Concurrent Chemotherapy and Radiation Therapy in Primary Cancer of the Cervix

Jeanne M. Schilder, MD and Frederick B. Stehman, MD

Address
Department of Obstetrics and Gynecology, Indiana University School of Medicine, 550 North University, UH 2440, Indianapolis, IN 46202-5274, USA.

Current Oncology Reports 1999, **1**:41–46
Current Science Inc. ISSN 1523-3790

Radiation therapy has been the most active agent for the treatment of patients with locally advanced cervical cancer for many years. Chemotherapy has shown some activity, but data has been lacking to support its routine use. Recently, data from five prospective, randomized trials evaluating this difficult population have matured. Reports from these trials are startlingly similar, leading to the common conclusion that concurrent cisplatin chemotherapy and radiation therapy substantially decrease the risk of relapse and increase the overall survival. These results are compelling evidence for the inclusion of cisplatin with irradiation as a new standard of care for patients with locally advanced cervical cancer.

Introduction

Carcinoma of the uterine cervix is the leading cause of cancer death in women worldwide. In the United States many factors, including early detection by Papanicolaou's smear (cervical cytology), have reduced the mortality rate from this disease; nevertheless, approximately 13,700 American women were diagnosed with invasive cervical cancer in 1998 [1]. The standard treatment for locally advanced cervical cancer is radiation therapy, and while treatment advances have resulted in cure for many of these patients, 5000 deaths occur each year in the United States. For these reasons, the treatment of locally advanced cervical cancer is a major area of research.

Chemotherapeutic agents have shown some activity against cervical cancer, but previous data has not supported routine use, and radiotherapy has remained the mainstay of treatment. On the basis of five recent prospective, randomized trials, authors report significant improvement in survival with concurrent chemoradiation therapy. The purpose of this article is to discuss the results of these trials and the rationale for combined chemotherapy and radiation therapy in the treatment of locally advanced cervical cancer.

Radiation

Surgical treatment and radiation are equally effective in the treatment of early-stage disease. For advanced disease, including FIGO (International Federation of Gynecologists and Obstetricians) stages IIB through IV and large IB lesions, radiation is the preferred modality. While radiation is the most active and versatile therapeutic agent, it has limitations. Large tumor volume limits the efficacy of radiation, and therefore bulky primary disease in the pelvis may be difficult to control. Increasing the total dose of radiation might improve the control rate but would also result in increased major morbidity, such as bowel and bladder complications. The tolerance of adjacent healthy tissue restricts the total dose that patients can be given.

To understand the other limitations of radiation treatment, it is helpful to review the mechanisms of radiation injury. The first mechanism is direct damage to the DNA strand by interaction with an incoming photon. While this occurrence may be lethal to the cell, double-strand breaks, or lethal injuries, are uncommon events. More common single-strand breaks can easily be repaired by healthy cells and thus constitute "sublethal damage." Accumulation of a number of single-strand breaks may lead to the death of the cell. In a well-oxygenated environment, radiation results in the formation of peroxides and superoxides by ionizing water within the cell. These peroxides and superoxides cause damage to cellular proteins and nucleic acids, resulting in cell death [2].

Improvements in radiation equipment with the development of megavoltage photon and particle beams in the 1960s led to better treatment with fewer side effects. Treatment of bulky, deep-seated tumors without excessive skin and intestinal morbidity was thus made possible. In the 1970s, advances in computed treatment planning further refined the ability to define treatment volumes and to minimize the amount of normal tissue exposed to radiation. These advances have led to an improvement in survival of patients with early disease (stages I and IIA, Table 1), but

Table 1. FIGO Staging for Carcinoma of the Cervix*

Stage 0:	Carcinoma in situ.
Stage I:	Disease limited to the cervix.
Stage II:	Disease extending onto the upper vagina (stage IIA), or into the parametria.
Stage III:	Disease involving the distal vagina (stage IIIA), or extending to the pelvic wall.
Stage IV:	Disease involving the mucosa of the bowel or bladder (stage IVA), or distant metastases.

