

# Treatment of Cervical Cancer Stage IB

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## Abstract

*Debate continues as to the efficacy of irradiation therapy versus radical surgery in Stage IB carcinoma of the cervix. The few reported randomized series demonstrate that the results are comparable in each series.*

*Radical hysterectomy in skilled hands is a safe procedure and mortality is reducible. In the meantime, the number of radioresistant lesions are small; radiation injuries are low but occur in later years and are difficult to treat. None of the available data show that combined treatment has a better survival rate than the use of one modality alone.*

*Patients with stage IB should be examined and discussed individually in conference with a gynecologic oncologist and radiation therapist. Utilizing all the above factors and the clinical parameters, young and healthy patients are more suitable for surgical treatment while the remainder may be treated by irradiation alone. In the meantime, some patients will benefit from modified methods of combined treatment.*

**Key words:** Cervical carcinoma, stage IB, radiotherapy, radical hysterectomy

In cancers of the cervix stage I lesions are of particular importance as they may constitute more than half of all such cancers diagnosed in one area.<sup>1</sup> This has been important since cytology, colposcopy and other tests have caused a reversal of the clinical staging percentages. Since the development of radical hysterectomy surgery in the late 19th century<sup>2</sup> and the use of radium in the early 20th century<sup>3</sup> for the treatment of cancer cervix, controversy has existed for many years regarding the best treatment for early

stages, while irradiation is universally employed in the more advanced cases. In accordance with the classification of the International Federation of Gynecology and Obstetrics, stage I lesions are subdivided into IA and IB.<sup>4</sup> This report is concerned with stage IB treatment. The criteria for stage IB are: lesion confined to the cervix, and microscopically the depth of the invasion measures more than 3 mm and/or there is lymphatic involvement.

Opinions differ as to the best initial treatment in tumors localized to the cervix. This controversy was heightened by Meigs' demonstration that no postoperative mortality occurred in his first 100 surgically treated patients.<sup>5</sup> This stimulated other institutions to use this surgical modality in treatment of tumors localized to the cervix while others continued to use irradiation as the main treatment of these lesions. This has led to a situation wherein treatment choice depends on therapist factors such as training, temperament and departmental policy rather than patient factors. With the expected increase in the number of Stage IB cases it becomes necessary to develop a realistic policy for choice of suitable treatment for each individual patient.

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## Radiotherapy or surgery

Cure of cancer of the cervix depends first on the nature and extent of the tumor, second and to a lesser degree, on the skill and experience of the therapist, and third, to some extent, on the modalities of treatment.<sup>6</sup> This could explain why the results of different methods of treatment — radiotherapy and surgery — do not differ materially.<sup>6,7,8</sup> The question then arises as to whether the different therapeutic regimes cure some tumors and fail to do so with others.

Selected series have no value in demonstrating the superiority of one method of treatment over the other. They only indicate the level of achievement in that selected series. The comparison of results between two institutions is seriously limited because of the preselection of patients.<sup>7,8</sup> Anyone who seriously believes that surgery is superior to radiotherapy should set up a random allocation of patients to each method of treatment, in order to come to a realistic conclusion on this subject.

## Controlled studies

There are a few small controlled series in the literature, where radiotherapy or surgical treatment alone has been assigned to patients with stage I lesions in the same clinic. Whombly and Taylor<sup>9</sup> compared the results of treatment with radiation plus radical operations to those of radiation alone in stage I and II, randomly assigned, with a five year salvage of 58% and 79%, respectively. Newton et al<sup>10</sup> reported a group of cases of stage I cancer treated by either irradiation or operation, in whom the treatment method was selected in a random fashion. In that series, no statistically significant difference in the cure rate was found. Masbuchi and associates,<sup>11</sup> in a large group of stage I and II disease, treated either by operation or irradiation, found no difference in cure rate between the two groups. In their series, as well the series of Twombly and Taylor, the surgical patients all received pre or post-operative irradiation. Recently, Roddick and Greenlaw<sup>12</sup> reported a well designed study to evaluate these two modalities of treatment in unselected patients representing all stages of disease. Their study showed that patients treated with irradiation fared better than those treated surgically, as there were many surgical failures and higher morbidity. Selim et al<sup>13</sup> comparing the results of surgical and irradiation treatment of a large group of stage I patients, selected for treatment by cytologic selection,<sup>8,14,15</sup> have shown that radiotherapy is superior to surgical treatment in management of locally invasive cervical cancer, as the former can treat the majority of patients and have lower morbidity than the latter. However, in experienced hands surgical treatment can be used in selected patients who are not suitable for radiotherapy.

