Modification of the Radiation Response of Patients With Carcinoma of the Uterine Cervix

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Studies comparing radiotherapy alone to radiotherapy plus other chemical agents have shown little survival advantage, with the exception of the recent NCI trials that show a survival advantage for cisplatin-based therapy given concurrently with irradiation.

Background: The purpose of this review is to summarize clinical trials for patients with cervical cancer treated with irradiation and modifiers of the irradiation response.

Methods: The Medline database was used to identify clinical studies that evaluated modifiers of the irradiation response for patients with carcinoma of the uterine cervix from 1970 through 1998. The studies included were prospective, randomized phase III clinical trials comparing irradiation alone to irradiation plus a chemical modifier for carcinoma of the uterine cervix.

Results: Various chemical agents have been combined with irradiation in the treatment of patients with carcinoma of the uterine cervix. These agents include hyperbaric oxygen, hydroxyurea, nitroimidazoles, neoadjuvant chemotherapy, and concurrent chemotherapy.

Conclusions: Many prospective, randomized studies evaluating the use of chemical agents to modify the irradiation response in patients with carcinoma of the uterine cervix indicate no improvement over radiation therapy alone. However, the February 1999 NCI clinical announcement describes a survival advantage for cisplatin-based therapy and concurrent irradiation.

Introduction

Patients with stage I through stage IVa carcinoma of the uterine cervix may be cured with pelvic radiotherapy. Patients may die of their disease because of undetected metastasis at diagnosis because irradiation failed to control their pelvic disease. Patterns of failure after radiotherapy include pelvic failures, distant metastasis, or both. It is postulated that failure to control the disease in the pelvis is due to decreased radiosensitivity of large cervical lesions.

Various chemical agents have been used in combination with pelvic irradiation for women with carcinoma of the uterine cervix. Several mechanisms of action were proposed as possible pathways to improvement of treatment outcome. These mechanisms include (1) selective cytotoxicity and radiosensitization of hypoxic cells, (2) inhibition of cell repopulation, (3) inhibition of repair of potentially lethal damage, (4) modification of the slope of the radiotherapy dose-response curve, (5) decrease in tumor bulk resulting in improved blood supply and cell recruitment, and (6) alterations in cell kinetics that can affect cell cycle synchronization and cell cycle blocks.

Many phase I and phase II clinical trials have attempted to exploit the chemical modification of the radiotherapy response for patients with carcinoma of the uterine cervix. These studies are the precursors to phase III studies. This article reviews the results of prospective, randomized phase III studies that compare radiotherapy alone to radiotherapy combined with other chemical agents. These results are reviewed by research theme and are presented in the Table in chronological order.

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Hyperbaric Oxygen

Laboratory data demonstrating the effect of the oxygen enhancement ratio on mammalian cells in tissue culture led the way to the development of the use of hyperbaric oxygen in clinical trials for multiple tumor sites. The Radiation Therapy Oncology Group (RTOG) performed a phase III study of hyperbaric oxygen for patients with advanced cervical carcinoma. The objective of the study was to determine if hyperbaric oxygen during external radiotherapy improved local control and survival compared to air breathing during external radiotherapy. Between 1972 and 1975, a total of 65 patients with stages IIB, III, and IVA cervical cancer were randomized to one of the two treatment arms. In one arm of the study, patients received hyperbaric oxygen during external radiotherapy consisting of 4 Gy x 10 fractions given in five weeks with brachytherapy. In the second arm, patients breathed air during external radiotherapy consisting of 2 Gy x 25 fractions in five fractions with brachytherapy. The major study findings were a 52% disease-free survival rate and a 24% local failure rate in the group breathing air compared to a 73% disease-free survival rate and a 26% local failure rate for the group receiving hyperbaric oxygen. These values were not statistically different. The complication rate was 24% for both groups. The conclusion of the study was that no significant difference in survival could be demonstrated.