*Stages are in abbreviated form. Substages are omitted.
FIGO—International Federation of Gynecologists and Obstetricians.

many patients with locally advanced disease (stages IIB–IVA) still cannot be cured with radiation alone [2,3].

Chemotherapy

Because of the limitations of radiation therapy alone, and because of the poor prognosis in patients with locally advanced disease, other regimens have been sought to improve outcome. Chemotherapeutic agents can have a direct cytotoxic effect, resulting in decreased tumor bulk and thus improving blood supply, which, in turn, leads to increased drug delivery and uptake. The local effectiveness of drug therapy depends on its ability to reach the tumor. In some tumors, flow may be perfusion-limited due to stasis or reversal of blood flow in tortuous tumor vessels. Hydrostatic pressure gradients in tumors tend to keep drugs concentrated in the periphery. This circumstance suggests that small soluble molecules (such as cisplatin and hydroxyurea) have an advantage [4]. Both cisplatin and 5-fluoruracil (5-FU) have shown activity against cervical cancer as single agents [5].

Certain drugs have been shown to be radiosensitizers both clinically and in vitro. Dramatic results of combined chemoradiation have been noted in squamous cell tumors of the anal canal [6], esophagus [7], and head and neck [8]. Hydroxyurea, 5-FU, and cisplatin have proven to be the most active and best-tolerated agents.

Hydroxyurea

Hydroxyurea is an S-phase–specific inhibitor of ribonucleotide reductase, an enzyme necessary for DNA synthesis and repair. Tumor cells are inhibited from passage from G1 into S-phase, resulting in cell synchrony in the radiosensitive G1 phase. Repair of sublethal radiation-induced injury is also inhibited [9].

The Gynecologic Oncology Group (GOG) has studied the effects of hydroxyurea with radiation in patients with carcinoma of the cervix for many years [10]. In a subsequent study GOG investigators published the results of a prospective randomized comparison of hydroxyurea versus misonidazole, each with radiation. A statistically significant advantage and less toxicity were seen for the hydroxyurea regimen [11].

5-Fluorouracil

Byfield *et al*. [12] found that 5-FU was most effective as a radiation potentiator when given by continuous infusion after radiation rather than by bolus dosing before radiation. This finding is consistent with the short half-life of 5-FU and with the hypothesis that 5-FU interferes with repair of radiation-induced lesions.

Thomas *et al*. [13] were among the first to investigate the combination of radiation therapy and 5-FU infusion in the treatment of cervical cancer. Their first reported study included 27 patients with extensive disease among whom a high complete response rate was observed. Subsequently, a series of phase II studies including over 200 patients was conducted between 1981 and 1988 [14]. Mitomycin-C was initially included in the regimen but was discontinued because it was found to increase gastrointestinal complications. Split-course radiation was abandoned in favor of continuous radiation and an increase in the dose of 5-FU. Twice-daily radiation was investigated during 5-FU infusion to maximize drug/radiation interaction. At the 3-year point in the study, pooled data demonstrated pelvic control and survival rates of 85% and 71% in stage IB and II, and 41% in stage III [15].

Cisplatin

Cisplatin is the most active single-agent cytotoxic agent in metastatic and recurrent squamous carcinoma of the cervix [16]. Because cisplatin is also an effective radiation potentiator, concurrent use of this drug with radiation therapy has been an attractive option. Investigators at the University of Minnesota were the first to study cisplatin used simultaneously with radiation in patients with carcinoma of the cervix [17,18]. Cisplatin was administered weekly to increase the number of radiation fractions that were given in proximity to drug. The weekly schedule was also used by Malfetano *et al*. [19–21].

A more traditional dose schedule of 100 mg/m^2 every 3 weeks was used by Runowicz, *et al*. [22] and resulted in an acceptable toxicity profile [22]. Sixty-four patients were entered in a randomized trial in which radiation alone was compared to radiation with weekly cisplatin. No drug deaths occurred, and long-term survival was similar in all groups.