## Radio-sensitivity testing

Unfortunately, not all cancer is controlled by irradiation. It is probable that a substantial proportion of the radio-resistant cases could be salvaged by surgery if recognized in time.

It becomes logical for investigators to turn their attention to radio-sensitivity testing of cervical cancer, in order to use the surgical and radiotherapeutic modalities in a complimentary fashion and to provide a treatment specifically suited to each patient.

The earliest attempt to codify radio-sensitivity and radio-resistance is that of Gluckman and co-workers<sup>16,17</sup> who analyzed the cells in squamous cell carcinoma in repeated serial biopsies of the cervix after the institution of radiation. The radiation response determined in these studies permitted them to predict the prognosis, and, through selection of poor responders, to improve survival by additional surgery.

Graham and Graham,<sup>8,14,15</sup> using the vaginal cytology in relation to cellular epithelial changes in nonmalignant cells prior to irradiation (SR) and after irradiation (RR), formed the basis for determining radiocurability depending upon a good or poor response by their criteria. The simplicity of obtaining smears and the confirmation by other investigators<sup>18,19</sup> have made this test of prime importance.

A cytochemical technique has been developed by Gusberg<sup>20</sup> in an attempt to correlate nucleoprotein cell content to radioresponsiveness. This is done after a test dose 400 R X 3 in three days with external irradiation via parallel opposing fields, and continuation with treatment of 2000 R while awaiting the proper interval for the response biopsies. Depending upon an alteration in DNA - RNA content, the response is reported as good or poor with evidence of prognostic accuracy for stage I of 77.5% to 46.1%.

Wentz and Lewis and others<sup>21,22</sup> suggested that there are 3 histological grades of squamous cancer and that small cell (undifferentiated) cancer was associated with lowest survival with radiotherapy and do better with surgery.

## Combined therapy

Authors, dissatisfied with the outcome of one modality or another in management of carcinoma of the cervix, thought that combining the two modalities, would improve the survival rate.<sup>23,25</sup> Unfortunately, the results were not better than with the use of one modality, and there was an increase in morbidity.<sup>4,8</sup>

Recently, Durrante et al<sup>26</sup> have published their impressive results with a modified method of combining irradiation followed by an extrafascial conservative hysterectomy in selected cases. They found this method to be suitable for patients with bulky lesions

or barrel shaped cervix, fibroid uterus, pyometria and pregnancy complicated by stage I and II cervical cancer. They used 4,000 rads to the whole pelvis followed by 4,000-5,000 mg-hr in one application. This gives effective irradiation to the vaginal mucosa, lateral parametria, as well as to the obturator and external iliac lymph nodes.<sup>27</sup> The addition of the extrafascial hysterectomy is to remove disease in the myometrium, which, despite some shrinkage after whole pelvis irradiation, is still at too great a distance from the radium source to receive an effective dose.<sup>27</sup> This method reduced the incidence of central failures and the morbidity associated with the radical hysterectomy after irradiation.<sup>24</sup> Rampone et al,<sup>28</sup> used a regimen consisting of preoperative radium followed by modified Wertheim hysterectomy and pelvic lymphadenectomy for all operable cases under age of 65 years. They demonstrated that the use of radium reduced the need for extensive parametrial dissection, for complete skeletonization of the lower ureter and for removal of a large vaginal cuff. Despite these modifications, the five year survival was comparable to other series using the more extended operation, with significant reduction in urologic complications (2.8%).