Fletcher and colleagues also performed a randomized study of hyperbaric oxygen for patients with advanced cervical cancer. The clinical trial was conducted from 1968 to 1974 and included 233 patients with stages IIB, III, and IVA cervical cancer who were randomized to receive radiotherapy or radiotherapy with hyperbaric oxygen. The authors reported no differences in survival, local control, distant metastasis, or toxicity between the two arms of the study. Details of the statistical analysis of this study were not provided in their report. The disease-free survival rates were 41% for the control arm and 33% for the experimental arm (P=0.1). The authors postulated that hyperbaric oxygen might be useful if higher daily doses of irradiation (greater than 2 Gy per day) were administered with hyperbaric oxygen. However, the authors did not continue to further investigate the use of hyperbaric oxygen in patients with cervical carcinoma.

The Medical Research Council (MRC) Working Party on radiotherapy and hyperbaric oxygen conducted two sequential prospective trials from 1966 to 1973 that included patients with carcinoma of the cervix. The first study randomized 320 patients with stages IIb, III, and IVA cervical cancer to receive radiotherapy alone or radiotherapy with hyperbaric oxygen. The authors reported that severe toxicity was greater in the experimental arm. They also reported that pelvic control of the disease was better in those receiving hyperbaric oxygen, but there were no significant differences in overall survival or metastasis-free survival. The study was limited in that it was conducted at four radiotherapy centers, and each center used a different radiotherapy fractionation schedule. The number of fractions varied from 6 to 27. Total irradiation doses ranged from 35 Gy to 72 Gy to point A. Brachytherapy was not performed in all patients; some patients underwent a hysterectomy rather than brachytherapy. Subset analysis revealed that hyperbaric oxygen was more likely to improve local control when the total irradiation dose to the pelvis was low. Because of these limitations, the MRC performed a second study of hyperbaric oxygen for patients with cervical cancer and reported preliminary results in 1979. The second study randomized 82 cases with stages IIB and III disease to receive external irradiation and brachytherapy either with or without hyperbaric oxygen. Hyperbaric oxygen was administered during external radiotherapy. Although the report of the second study does not state the total irradiation doses administered, it states that all patients were prescribed the same irradiation dose with combined external radiotherapy and brachytherapy. Analysis of the data at 4 years indicated that the actuarial survival was 50% for the entire group and that there were no significant differences in survival between the two groups (P=0.05). They also reported no differences in the two groups concerning local control, distant metastasis, or toxicity. The authors conclude from their data that there is no justification for the administration of hyperbaric oxygen with irradiation for patients with advanced cervical carcinoma.

Hydroxyurea

The mechanism of action of hydroxyurea is synchronization of the cell cycle by blocking the cell cycle at the G1-S interface. In vivo irradiation of mammalian cells after pretreatment with hydroxyurea indicated enhanced cell killing when compared to irradiation without pretreatment with hydroxyurea. Early studies in human beings gave promising results. Subsequently, the Gynecologic Oncology Group (GOG) performed a prospective, randomized phase III study of irradiation alone vs irradiation and hydroxyurea for patients with stages IIb and IVA carcinoma of the cervix. The study was performed from 1970 to 1976. The three-year progression-free survival rates were 13% in the control arm and 26% in the hydroxyurea arm (P=0.05). Toxicity, primarily hematologic, was 47% in the hydroxyurea arm compared to only 11%, in the control arm. Because of the improvement in overall and progression-free survival, the GOG proceeded to use hydroxyurea and irradiation as the standard arm for future studies.

Piver and colleagues reported the only other phase III study of hydroxyurea plus irradiation vs irradiation alone for women with cervical cancer. This study, which began in 1972 and was completed in 1976, included 45 patients with stage IIb cervical cancer who underwent surgical staging and randomization to either pelvic irradiation or pelvic irradiation plus hydroxyurea. The disease-free survival rate at 5 years was 54% for those receiving irradiation and hydroxyurea compared to 18% for those receiving irradiation alone. No statistical tests of equivalency of the survival results were presented. The authors concluded that pelvic irradiation plus hydroxyurea was standard therapy for this population of patients.

