–	4 (18.0)	6 (27.2)	12 (54.5)
IVB	12 (1.6)	–	–	–	–	–	–	12 (100.0)
Total	778 (99.9)	38 (4.8)	14 (1.7)	25 (3.2)	393 (50.5)	422 (54.2)	78 (10.0)	24 (3.0)

Co: conization of the cervix, Amp: amputation of the cervix, Hyst. cl: classic hysterectomy, WM: Wertheim-Meigs hysterectomy, RT: radiotherapy, CT/RT: chemoirradiation, Pal. ther: palliative therapy

removed, but CIN (cervical intraepithelial neoplasia) has remained in the resection margins, excision should be repeated in order to remove residual CIN and prevent further disease spread. If simple hysterectomy is carried out, the ovaries do not have to be removed in order to treat the cancer. Moreover, there are no indications for removal of the vaginal cuff; it is done only if there is invasion to the vaginal fornices, which should be recognized on colposcopic evaluation. Since lymph node metastases are very rare in this patient group, lymphadenectomy is not required [7].

Lymphovascular invasion is generally believed to be a poor prognostic factor in cervical carcinoma, but the prognostic significance of lymphovascular space involvement in stage Ia1 has not been yet clearly determined. Some authors think that the presence of lymphovascular invasion in Ia1 stage requires radical management [8].

The recommended treatment options for cervical cancer in Ia1 stage with lymphovascular invasion are modified radical hysterectomy with pelvic lymph node dissection or radical trachelectomy with laparoscopic pelvic lymph node dissection, if fertility is to be preserved (Table 2).

Stage Ia2 carcinoma of the uterine cervix

This stage is defined, according to FIGO, as cancer with 3-5 mm deep and < 7 mm wide disease invasion. With depth of invasion, the incidence of lymphovascular invasion rises, as well as the incidence of metastases to pelvic nodes. In stage Ia2 the risk of nodal involvement is around 7%; such patients should be treated with radical hysterectomy, modified radical hysterectomy with pelvic lymphadenectomy or primary irradiation, except when there are strong reasons for conservative management. Radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy should be considered if fertility is to be preserved. Stage Ia2 cervical carcinoma without lymphovascular invasion can be effectively treated with complete excision (conization or extrafascial hysterectomy), though radical trachelectomy - hysterectomy could be justified too, while nodal pelvic dissection is controversial in these patients [9].

Stage Ia2 cervical carcinoma with unfavorable pathologic characteristics (lymphovascular invasion) should be treated with:

- Radical hysterectomy with pelvic lymph node dissection
- Radical trachelectomy with laparoscopic pelvic lymph node dissection in young patients who want their fertility preserved.

In patients with increased risk of operative mortality because of old age or general health status, early invasive carcinoma of the uterine cervix can be treated only with intracavitary radiation therapy (Table 2).

Stage Ib-IIa carcinoma of the uterine cervix

There is no standard approach to the treatment of stage Ib-IIa carcinoma of the uterine cervix. Many patients are treated either with radical surgery or radical radiation therapy; these modalities have been demonstrated to be equally effective, but with different associated morbidity. Radical surgery may preserve ovarian function and secondary vaginal stenosis induced by radiotherapy can be avoided, which is very important for young patients. Additionally, with surgical treatment possible radiation-induced chronic injuries to other adjacent organs (bladder, small and large bowel), which are difficult to treat, can be avoided. A combination of surgery and radiotherapy is also utilized, though treatment protocols may significantly vary. Individual therapeutic decisions should be based on numerous factors such as age, health status, cancer-related factors, and also on the characteristics of particular modalities, in order to choose the best treatment with minimal complications (Table 2) [10].

Stage Ib1 and early stage IIa carcinoma of the uterine cervix

A standard treatment of stage Ib1 and IIa cervical carcinoma is surgery - radical hysterectomy with pelvic lymphadenectomy (Table 2). Primary surgery has the advantages of cancer removal and precise surgical staging, enabling appropriate use of any adjuvant therapy afterwards [10]. Surgical treatment involves the removal of uterus, paracervical tissue surrounding the cervix and 2 cm of the vaginal fornices. In younger women ovaries can be conserved in order to avoid early menopause. A study comparing survival, morbidity and relapse in type II and type III of radical hysterectomy in stage Ib-IIa of cervical cancer found equal efficacy, but the latter was associated with a higher rate of late complications [11,12]. Some recent studies have demonstrated that early cervical cancer can be effectively treated with laparoscopically-assisted radical vaginal hysterectomy (LARVH), with similar efficacy and recurrence rate compared to radical hysterectomy [13]. Finally, radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy could be used for smaller (<2 cm) carcinomas if fertility is to be preserved. There

are studies which have demonstrated recurrence comparable to that for radical hysterectomy, as well as an encouraging percentage of pregnancies with live births [14]. Radical trachelectomy can be performed transabdominally as well. Since this procedure is still being investigated, adequate cases should be referred to the centres specialized for gynecologic cancer.