Concurrent Chemotherapy and Radiation Treatment

Theoretic advantages of combined chemotherapy and radiation treatment include the different mechanisms and sites of action of these two agents. Though concurrent chemoradiotherapy in carcinoma of the cervix is used primarily to potentiate the effects of radiation therapy on the primary lesion in the pelvis, any possible systemic effect on micrometastatic disease outside the pelvic radiation field would be beneficial. In the 1970s and 1980s, results from laboratory and clinical trials suggested a synergistic effect for combined treatment, rather than simply an additive effect [23]. Chemotherapeutic agents can directly influence the effect of radiation by inhibiting repair of sublethal damage, decreasing recovery from potentially lethal damage, and increasing the proportion of cells in the most radiosensitive phase of the cell cycle [2,9]. Radiation injury also disrupts the integrity of small blood vessels, and this increased vascular permeability may enhance drug delivery [4].

The concept of concurrent chemotherapy with radiation is not new. In 1968, Goolsby *et al*. [24] treated 22 patients with cervical cancer with radiation and 5-FU. The authors concluded that the results of therapy were not better than could be expected from radiotherapy alone, and the report stirred no enthusiasm for further research at that time.

Several phase I and II trials have demonstrated activity of various cytotoxic agents in combination with radiation [22,25]. These studies have been criticized for lacking an appropriate control group and for substandard radiation doses compared with doses in current treatment regimens. Results were uniformly promising, however, in the groups treated with combination therapy, thus providing the rationale to proceed with phase III studies.

Prospective, Randomized Trials

Multiple reports substantiate the dosage, schedule, and tolerance of cisplatin and intravenous infusion of 5-FU concurrently with radiation therapy [25–28]. These promising results required validation in a large prospective trial. The results of five such trials, conducted between 1986 and 1998, were first reported in a Clinical Announcement from the National Cancer Institute (NCI) of the US National Institutes of Health [29]. Each of these trials independently showed a significant survival advantage in patients treated with concurrent chemoradiation, the first significant impact on survival in locally advanced cervical cancer in nearly 40 years [30–34].

These five trials were supported by NCI's cooperative clinical group program. Three of the five studies were primarily managed by GOG, and one each by the Radiation Therapy Oncology Group (RTOG) and the Southwest Oncology Group (SWOG). While the protocols vary somewhat from study to study, there are many similarities, and outcome is similar for all (Tables 2 and 3). Each study showed an improved progression-free interval and overall survival rate in patients receiving cisplatin in combination with radiation compared to radiation alone or radiation in combination with non–platinum-containing agents.

Eligibility requirements were similar for each of the studies. Eligible patients had biopsy-proven primary squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix. Stage–eligibility varied from study to study, but essentially included patients who were not candidates for surgical treatment alone, *ie*, patients in stages IA through IIA with high-risk factors such as positive margin status, bulky IB disease, and IIB through IVA tumors. Good performance status (GOG performance grade>4) and adequate bone marrow, renal, and hepatic function were required. Patients were ineligible if they had received prior radiation or chemotherapy, had a rare histology, had medical contraindications to chemotherapy or surgery, had a previous malignancy other than nonmelanoma skin cancer, or were unable to complete the treatment course or follow-up.

The protocols varied somewhat with regard to lymph node status eligibility and use of extended field radiation. Keys *et al*. [31••] used posttreatment hysterectomy, and Peters *et al*. [34••] randomized patients after radical hysterectomy. In addition, chemotherapy doses and regimens and use of additional nonplatinum agents varied somewhat; however, all protocols included radiation with or without cisplatin. Radiation included external beam and intracavitary brachytherapy, with similar doses. Total doses ranged from 40.8 to 49.3 Gy for external radiation, and from 30–40 Gy for brachytherapy.

Experimental groups received cisplatin ranging from 40 to 75 mg/m^2. Cisplatin was given by intravenous infusion every 1 to 3 weeks, and was withheld if the patient had significant abnormalities in bone marrow or renal function. External radiation continued uninterrupted unless granulocyte and platelet counts fell below individual protocol criteria, in which case it was suspended until the counts were acceptable. Specific criteria are described in each report.