Nitromidazoles

Hypoxic cell sensitizers are groups of compounds that were developed as chemical agents to mimic oxygen in their sensitization of hypoxic tumor cells. Two nitromidazole drugs – misonidazole and pimonidazole – have been combined with irradiation for the treatment of patients with carcinoma of the cervix. Misonidazole was the first of these chemical sensitizers to undergo widespread clinical trials.

Misonidazole

The MRC Working Party on misonidazole for cancer of the cervix was the first report of a phase III study in this disease site. A total of 153 patients with stage III carcinoma of the cervix enrolled in a randomized, controlled phase III trial from 1979 through 1981. Patients were treated with irradiation or irradiation and misonidazole. Analysis of the
The RTOG also conducted a phase III trial for women with cervical cancer.\(^8\) In this study, 119 patients with stages IIb and Iva cervical cancer were randomized to receive irradiation or irradiation and misonidazole. Patients were entered into this study from 1980 to 1984. Accrual was terminated prior to reaching the original sample size because an interim analysis of the data indicated that the irradiation plus misonidazole regimen was unlikely to demonstrate a benefit. The survival at 18 months was 64% for those receiving irradiation therapy and 54% for those assigned to the radiation plus misonidazole regimen. Life-threatening complications occurred in five patients receiving radiotherapy and in one patient receiving radiotherapy plus misonidazole. Misonidazole toxicity (grade 3) was limited to severe nausea and vomiting in two patients. The authors concluded that the addition of misonidazole to radiation failed to improve survival and that more effective radiosensitizing agents are needed.

The Danish Cancer Society conducted a study similar to the RTOG study. In the Danish Study,\(^9\) 331 women with stages IIb, III, and Iva cervical cancer were randomized to receive radiation therapy plus placebo or radiation therapy plus misonidazole. The study was conducted from 1979 to 1982. With a minimum of four years of follow-up, the disease-free survival was 47% for the misonidazole regimen and 46% for the placebo group. The local tumor control rate was 50% for the misonidazole group and 54% for the radiation-alone group. These authors also concluded that the addition of misonidazole did not enhance the radiation response in advanced cervical carcinoma.

### Pimonidazole

Following completion of their misonidazole study, the MRC Working Party on cervical cancer performed a study of pimonidazole, a hypoxic cell sensitizer.\(^10\) The prospective, randomized study of radiation therapy vs radiation therapy plus pimonidazole involved 183 patients with stages II and III cervical cancer and was conducted from 1986 to 1989. The pimonidazole arm included 91 patients, and the control arm included 92 patients. Following an interim analysis of the data, the study was suspended because of the poor outcome of patients receiving pimonidazole. Data analysis indicated a worse local tumor control and an inferior survival in those receiving pimonidazole compared to controls. Pelvic recurrence occurred in 33 patients in the experimental arm and in 18 patients in the control arm. The disease-free survivals and overall survivals were significantly worse for those receiving pimonidazole with hazard ratios (1.50 and 1.58, respectively). The investigators concluded that pimonidazole provided no benefit in the radiotherapy of advanced cervical cancer.

### Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy before surgery or irradiation has been utilized for many different tumor sites. The rationale for the use of neoadjuvant chemotherapy for women with cervical cancer is multidimensional. The rationale includes the following: (1) Blood flow for the adequate delivery of chemotherapeutic agents is compromised in previously untreated patients, (2) previously untreated patients will tolerate chemotherapy better than treated patients will, (3) subclinical metastasis can be eradicated if chemotherapy is given as the first treatment, and (4) there may be improved radiosensitivity secondary to chemotherapy debulking and avoidance of radiation-induced chemoresistance with neoadjuvant chemotherapy.