Standard surgical treatment of stage Ib-IIa of cervical cancer is pelvic lymphadenectomy as well. Pelvic lymph nodes are carefully dissected, with the intention to remove as many of them as possible. We should, on the average, remove 25-30 lymph nodes. This could be explained by the fact that the percentage of involved nodes rises from 10.5% when less that 20 nodes have been removed, to 26.5% with more than 50 nodes removed [15].

Many studies describe the prognostic significance of lymph node metastases in cervical carcinoma. Lymph nodes have been described as the most important independent predictor of overall survival. Overall survival of patients with negative lymph nodes is 90% after radical hysterectomy and dissection of pelvic nodes [16]. Patients with positive lymph nodes have 5-year survival of 60%, with risk of pelvic and distant recurrence [16]. In patients with nodal metastases, postoperative pelvic radiation is a standard procedure; it can enhance local control, but there are no controlled studies which would demonstrate the impact on survival - adjuvant pelvic radiation has no impact on distant metastases.

The diagnosis of enlarged and involved paraaortic lymph nodes (PALN) rises the issue of the best possible treatment. Extended-field radiation is a standard treatment achieving long-term survival - even up to 40% for Ib stage and positive PALN patients [17]. However, significantly better results in these women can be achieved, as randomized studies show, with radiation and simultaneous chemotherapy based on cisplatin.

The combination of surgery with radiotherapy increases the number and severity of complications – the morbidity is higher than with either of the modalities used alone. In order to reduce this morbidity there is a number of options for patients with positive lymph nodes detected during radical hysterectomy. Some authors advocate extensive surgery if all lymph nodes are positive, while others recommend laparoscopic lymphadenectomy in order to identify nodal metastases and avoid radical surgery [18].

In contrast to the above mentioned authors, some experts resect all identified massive nodes, even if primary radiation is planned, convinced that radiation cannot eradicate bulky nodal disease. Surgical removal of massive lymph nodes demonstrates reduced morbidity and systemic spread of this carcinoma [19]. Survival of women with removed massive lymph nodes is significantly higher compared to those in whom this procedure has not been done (32 vs. 6%).

Other factors, such as voluminous tumors, deep stromal invasion, lymphovascular invasion, as well as parametrial invasion with positive surgical margins, unfavorable tumor histology, mean poor prognosis in stage Ib and IIa cervical carcinoma. A large number of studies recommend adjuvant radiotherapy to improve prognosis even if lymph nodes are negative [20].

On the other hand, evaluation of unfavorable prognostic factors before surgical decision-making, enabled less radical approaches to be utilized in stage Ia1-Ib2 disease. Moreover, modified parametrectomy has been shown to be feasible and completely safe. Follow-up has demonstrated average 5-year survival of 95% for those with negative nodes (on frozen section) treated with modified radical hysterectomy, compared to 74% in women with intraoperatively identified nodal metastases treated with conventional radical hysterectomy [21].

Stage Ib2 carcinoma of the uterine cervix

Massive stage Ib2 carcinomas (primary lesion > 4 cm) of the uterine cervix are more difficult to treat; regardless of the treatment approach recurrence rates are higher compared to Ib1 stage. While some centres prefer primary surgery similar as for stage Ib1, plus postoperative radiation with or without chemotherapy, others prefer primary radiation therapy (Table 2). However, the rate of pelvic relapse is significantly higher among stage Ib2 patients which were only irradiated (30%) compared to those who were surgically treated and adjuvantly irradiated (20%) [22].

Neoadjuvant chemotherapy is an acceptable alternative in the treatment of bulky cervical Ib2-IIa carcinomas. In addition to the eradication of micrometastatic disease, the rationale for neoadjuvant therapy is also the tumor reduction, which should improve the outcome of subsequent surgery or radiotherapy. Neoadjuvant chemotherapy with subsequent radical surgery is a valid alternative to conventional chemoradiation, which is expected to improve survival in stage Ib2 patients [23]. This approach favors surgical treatment - neoadjuvant chemotherapy should eliminate the minimal risk of extracervical spread, avoiding the combination of surgery and radiation therapy.