Patients were evaluated at routine intervals for signs of progression or treatment-related toxicity. Primary outcome variables were progression-free survival (time from entry to recurrence) and survival (time from entry to death). Recurrences were classified as local if detected in the pelvis, cervix, or vagina, and distant if detected in extra-pelvic locations.

In all of these cooperative group trials, centralized quality control was maintained for eligibility and treatment factors. Data was submitted to central managing offices for compilation and review. Statistical designs and tests, described in reports from the investigators of each study, are appropriate for randomized, controlled trials.

Results

In these five prospective, randomized trials, 1894 patients with locally advanced cervical cancer were evaluated between 1986 and 1998. Patient and tumor characteristics

Table 2. Study Details

Author	Keys *et al.* [31••]	Peters *et al.* [34••]	Morris *et al.* [33••]	Whitney *et al.* [30••]	Rose *et al.* [32••]
Study	GOG #123	SWOG #8797	RTOG #90-01	GOG #85	GOG #120
Years	1992–1997	1987–1998	1990–1997	1986–1991	1992–1997
Stage	IB≥4 cm	IA2, IB, IIA*	IB–IVA	IIB–IVA	IIB–IVA
Surgery	Posttreatment extrafascial hysterectomy	Radical hysterectomy, LND	Optional para-aortic LND	Para-aortic LND	Para-aortic LND
External-beam radiotherapy (cGy)	4500	4930	4500	4080	4080
Brachytherapy (cGy)-Point A	3000	None	4000	4000	4000
Control arm	RT alone	RT alone	Extended field radiation	HU	HU
Cisplatin dose	40 mg/m^2, 6 courses weekly	70 mg/m^2, 4 courses at 3-week intervals	75 mg/m^2, 3 courses at 3-week intervals	50 mg/m^2 on day 1 and day 29	1: 40 mg/m^2, 6 courses weekly 2: 50 mg/m^2 on day 1 and day 29
Additional chemotherapy in experimental arm	None	5-FU	5-FU	5-FU	1: none 2: 5-FU and HU

*with positive nodes or margins
5-FU—5-fluorouracil; cGy–Centrigray; GOG—Gynecologic Oncology Group; HU—hydroxyurea; LND—lymphnode dissection; RTOG—Radiation Therapy Oncology Group; SWOG—Southwest Oncology Group.

Table 3. Study Results

Author	Keys *et al.* [31••]	Peters *et al.* [34••]	Morris *et al.* [33••]	Whitney *et al.* [30••]	Rose *et al.* [32••]
N					
Control	186	116	193	191	177
Experimental	183	127	195	177	1:176 2:173
Median months of follow-up	35.7	43	43	92.8	34.7
3-year survival (%)					
Control	74	77	63	57	47
Experimental	83	87	75	67	1:65 2:65
Relative risk: progression	0.51	0.5	0.48	0.79	1:0.57 2:0.55
Relative risk: death	0.54	0.5	0.65	0.74	1:0.61 2:0.58

were well balanced between control and experimental regimens. Stage distribution by treatment arm was similar. Adherence to the radiation therapy dose, volume, and time requirements was good in all five studies, and the distribution of the doses given to point A and point B was similar between the treatment regimens. Some examples of toxicity were more common in those patients receiving combined treatment, ranging from twofold reported by Whitney *et al*. [30••] and Rose *et al*. [32••] to eightfold in Morris *et al*. [33••]. Adverse effects were confined almost exclusively, however, to transient hematologic and gastrointestinal toxicities. Patients requiring surgical intervention for obstruction or fistula formation were rare and equally divided between the two treatment groups. A higher frequency of grade 1 and 2 (mild or moderate) genitourinary and neurologic adverse effects was seen in the cisplatin groups. The incidence and seriousness of late effects were not significantly different between treatment groups. There were no deaths attributed solely to treatment among patients participating in any of the five studies.