The first published report of a randomized trial of neoadjuvant chemotherapy and radiation for patients with cervical cancer was by Ayala Hernandez and colleagues in 1991.\(^11\) Fifty-five patients with stage III cervical cancer were randomized to receive radiation, neoadjuvant bleomycin and radiation, or radiation followed by bleomycin. The actuarial survival was 62% for radiation, 30% for neoadjuvant bleomycin, and 36% for postirradiation bleomycin. They concluded that the addition of bleomycin to radiotherapy failed to increase the recurrence-free survival.

Souhami and associates\(^12\) evaluated the use of neoadjuvant bleomycin, vincristine, mitomycin, and cisplatin in 107 patients with stage IIB cervical cancer. The patients were treated from 1984 to 1986. Patients were randomized to receive radiation therapy or three cycles of chemotherapy followed by radiation therapy. The overall five-year survival rates were 30% for the radiotherapy arm and 23% for the neoadjuvant chemotherapy plus radiotherapy arm (P=0.22). The toxicity was severe in the chemotherapy arm and included fatal pulmonary toxicity in four patients. It was concluded that neoadjuvant chemotherapy, as administered in this study, adversely affects survival in stage IIB cervical cancer and was associated with unacceptable toxicity.

Two prospective, randomized studies of neoadjuvant bleomycin, ifosfamide, and cisplatin have been performed. Buxton\(^13\) randomized 66 patients to radiotherapy or neoadjuvant chemotherapy followed by radiation therapy. The study resulted in a 75% complete response after radiation in the neoadjuvant arm compared to a 56% complete response in the radiotherapy arm. The author concluded that there was no evidence that this neoadjuvant chemotherapy regimen enhances the acute toxic effects of pelvic radiotherapy and that the approach has the potential to improve the therapeutic outcome in patients with poor-prognosis cervical cancer. Kumar and colleagues\(^14\) performed a study of neoadjuvant bleomycin, ifosfamide, and cisplatin that randomized 184 patients to radiotherapy or neoadjuvant chemotherapy and radiation. Following radiotherapy, the complete response rates were 70% for the neoadjuvant arm and 69% for the radiotherapy arm. The overall disease-free survivals and the toxicities of therapy were the same in the two arms of the study.

Three prospective studies have been performed using neoadjuvant bleomycin, vincristine, and cisplatin. Sardi et al\(^15\) randomized 155 patients with stage IIB cervical cancer to radiotherapy, neoadjuvant chemoradiotherapy, or neoadjuvant chemotherapy, surgery, and radiotherapy in a study that began in 1988. The overall survivals at 4 years were 37% for the radiotherapy arm, 53% in the neoadjuvant chemoradiotherapy plus radiotherapy arm, and 63% in the neoadjuvant chemoradiotherapy, surgery, and radiotherapy arm. The authors concluded that more effective chemotherapy agents should be evaluated. In another study by Sardi and colleagues,\(^16\) 205 patients with stage IIB cervical cancer (>2 cm) were randomized to receive standard radiotherapy vs neoadjuvant chemotherapy surgery, and radiotherapy. For patients with tumors of >2 cm but <4 cm, there was no difference in outcomes between the two arms (77% vs 82% for the control arm vs the neoadjuvant arm, respectively). However, for the 117 patients with tumors larger than 4 cm, the survival outcomes were 61% for the control arm and 80% for the neoadjuvant arm (P<0.05). The authors concluded that neoadjuvant chemotherapy improved survival in this population of patients treated with surgery and radiotherapy.