Recent reports<sup>29</sup> have suggested that the improvement in survival of patients with squamous cell carcinoma has not been reflected in survival of patients with adenocarcinoma. Some authors<sup>30,31</sup> have advocated treating adenocarcinoma of the cervix by irradiation followed by extrafascial hysterectomy rather than irradiation alone, because the lesions are endocervical and tend to extend into the lower uterine segment. Since tumor in the lower uterine segment is not optimally irradiated by conventional radium application, this under-irradiated tumor will be ablated by hysterectomy after completion of irradiation.

### Comment and conclusion

The development of the various forms of radical surgery and radiotherapy has provided the therapist with two excellent modes of treatment of cancer of the cervix stage IB.

In recent decades, it became clear that radical hysterectomy in skilled hands is a relatively safe operation.<sup>5,8,13,20</sup> In the meantime, it has been demonstrated that radiation resistant lesions are relatively few<sup>7,8,20</sup> and that adenocarcinoma of the cervix, is similar to squamous carcinoma in its response to radiation.<sup>7,8</sup> Radiation injury in skilled hands is limited, and mortality from radical surgery is reducible.<sup>5,8,13,18</sup>

It also has become clear that irradiation can destroy metastasis in lymph nodes,<sup>32</sup> and that radiotherapy cures cancer spread beyond the cervix more often than radical operation does.<sup>33</sup>

The techniques of radiosensitivity testing have

given us valuable information about cervical cancer, but unfortunately they are still inadequate.<sup>7,8,20</sup> There are many factors that influence the radio-curability of cancer of the cervix. These include: (1) experience of the radiotherapist, (2) virulence of the tumor, (3) radiosensitivity of the tumor, and (4) general health and metabolic status of the host.<sup>19</sup> Radiosensitivity is only one factor in the control of this disease and radiocurability does not have direct correlation to radiosensitivity.<sup>7</sup>

Randomized series and series depending on sensitivity testing<sup>9-22</sup> have demonstrated that the majority of patients of stage I can be treated by means of radiation, while some selected patients will benefit more from surgical therapy.

The significance of combined treatment is impossible to assess due to lack of adequate controlled studies. None of the available studies has demonstrated that the survival rate from the generally accepted forms of treatment for carcinoma of the cervix is unsatisfactory, nor that the results of combined therapy produce an overall better survival rate.

It would appear logical at this stage of discussion that if one wants a rational plan for therapeutic selection of patients, he has to individualize the treatment of cancer cervix as he does for other gynecologic disease. In order to make a choice between surgery and radiotherapy for individual patients, one must utilize all the clinical parameters available, keeping in mind that radiation will give as good a cure rate in stage IB as will radical surgery. Moreover, radiotherapy has a greater rate of applicability, and radioresistance is a rarity. At the same time one must acknowledge that some patients will benefit more from surgical treatment, in an era when morbidity from surgery is infrequent and occurs early, while morbidity from radiotherapy may be cumulative and late. The young healthy patient can often withstand the rigors of operation with a resultant preservation of ovarian function, while older patients may not be able to sustain such a major operation and the ovarian factor is not as important. Patients with lupus erythematosus, ulcerative colitis, severe rheumatoid arthritis and/or renal transplant are not good candidates for radiotherapy and are more suitable for surgery.

In order to reduce central failure, patients with bulky or barrel shaped cervix, those with fibroid uterus, or associated pyometria, those who are pregnant, and patients with adenocarcinoma, can be treated by the combined method described by Durrante et al.<sup>26</sup> The morbidity of radical hysterectomy can be reduced without reduction in survival by using preoperative radium and modified Wertheim hysterectomy and pelvic lymphadenectomy.<sup>28</sup>

In summary, the young and healthy patients with cancer cervix stage IB are suited for surgical treatment and the remainder may be treated by irradiation

alone. Still, some patients will benefit from modified methods of combined treatment. Improved understanding between the radiotherapists and gynecologic oncologists will show them that when their knowledge is applied to a common purpose they augment each other in providing an improved cure for cervical cancer patients.

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