The median duration of follow-up ranged from 35.7 months [31] to 8.4 years [30]. Overall, a 50% reduction of

disease recurrence was reported in those patients receiving combination therapy with cisplatin compared to those receiving radiation either alone or without cisplatin. This difference predominantly reflects fewer pelvic relapses in the cisplatin regimen. The frequency of distant relapse is slightly lower for cisplatin. Outcome was significantly improved in the cisplatin groups, with striking consistency noted in relative risk for both progression-free survival (0.48–0.79) and survival (0.54–0.74) among the five trials.

Discussion

While radiation is the most active and versatile therapeutic agent, it has limitations. Large tumor volume limits the efficacy of radiation, and therefore bulky primary disease in the pelvis may be difficult to control [35]. Until now, the role of chemotherapy in the primary management of locally advanced cervical cancers has been uncertain. Various chemotherapy agents have been used in clinical trials and increasingly in clinical practice over the past 15 years [10,11,13–15,18–22,24,25–28]. Whereas many people believed that chemotherapy had a place in the treatment of cervical cancer, especially when combined with radiotherapy, a definitive answer was lacking. With the publications based on these five prospective randomized trials, conclusive evidence now exists that combined chemoradiation in the treatment of advanced cervical cancer is superior to either modality alone.

The significance of these studies led to the previously mentioned NCI Clinical Announcement based on their findings [29]. Results from each trial indicate a statistically significant reduction in risk of recurrence and death with concurrent cisplatin and radiation.

Each of the five trials has deficits that could be criticized, and each leaves questions unanswered. For example, Whitney *et al.* [30••] and Rose *et al.* [32••] used hydroxyurea as a control arm, and Morris *et al.* [33•] used extended-field radiation. These control arms have not won wide acceptance as "standard of care." Keys *et al.* [31••] applied extrafascial hysterectomy after radiation in both groups, and Peters *et al.* [34••] administered chemotherapy during and after radiation. Taken in the context of five similar trials with strikingly similar results, however, these deficits are minimized, and the conclusions are strengthened. The differences among studies may also emphasize the generalizability of the conclusions: that the chemoradiation regimen is consistently superior.

Conclusions

Clinical trials are rarely perfect. Inevitably, some flaws in study design, difficulty with patient accrual or follow-up, patient compliance, adherence to the protocol, and other factors will be recognized. Even well-designed randomized, controlled studies may result in conflicting data more often than we would hope. With these prospective, randomized, controlled trials evaluating concurrent chemotherapy and radiotherapy, however, we are fortunate to have the opposite situation: five similar trials that reach a remarkably similar conclusion.

While these five randomized cervical cancer trials involve differing stages and treatment combinations, they share a common result. With remarkable similarity in reduction of relative risk of relapse or death, all five studies demonstrate improved outcomes in patients treated with combined cisplatin and radiation compared to non–platinum-containing radiation treatments. While future studies are needed to delineate the optimal dosing schedule and to determine whether additional agents may provide increased benefit, the remarkable consistency of results is compelling evidence for the inclusion of cisplatin with radiation as a new standard of care for patients with locally advanced cervical cancer.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:

- • Of importance
- •• Of major importance

1. Landis SH, Murray T, Bolden S, *et al.*: **Cancer statistics 1998.** *Ca Cancer J Clin* 1998, **48:**6–29.
2. Fu KK: **Biological basis for the interaction of chemotherapeutic agents and radiation therapy.** *Cancer* 1985, **55:**2123–2130.
3. Perez CA, Grigsby PW, Chao CK, *et al.*: **Chemotherapy and irradition in locally advanced squamous cell carcinoma of the uterine cervix : a review.** *Semin Radiat Oncol* 1997, **7 (suppl 2):**45–65.
4. Potchen EJ, Kinzie J, Curtis C, *et al.*: **Effect of irradiation on tumor microvascular permeability to macromolecules.** *Cancer* 1972, **20:**639–642.
5. Thigpen T, Vance RB, Balducci L, *et al.*: **Chemotherapy in the management of advanced or recurrent cervical and endometrial carcinoma.** *Cancer* 1981, **48:**658–665.
6. Cummings BJ, Rider WR, Harwood AR, *et al.*: **Combined radical radiation therapy and chemotherapy for primary squamous cell carcinoma of the anal canal.** *Cancer Treat Rep* 1982, **66:**489–492.
7. Herskovic A, Martz K, al-Sarraf M, *et al.*: **Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus.** *N Engl J Med* 1992, **226:**1593–1598.
8. Stupp R, Weichselbaum R, Vokes E: **Combined modality therapy of head and neck cancer.** *Semin Oncol* 1994, **21:**349–358.
9. Sinclair W: **Hydroxyurea: differential lethal effects on cultured mammalian cells during the cell cycle.** *Science* 1965, **150:**1729–1731.
10. Hreschyshyn MM, Aron BS, Boronow RC, *et al.*: **Hydroxyurea or placebo combined with radiation to treat stages IIIB and IV cervical cancer confined to the pelvis.** *Int J Radiat Oncol Biol Phys Oncol* 1979, **5:**317–322.
11. Stehman FB, Bundy BN, Thomas G, *et al.*: **Hydroxyurea versus misonidazole with radiation in cervical carcinoma: long term follow-up of a Gynecologic Oncology Group trial.** *J Clin Oncol* 1993, **11:**1523–1528.
12. Byfield JE, Calabro-Jones P, Klisak I, *et al.*: **Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-flurouracil or ftorafur and x rays.** *Int J Radiat Oncol Biol Phys* 1982, **8:**1923–1933.

13. Thomas G, Dembo A, Beale F, *et al.*: **Concurrent radiation, mitomycin C and 5-fluorouracil in poor prognosis carcinoma of the cervix: Preliminary results of a phase I-II study.** *Int J Radiat Oncol Biol Phys* 1984, **10:**1785–1790.
14. Thomas G, Dembo A, Fyles A, *et al.*: **Concurrent chemoradiation in advanced cervical cancer.** *Gynecol Oncol* 1990, **38:**446–451.
15. Thomas G, Dembo A, Ackerman I, *et al.*: **A randomized trial of standard versus partially hyperfractionated radiation with or without concurrent 5-fluorouracil in locally advanced cervical cancer.** *Gynecol Oncol* 1998, **69:**137–145.
16. Bonomi P, Blessing JA, Stehman FB, *et al.*: **Randomized trial of three cisplatin dose schedules in squamous cell carcinoma of the cervix.** *J Clin Oncol* 1985, **3:**1079–1085.
17. Twiggs LB, Potish RA, Mcintyre S, *et al.*: **Concurrent weekly cis-platinum and radiotherapy in advanced cervical cancer: a preliminary dose escalating toxicity study.** *Gynecol Oncol* 1986, **24:**143–148.
18. Monyak DJ, Twiggs LB, Potish RA, *et al.*: **Tolerance and preliminary results of simultaneous therapy with radiation and cisplatin for advanced cervical cancer.** *NCI Monogr* 1988, **6:**369–373.
19. Malfetano JH, Keys H: **Aggressive multimodality treatment for cervical cancer with para-aortic lymph node metastasis.** *Gynecol Oncol* 1991, **42:**44–47.
20. Malfetano JH, Keys H, Kredentser D, *et al.*: **Weekly cisplatin and radical radiation therapy for advanced, recurrent and poor prognosis cervical carcinoma.** *Cancer* 1993, **71:**3703–3706.
21. Malfetano JH, Keys, H, Cunningham MJ, *et al.*: **Extended field radiation and cisplatin for stage IIB and IIIB cervical cancer.** *Gynecol Oncol* 1997, **67:**203–207.
22. Runowicz CD, Wadler S, Rodriguez LR, *et al.*: **Concomitant cisplatin and radiotherapy in locally advanced cervical carcinoma.** *Gynecol Oncol* 1989, **34:**395–401.
23. Begg AC: **Cisplatin and radiation: Interaction probabilities and therapeutic possibilities.** *Int J Radiat Oncol Biol Phys* 1990, **19:**1183–1189.
24. Goolsby CD, Daly JW, Skinner OD, *et al.*: **Combination of 5-fluorouracil and radiation as primary therapy of carcinoma of the cervix.** *Obstet Gynecol* 1968, **32:**674–676.
25. Ludgate SM, Crandon AJ, Hudson CN, *et al.*: **Synchronous 5-fluorouracil, mitomycin-c and radiation therapy in the treatment of locally advanced carcinoma of the cervix.** *Int J Radiat Oncol Biol Phys* 1988, **15:**893–899.
26. Heaton D, Yordan E, Reddy S, *et al.*: **Treatment of 29 patients with bulky squamous cell carcinoma of the cervix with simultaneous cisplatin, 5-fluoracil, and split-course hyperfractionated radiation therapy.** *Gynecol Oncol* 1990, **38:**323–327.
27. Roberts WS, Kavanagh JJ, Greenberg H, *et al.*: **Concomitant radiation therapy and chemotherapy in the treatment of advanced squamous carcinoma of the lower female genital tract.** *Gynecol Oncol* 1989, **34:**183–186.
28. Kuske RR, Perez CA, Grigsby PW, *et al.*: **Phase I/II study of definitive radiotherapy and chemotherapy (cisplatin and 5-fluorouracil) for advanced and recurrent gynecologic malignancies.** *Am J Clin Oncol* 1989, **12:**467–473.
29. National Cancer Institute: **Concurrent chemoradiation for cervical cancer.** *Clinical Announcement.* Washington, DC: National Cancer Institute; February 22, 1999.
30. •• Whitney CW, Sause W, Bundy BN, *et al.*: **A randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study.** *J Clin Oncol* 1999, **17:**1339–1348.