Other studies using various chemotherapy regimens have been performed. Cardenas and associates\(^18\) randomized patients with stage IIB cervical cancer to receive radiation vs neoadjuvant cisplatin, epirubicin, and cyclophosphamide plus radiation. They reported survival rates of 63% in the neoadjuvant arm vs 60% in the radiotherapy arm. The final results of these studies have not been published. Chauvengre et al\(^19\) randomized 151 patients with stages IIb and III cervical cancer to receive neoadjuvant chemotheraphy and radiotherapy vs radiotherapy alone. The neoadjuvant chemotherapy consisted of methotrexate, chlorambucil, vincristine, and cisplatin. The authors reported that the tolerance to therapy was not significantly different between the two treatment groups. The disease-free survivals were 40% in the neoadjuvant arm and 55% in the control arm; the median survival was 42 and 45 months, respectively (P=NS). Tattersall and associates\(^20\) randomized 260 patients with stages IIb, III, and Iva cervical cancer to receive standard pelvic radiotherapy or primary chemotherapy with cisplatin and epirubicin followed by pelvic radiotherapy. The results demonstrated that patients who received primary chemotherapy had a significantly higher pelvic failure rate than those who received radiotherapy (P=0.003). Patients who received primary chemotherapy also had a significantly inferior survival compared to those treated with radiotherapy alone (P=0.02). The authors concluded that primary chemotherapy with cisplatin and epirubicin followed by pelvic radiotherapy produced an inferior local control rate and survival compared with standard pelvic radiotherapy alone.

Sundor and associates\(^21\) performed a prospective, randomized study of radiotherapy and neoadjuvant chemotherapy for patients with cervical carcinoma. Patients were randomized to receive treatment with either neoadjuvant chemotherapy followed by standard pelvic radiotherapy or standard pelvic radiotherapy without chemotherapy. The neoadjuvant chemotherapy consisted of cisplatin and 5-fluorouracil (5-FU) for three cycles. In this study, 47 patients were randomized to each arm. Pelvic failure or distant metastasis occurred in 30 patients in the experimental arm and in 33 patients in the radiotherapy alone arm. The survival rates for the two groups were not statistically different. The authors concluded that sequential chemotherapy and radiotherapy did not improve the survival, local control, or metastasis rate compared with radiotherapy alone.
A randomized study performed by Symonds and colleagues\textsuperscript{22} compared treatment with three cycles of neoadjuvant cisplatin and methotrexate followed by pelvic radiotherapy to pelvic radiotherapy alone. The patient population consisted of 204 women with stages Ib, II, and IVA cervical cancer. The three-year survival rates were 40\% for the radiotherapy alone arm and 48\% for the neoadjuvant chemotherapy arm. The estimated death ratio was 0.81 (P=0.25).

Leborgne and colleagues\textsuperscript{23} performed a prospective trial of neoadjuvant chemotherapy and irradiation vs irradiation alone for patients with stages Ib to IVA cervical carcinoma. The chemotherapeutic consisted of three cycles of cisplatin, bleomycin, and vincristine. Pelvic irradiation was administered with external irradiation and brachytherapy to a total point A dose of 75 Gy to 80 Gy. Forty-seven patients were randomized to receive chemotherapy and 49 patients were randomized to receive irradiation alone. Pelvic tumor control was achieved in 68\% of those treated with chemotherapy and in 65\% of those treated with irradiation alone. The five-year disease-free survivals were 45\% for the radiation group and 38\% for the neoadjuvant chemoradiotherapy group (P=0.35). The severe complication rate was 10\% for the experimental arm and 9\% for the control arm. Treatment-related mortality occurred in four patients, two in each treatment arm. The study was designed to enroll 75 cases in each treatment arm. The hypothesis to be tested was the detection of a 20\% difference in disease-free survival rate with a power of 0.80 and a one-sided significance level of 0.05. The investigators ended the study when their interim analysis of 97 cases demonstrated that there was a low probability that the hypothesized difference in disease-free survival between the two treatment arms would be reached by randomizing additional cases.

### Concurrent Chemotherapy

Concurrent chemoradiotherapy has been administered to patients with cervical cancer in several phase I and phase II studies. However, only a limited number of phase III studies have been performed utilizing this treatment strategy. The rationale for this treatment strategy is for the chemotherapeutic agent(s) to act as a radiosensitizer and as a direct cytotoxic agent. With this approach, there is no delay in starting definitive radiotherapy compared to the delay in starting radiotherapy when neoadjuvant chemotherapy is administered.