Stage IIb-IVa carcinoma of the uterine cervix

For a long time radiotherapy has been the mainstay of treatment of locally advanced cervical carcinoma. Standard treatment of advanced cervical carcinoma consisted of radical external beam radiotherapy combined with brachytherapy (Table 2). Adequate dosage is very important, both to the tumor volume itself and to the lateral pelvic nodes.

Modern approach to the treatment of advanced cervical cancer is contained in the modification of the traditional role of radiotherapy as a sole treatment modality. Nowadays, treatment of advanced cervical cancer depends on the findings of locally advanced disease and massive lymph nodes on preoperative computerized tomography (CT) scans.

There is convincing evidence that chemotherapy should be incorporated into radiation treatment of advanced cervical carcinoma. Today, for locally advanced, metastatic or recurrent cervical carcinoma, the treatment of choice is cisplatin-based chemoradiation [24]. Concurrent chemoradiation is also significantly better than radiotherapy alone only for locally advanced or recurrent cervical carcinoma [23].

Most studies agree that the addition of chemotherapy significantly improves the cumulative survival rate of 8 years (67 vs. 41%). At the same time, the introduction of chemotherapy prevents the delay of radiation therapy. Hematologic and gastrointestinal toxicity is more common with chemotherapy, but unfavorable effects are short-lived and resolve after medical treatment. Late toxicity is rare, and the rate of late complications is not increased [25].

A new surgical approach with surgical extraperitoneal mass reduction of all macroscopic lymph nodes instead of pre-irradiation therapy, and with extended field radiotherapy and brachytherapy afterwards, has shown encouraging results in view of the prognosis in these patients [18]. Survival of the patients with complete resection of bulky pelvic and iliac lymph nodes is comparable to the survival of those with micrometastases.

Recurrent carcinoma of the uterine cervix

Persistent, as well as locally recurrent pelvic carcinomas of the cervix, are characterized by advanced malignant progression and often present a complex anatomic topography, making the treatment very complex and rarely successful. Recurrence rates for this carcinoma range from 10 to 20% for FIGO stages Ib-IIa, and 50-70% for locally advanced IIb-IVa stages [1].

The treatment of recurrent cervical cancer depends on previous treatments, its site and spread, and general health of the patient. Current protocols recommend chemoradiation after surgery, and pelvic relapses, after primary or adjuvant radiation, should be treated surgically too. Radical hysterectomy might be appropriate for tumors < 2 cm, while in most patients pelvic exenteration is required.

Pelvic exenteration should be performed in selected cases of central pelvic recurrence, without evidence of distant metastases. Exenteration is not acceptable if there is malignant involvement of the pelvic wall. According to the original description of pelvic exenteration given by Brunschwig [26], the operation consists of the removal of bladder, urethra, rectum, anus, portion of perineum and genital organs, including vulva and vagina. Later modifications were anatomically defined with respect to the disease extent and taking into account which of the pelvic organs was to be left *in situ* (anterior or posterior exenteration) in order to maximize survival and diminish anatomical distortion.

Five-year survival after this operation has been significantly improved - it is even 30-60% for anterior and 20-40% for posterior exenteration. Since pelvic exenteration results in significant changes, the patients require appropriate extensive psychological advice and support in order to better accept their new appearance and lifestyle [26].

There are studies today which advocate a new "salvage" therapy for patients with locally advanced and recurrent cervical cancer involving the pelvic wall, performed in the form of laterally extended endopelvic resection (LLER). As a part of exenteration, LLER involves the system of blood vessels of iliaca interna, endopelvic portion of m. obturatorius internus, m. coccygeus, m. iliococcygeus and m. pubococcygeus. Complications, disease-free period, overall survival and quality of life of patients with involved lateral pelvic wall are comparable with cases with central pelvic disease treated with conventional exenteration [27].

In patients with recurrent or metastatic cancer of the uterine cervix chemotherapy is only a method of palliation. There are no standards for the time being, but when indicated, chemotherapy consists of cisplatin 50-100 mg/m^2 every 3 weeks [28].

Conclusion

The first and general conclusion should be a reminder that, despite screening, the incidence of invasive cervical carcinoma remains the same or increases.

Treatment advances (especially systemic therapy) have generally improved the outcome of cervical cancer, but there has not been any significant change of prognosis related to disease stage. Surgery and radiotherapy have proven value and are effective in the treatment of invasive cancer of the uterine cervix. As an integral treatment part, chemotherapy is now accepted not only for palliation but also in patients with potentially curable disease. Finally, treatment decisions should be individualized for invasive cervical cancers and should be based upon numerous patient-related factors in order to choose the most effective modality with minimal complications.

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