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Review Article

MANAGEMENT OF CERVICAL CANCER

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ABSTRACT

In developing countries, cervical carcinoma is the second most frequent cause of cancer death in women, after breast carcinoma. Cervical cancer is preventable disease as the different screening, diagnostic and therapeutic procedures are effective. The treatment of cervical cancer is similar to the treatment of any other type of malignancy in that both the primary lesion and potential sites of spread should be evaluated and treated. The stage of the disease affects the treatment of invasive cervical cancer. Stage I A has limited metastatic potential and therefore is most likely treated by non-radical treatment. There is no standard management of stage Ib-IIa cervical carcinoma. Both radical surgery and radical radiotherapy have proven to be equally effective, but differ in associated morbidity and complications. Most often, stage Ib1 cervical cancer is treated by radical hysterectomy with pelvic lymphadenectomy. Radical vaginal trachelectomy with laparoscopic pelvic lymphadenectomy may be an option in small cervical cancer where preservation of fertility is desired. Neoadjuvant chemotherapy followed by radical surgery has emerged as a possible alternative, which may improve a survival in patients with stage Ib2 disease. In countries with access to radiotherapy facilities and financial resources to supply chemotherapy, concomitant chemoradiation is becoming a new accepted standard in treatment of advanced disease stages IB2 to IVA. The management options should be individualized and always be based on various factors including the stage of the disease, age, medical condition of the patient, tumor-related factors and treatment preferences, to achieve the best treatment with minimum complications.

Keywords: cervical cancer, management, radiotherapy, chemotherapy, chemoradiation

INTRODUCTION

The treatment of invasive cervical cancer is hugely based upon the stage of the disease. Cervical cancer is clinical ly staged disease. The FIGO (International Federation of Gynaecology and Obstetrics) staging system is the standard and is applicable to all histologic types of cervical cancer.

The FIGO staging system is presented as below:

Stage I

Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded. The diagnosis of both Stages IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion.

- **Stage IA**: Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm.
- **Stage IA1**: Stage IA1: Measured invasion of the stoma no greater than 3 mm in depth and no wider than 7 mm diameter.
- **Stage IA2**: Stage IA2: Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm in diameter.
- **Stage IB**: Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
- **Stage IB1**: Stage IB1: Clinical lesions no greater than 4 cm in size.
- **Stage IB2**: Stage IB2: Clinical lesions greater than 4 cm in size.

Stage II

Stage II is carcinoma that extends beyond the cervix, but does not extend into the pelvic wall. The carcinoma involves the vagina, but not as far as the lower third.

- **Stage IIA**: No obvious parametrial involvement. Involvement of up to the upper two-thirds of the vagina.
- **Stage IIB**: Obvious parametrial involvement, but not into the pelvic sidewall.

Stage III

Stage III is carcinoma that has extended into the pelvic sidewall. On rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall. The tumour involves the lower third of the vagina. All cases with hydronephrosis or a non-functioning kidney are Stage III cancers.

- **Stage IIIA**: No extension into the pelvic sidewall but involvement of the lower third of the vagina.

- **Stage IIIB**: Extension into the pelvic sidewall or hydronephrosis or non-functioning kidney.

Stage IV

Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

- **Stage IVA**: Spread of the tumour into adjacent pelvic organs.
- **Stage IVB**: Spread to distant organs.

DISCUSSION

The FIGO system is based on clinical evaluation and anatomical extent of the disease. When there is doubt concerning the stage to which a cancer should be allocated, the earlier stage should be selected. The stage should not be changed because of subsequent findings by either extended clinical staging or surgical staging .[1] In an effort to maintain consistency and international relevancy, the FIGO system is based on limited examination methods, including palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous pyelography, chest radiography, and skeletal radiography[2].

Various investigators used lymphangiography, computed topography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) in an attempt to improve the accuracy of clinical staging[3-11]. The accuracy if FIGO clinical staging is limited, and surgical evaluation, although not feasible in all patients, can more accurately identify metastatic disease. Surgical staging is advised by the providers who believe that the informations received surgically describes the extent of disease, which allows the treatment to be customized to the individual [12].