Wong et al\textsuperscript{24} published the first phase III report of the use of irradiation and concurrent chemoradiotherapy. They randomized 64 patients with stages IIb and III cervical cancer to receive irradiation alone, irradiation plus weekly cisplatin, or irradiation plus twice-weekly cisplatin. This study was performed from 1982 to 1983 and demonstrated no differences in the response rates at the completion of radiotherapy among the three treatment groups. Long-term survival and toxicity were similar among the three treatment groups. The authors concluded that potentiation of radiotherapy with cisplatin failed to show a significant improvement in long-term survival.

Several additional studies have been published. Some of these studies include too few patients to adequately test the use of concurrent chemotherapy. Lira-Puerto and colleagues\textsuperscript{25} tested radiotherapy alone compared to radiotherapy with weekly cisplatin. Only 24 patients were entered onto this two-arm study. No valid conclusions can be made. Mickiewicz and associates\textsuperscript{26} entered 100 patients onto a two-arm phase III study testing radiotherapy alone compared to radiotherapy with chemotherapy (mitomycin-C, 5-FU, and cisplatin). Treatment was completed in 56 patients; 18 patients received chemotherapy and radiotherapy, and 38 patients received radiotherapy alone. The authors concluded that their data provided no evidence that the combination of chemotherapy and radiotherapy was superior to radiotherapy alone. The authors suggested that different chemotherapy regimens should be tested in these patients.

Chia and colleagues\textsuperscript{27} performed a randomized study from 1989 to 1991 of radiotherapy alone vs radiotherapy with chemotherapy. Patients randomized to receive chemoradiotherapy were treated with two cycles of cisplatin before radiotherapy and four cycles of cisplatin after radiotherapy. Sixty-four patients with stages Ib and III cervical cancer were entered onto the study. Response rates, survival rates, progression-free survivals, and toxicity were not significantly different between the two arms of the study. The authors concluded that there was no benefit to the use of chemotherapy with irradiation as administered in this study. This was a prospective, two-arm phase III study that enrolled 64 patients. As previously noted, this type of study, in this patient population, would require more than 300 patients to be a valid scientific study with sufficient power to test the equivalence of the two treatments.

Lorvidhaya and associates\textsuperscript{28} reported an interim analysis of a four-arm phase III study of patients with stages Ib, IIb, and IVA cervical cancer. The control arm of the study was radiotherapy alone. The three experimental arms of the study are radiotherapy with maintenance chemotherapy, radiotherapy with concurrent chemotherapy, and radiotherapy with concurrent chemotherapy plus maintenance chemotherapy. From 1988 to 1992, 673 patients were entered onto the study. The concurrent chemotherapy consisted of two cycles of mitomycin-C (10 mg/m$^2$ per day x 2 cycles) and 5-FU (300 mg/day PO on days 1-14 and 42-56). Maintenance chemotherapy consisted of 5-FU (200 mg/day PO for 4 weeks, followed by a two-week break and then repeated for two additional cycles). External radiotherapy was administered at 2 Gy per day. The whole pelvis dose ranged from 30 Gy to 46 Gy. A midline shield was then placed and the total dose to the pelvic lymph nodes was 50 Gy. An additional parametrial boost of 10 Gy to 16 Gy was given depending on the tumor bulk. Brachytherapy was administered with either high-dose rate or medium dose rate schedules. Brachytherapy doses were not described in their report. The authors reported that toxicity was greater in the three experimental arms compared to the control arm. However, this toxicity was hematologic, and no significant differences in severe toxicity were observed among the four treatment arms. Their data indicate that pelvic tumor control and disease-free survival were better in each of the three experimental arms compared to the control arm. This study has not completed patient accrual. It has entered 673 patients, and the median follow-up is 25 months.

