Pelvic Radiation with Concurrent Chemotherapy Compared with Pelvic and Para-Aortic Radiation for High-Risk Cervical Cancer

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To conduct a large randomized prospective trial of radiotherapy alone versus combined radiotherapy and chemotherapy. The results of this trial will be reported in the April 15, 1999 issue of the New England Journal of Medicine. Because of the implications of this article for public health, the article has been released early and is published in full on the Internet.

Materials and Methods

Women of any age with squamous cell carcinoma, adenosquamous or adenocarcinoma of the cervix and International Federation of Gynecology and Obstetrics (FIGO) stage IIB through IVA were eligible for enrollment. Patients with FIGO stage IB or IIA cervical cancer were eligible if the tumor measured 5 cm or more in greatest dimension or had spread to the pelvic lymph nodes. Exclusion criteria included a performance status less than sixty, para-aortic lymph node metastasis, prior chemotherapy or radiotherapy, or a transperitoneal staging procedure.

All women underwent complete staging, including cystoscopy, proctoscopy and either lymphangiogram or retroperitoneal lymph node biopsy. Eligible patients were randomized to receive either external beam radiotherapy to the pelvic and para-aortic areas (termed extended field radiotherapy) and intracavitary radiation or external beam radiotherapy to the pelvis and intracavitary radiation concurrent with chemotherapy.

External beam radiotherapy was delivered at a dose of 180 cGy per day to a total dose of 4500 cGy using either anterior-posterior fields, or a fourfield technique (anterior, posterior and two lateral fields). The upperborder of the field was set at L4-5 for pelvic radiotherapy and L1-2 for extended field radiotherapy. Intracavitary radiation was delivered in two sessions, the first before or during external beam radiotherapy and the second within two weeks after completion of external beam radiotherapy. The total treatment time was kept under eight weeks whenever possible. At least 8500 cGy was delivered to point A (a reference point located two centimeters superior and two centimeters lateral to the cervical os).

Patients randomized to the chemotherapy arm received three cycles of chemotherapy beginning on day one of external beam radiotherapy with at least one cycle administered during intracavitary radiotherapy. Chemotherapy consisted of two drugs, cisplatin and 5-fluorouracil. Cisplatin was dosed over four hours at 75 mg per square meter of body surface area and 5-fluorouracil was administered over 96 consecutive hours, one gram each day.

Results

Between 1990 and 1997, 403 patients were enrolled in the study, fifteen of whom were ineligible mostly due to lack of adequate evaluation of the para-aortic lymph nodes. 193 patients were assigned to receive radiotherapy alone and 195 combined modality therapy. The two groups had similar rates of treatment protocol violations. Minor deviations occurred in approximately 80% of patients in both groups and major, "but acceptable" deviations occurred in 11 and 9 percent of patients in the combined modality therapy group and radiotherapy group, respectively. In each study arm the median total duration of treatment was 59 days and the median doseto point A was 8900 cGy.

In the combined modality group, four patients did not receive any chemotherapy but were included in this group on the intent to treat analysis. In total, 159 (81%) and 133 (68%) of patients received two and three cycles of chemotherapy. The primary reason for not receiving the scheduled chemotherapy was refusal to continue (17 patients).

Estimated rates of survival at five years revealed a significant difference favoring the group of patients receiving combined chemotherapy and radiotherapy. Specifically, Kaplan-Meier survival plots estimate that 73% of patients receiving combined...
treatment were alive at five years compared to 58% in the radiotherapy alone group. Disease-free survival at five years was also significantly higher in those receiving combined treatment (67% vs. 40%).

Administration of chemotherapy impacted on both local and distant disease control. The rates of distant and local relapse in the combined therapy group (14% and 10%) were significantly lower than those rates in the radiotherapy alone group (33% and 35%).

The incidence of moderate and severe side effects was higher in patients receiving combined modality treatment, but the majority of these either resolved spontaneously or responded rapidly to medical treatment. Late effects were similar in both groups.

Conclusions

Previous studies examining the role of chemotherapy in addition to radiotherapy in the treatment of high risk cervical cancer have been inconclusive. This study is unique in utilizing higher doses of both radiotherapy and chemotherapy compared to earlier studies, and one cycle of chemotherapy was administered during intracavitary radiation, which delivers 25% of the central radiation dose. In addition, an emphasis was placed on completing treatment within eight weeks - a known good prognostic factor.

Delivering radiotherapy to the para-aortic lymph nodes has been controversial. A randomized prospective study by the RTOG published in Journal of the American Medical Association in 1995, found a survival advantage to including the para-aortics in the radiation field compared to pelvic radiotherapy alone. The trial reported here provides evidence that when no disease is evident in the para-aortic lymph nodes (either only lymphangiogram or biopsy) radiotherapy limited to the pelvis combined with chemotherapy provided better disease control than pelvic and para-aortic radiotherapy. Whether combining extended field radiotherapy with chemotherapy would improve on the results of the combined arm reported in this trial is unknown. However, a pilot study of hyperfractionated extended field radiotherapy with the same chemotherapy used in this trial was associated with severe acute toxicity. The authors conclude that patients with high risk cervical cancer should be treated with pelvic radiation concurrent with cisplatin and 5-fluorouracil.