Stage-Based Therapy:

FIGO stage IA1:

Patients with stage IA1 disease should be diagnosed on the basis of conisation using a technique that does not result in cauterized margins, which may obscure surgical margins. If the lymphovascular space is not involved, these patients have less than a 1% risk of lymph node spread. These women can be treated conservatively by simple hysterectomy or by conisation, if they wish to preserve fertility[13].The importance of involvement of the lymphovascular space in stage IA1 disease is not clear, but most practitioners favour radical surgery or radiation if it is present.

The treatment of choice for stage IA1 disease is surgery. Total hysterectomy, radical hysterectomy, and conization are accepted procedures. Lymph node dissection is not required if the depth of invasion is less

than 3 mm and no lymphovascular invasion is noted.

Selected patients with stage IA1 disease but no lymphovascular space invasion who desire to maintain fertility may undergo therapeutic conization with close follow-up, including cytology, colposcopy, and endocervical curettage. Patients with comorbid medical conditions who are not surgical candidates can be successfully treated with radiation.

FIGO stage IA2, IB, and IIA:

Radical hysterectomy is the treatment of choice for young healthy patients because it preserves ovarian function. Radiotherapy is thought to be equally effective for patients with early stage disease. An RCT comparing primary surgery with primary radiotherapy in 347 patients with stage IB-IIA cervical cancer showed that disease free and overall survival for the two groups were the same [14].

For patients with stage IB or IIA disease, there are 2 treatment options:

- Combined external beam radiation with brachytherapy
- Radical hysterectomy with bilateral pelvic lymphadenectomy

Radical vaginal trachelectomy with pelvic lymph node dissection is appropriate for fertility preservation in women with stage IA2 disease and those with stage IB1 disease whose lesions are 2 cm or smaller[15]. The principal problems with pregnancy after trachelectomy are premature labor and the need to undergo cesarean section for delivery[16].

In a retrospective review of 62 patients with stage IB1 cervical carcinoma who underwent attempted radical trachelectomy and underwent preoperative magnetic resonance imaging (MRI), Lakhman et al found that pretrachelectomy MRI helped identify high-risk patients who were likely to need radical hysterectomy and helped confirm the absence of residual tumor after a cone biopsy with negative margins [17].A tumor size of 2 cm or larger and deep cervical stromal invasion on MRI were associated with an increased chance of radical hysterectomy.

Current surgical guidelines for stage IA2 to IIA cervical cancers allow for minimally invasive techniques, such as traditional laparoscopic and robotically assisted laparoscopic techniques, in the surgical management of these tumors. Indeed, it has been shown that these less morbid procedures are equally effective in achieving adequate surgical margins and lymph node dissection while possessing the added advantage of shorter postoperative recovery times[18-20].

An analysis of women from the Surveillance, Epidemiology, and End Results (SEER) database who underwent radical hysterectomy with lymphadenectomy revealed that patients with node-negative early-stage cervical cancer who underwent a more extensive lymphadenectomy had improved survival[21].Compared with patients who had fewer than 10 nodes removed, patients who had 21-30 nodes

removed were 24% less likely to die of their tumors, and those who had more than 30 nodes removed were 37% less likely to die.

Patients with stage IB2 disease (tumour >4 cm) are poor candidates for primary radical surgery because most will ultimately need adjuvant radiotherapy. Chemoradiotherapy is the treatment of choice. An RCT showed that adding weekly cisplatin to pelvic radiotherapy before hysterectomy reduced the risk of recurrence of disease and death in women with stage IB2 cervical cancer compared with radiotherapy and hysterectomy alone[22].

Patients with early stage disease have an intermediate risk of recurrence postoperatively if they have two of the following factors: large tumour size, deep stromal invasion, or involvement of the lymphovascular space. An RCT evaluating 277 women with stage IB disease (radiotherapy versus "no further treatment") and at least two risk factors showed that adjuvant radiotherapy decreased the rate of recurrence and improved disease free survival. However, the two groups showed no overall difference in survival [23]. Therefore, despite the positive findings, options regarding adjuvant radiotherapy for surgical patients with selected risk factors remain debatable.