Tseng et al\textsuperscript{29} tested radiotherapy alone compared to radiotherapy with concurrent chemotherapy consisting of cisplatin, vincristine, and bleomycin in a study that was performed from 1990 to 1995. Chemotherapy was administered every three weeks for four cycles. The design of the study was to detect a 25\% difference in survival at the a = 0.05 level. This design required 60 patients to be randomized to each arm of the study. Sixty-two patients were randomized to the control arm, and 60 were randomized to the experimental arm. Tumor response was observed in 74\% of the radiotherapy arm and in 88\% of the experimental arm (P=0.04). Despite an observed difference in tumor response, there was no statistically significant difference in the mean survival times between the two groups. The mean survival was 42 months for the radiotherapy arm and 38 months for the experimental arm (P=0.27). Treatment-related toxicity occurred in 37\% of the patients treated with chemotherapy and irradiation and in 18\% of those treated with radiotherapy alone (P=0.02). The authors concluded from their study that radiotherapy with chemotherapy did not prove to be superior to radiotherapy alone in their patient population. They speculated that the failure to improve survival with the addition of chemotherapy was due to increased toxicity resulting in prolongation of the overall treatment time in patients receiving chemotherapy as compared to those receiving irradiation alone.

Most recently, Thomas and colleagues\textsuperscript{30} reported the results of a randomized trial of standard vs partially hyperfractionated radiation, with or without concurrent 5-FU in women with locally advanced cervical cancer. This four-arm study included women with stage Ib (5 cm) to stage IVA and was conducted from 1987 to 1995. The control arm of the study was standard fractionation, daily pelvic radiotherapy. The three experimental arms were (1) daily pelvic irradiation and infusion 5-FU in a dose of 1 g/m$^2$ daily on the first 4 days and the last 4 days of irradiation, (2) partially hyperfractionated irradiation delivered as two fractions per day on the first four and last four days of irradiation, and (3) partially hyperfractionated irradiation with infusion 5-FU. Two hundred thirty-four patients were entered onto the study. The original design of the study was to enroll 292 patients. The study was terminated before reaching the planned accrual goal because of multiple factors, including a decline in the number of available patients who were eligible to enter the study. The authors concluded that for patients with advanced cervical cancer, there was a non-significant trend toward improved outcomes when concurrent 5-FU was added to standard irradiation. They also stated that the number of patients entered into the study was too low to conclude that concurrent infusion 5-FU with pelvic irradiation should become the standard therapy for these patients.

### Conclusions

Failure to cure patients with advanced cervical cancer results from inability to control the disease in the pelvis and inability to effectively treat metastatic disease. Attempts to modify the local radiation response in patients with cervical cancer have been targeted at improving the response rate in the pelvis and at treating presumed micrometastatic disease that is present at the time of initial diagnosis. This review article has analyzed the published phase III studies performed on patients with advanced cervical cancer. These studies include the use of hyperbaric oxygen, hypoxic cell sensitizers, neoadjuvant chemotherapy, and concurrent chemoradiotherapy. Many of these phase III studies do not have the statistical power to detect the hypothesized differences in the control vs experimental arm(s) of the study. Some studies do have adequate statistical power, yet none have demonstrated an improvement in local control or survival with the experimental arm. Current randomized studies continue to evaluate the use of cytotoxic chemotherapy, either as neoadjuvant chemotherapy or concurrent chemotherapy during irradiation.

The recent National Cancer Institute Clinical Announcement regarding concurrent chemoradiation for cervical cancer (February 1999) showed a survival advantage for cisplatin-based therapy given concurrently with irradiation. Four of the five studies on which this announcement was based have been published.\textsuperscript{31-34} All five studies show an advantage
from incorporating cisplatin with radiation in terms of overall survival in comparison with using radiation alone. These studies set the stage for further refinement and modification of the combined modality approach to improve the outcomes for women with advanced carcinoma of the cervix.

References