Patients with early stage disease have a high risk of recurrence postoperatively if they have one of the following risk factors: positive nodes, parametrial invasion, or positive surgical margins. Such patients should receive adjuvant cisplatin based chemoradiotherapy after hysterectomy, as shown by an RCT.[24]

FIGO Stage IIB, III, or IVA cancer:

For locally advanced cervical carcinoma (stages IIB, III, and IVA), radiation therapy was the treatment of choice for many years. Radiation therapy begins with a course of external beam radiation to reduce tumor mass and thereby enable subsequent intracavitary application. Brachytherapy is delivered by means of afterloading applicators that are placed in the uterine cavity and vagina.

Additionally, the results from large, well-conducted, prospective randomized clinical trials have demonstrated a dramatic improvement in survival when chemotherapy is combined with radiation therapy[22, 25, 26]. Consequently, the use of cisplatin-based chemotherapy in combination with radiation has become the standard of care for primary management of patients with locally advanced cervical cancer[15].

FIGO Stage IVB and recurrent cancer:

Treatment is only palliative in patients with stage IVB disease, so quality of life and toxicity profiles must influence the choice of treatment. The only RCT to identify a chemotherapy regimen that gave these patients an overall survival advantage and that included quality of life measurements compared cisplatin with cisplatin plus topetecan.[27] Progression free survival and overall survival favored combination chemotherapy, but toxicity was more common, although it did not significantly reduce quality of life.[27]

Recurrent cervical cancer is almost always incurable and less than 5% of patients who develop recurrence are alive at five years. Patients who develop pelvic recurrence after radical hysterectomy may be salvaged with chemoradiotherapy if they have not previously been irradiated. Central pelvic recurrences after radiation or chemoradiotherapy may undergo curative surgery with pelvic exenteration in the absence of metastatic disease.

Treatment of pelvic recurrences after primary surgical management should include single-agent chemotherapy and radiation, and treatment for recurrences elsewhere should include combination chemotherapy[28-30]. For central pelvic recurrence after radiation therapy, modified radical hysterectomy (if the recurrence is smaller than 2 cm) or pelvic exenteration should be undertaken.[31, 32]

For disease recurring after chemotherapy and radiation therapy, a disease-free interval of more than 16 months is considered to designate the tumor as platinum-sensitive[33]. The standard of care in these cases is chemotherapy with a platinum-based doublet of paclitaxel and cisplatin [29, 30, 34, 35].

Complications of Therapy:

Radiation-related complications:

During the acute phase of pelvic radiation therapy, the surrounding normal tissues (e.g., intestines, bladder, and perineal skin) often are affected. Acute adverse gastrointestinal (GI) effects include diarrhea, abdominal cramping, rectal discomfort, and bleeding. Diarrhea can usually be controlled by giving either loperamide or atropine sulfate. Small steroid-containing enemas are prescribed to alleviate symptoms from proctitis.

Cystourethritis also can occur, leading to dysuria, frequency, and nocturia. Antispasmodics often are helpful for symptom relief. Urine should be examined for possible infection. If urinary tract infection (UTI) is diagnosed, therapy should be instituted without delay.

Proper skin hygiene should be maintained for the perineum. Topical lotion should be used if erythema or desquamation occurs.

Late sequelae of radiation therapy usually appear 1-4 years after treatment. The major sequelae include rectal or vaginal stenosis, small bowel obstruction, malabsorption, radiation enteritis, and chronic cystitis.

Surgical complications:

The most frequent complication of radical hysterectomy is urinary dysfunction resulting from partial denervation of the detrusor muscle. Other complications include foreshortened vagina, ureterovaginal fistula, hemorrhage, infection, bowel obstruction, stricture and fibrosis of the intestine or rectosigmoid colon, and bladder and rectovaginal fistulas. Invasive procedures (e.g., nephrostomy or diverting colostomy) sometimes are performed in this group of patients to improve their quality of life.

CONCLUSIONS

The management options should be individualized and always be based on various factors including the stage of the disease, age, medical condition of the patient, tumor-related factors and treatment preferences, to achieve the best treatment with minimum complications.

Over the past few years, in most industrialised countries women with cervical cancer have benefited from improved imaging techniques, better treatments (including chemoradiotherapy), and more conservative surgical approaches. In low resource settings— where facilities for radiology, chemoradiotherapy, and supportive care are limited or unavailable , it is important to identify which resources fill healthcare needs most effectively and to consider alternative approaches. In the near future, the best way to improve mortality and morbidity from cervical cancer will probably be to focus on primary prevention with prophylactic vaccines against human papillomavirus.

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