In this study, patients with stage IIB to IVA cervical cancer, negative para-aortic lymph nodes, and pelvic washings were randomized to receive pelvic radiotherapy concurrently with either hydroxyurea or combined 5-FU and cisplatin. The relative risk of both progression-free survival and overall survival was significantly in favor of the group receiving cisplatin. Sites of progression were not significantly different between the two groups, and toxicity was acceptable.

31. •• Keys HM, Bundy BN, Stehman FB, *et al.*: **Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma.** *N Engl J Med* 1999, **340:**1154–1161.

Patients with bulky stage IB cervical cancer greater than or equal to 4 cm were randomized to radiation alone versus concurrent radiation and weekly cisplatin chemotherapy. Both groups received posttreatment hysterectomy. The relative risk of death in the combined therapy group compared to the group given radiation alone was 0.54. The authors concluded that adding weekly infusions of cisplatin to pelvic radiotherapy followed by hysterectomy significantly reduced the risk of disease recurrence and death in women with bulky stage IB cervical cancers.

32. •• Rose PG, Bundy BN, Watkins EB, *et al.*: **Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer.** *N Engl J Med* 1999, **340:**1144–1153.

Report on a study in which patients with stage IIB to IVA cervical cancer and negative para-aortic lymph nodes were randomized to one of three treatment arms. The control arm, radiation therapy with concurrent hydroxyurea, was compared with radiation plus cisplatin and radiation plus cisplatin, 5-FU, and hydroxyurea. Both cisplatin-containing arms showed similar improvements in survival rate and progression-free survival. Patients receiving cisplatin alone had lower toxicity than those receiving the multidrug regimen.

33. •• Morris M, Eifel PJ, Lu J, *et al.*: **Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer.** *N Engl J Med* 1999, **340:**1137–1143.
34. •• Peters WA III, Liu PY, Barrett R, *et al.*: **Cisplatin, 5-flurouracil plus radiation therapy are superior to radiation therapy as adjunctive therapy in high-risk, early-stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: report of a phase III inter-group study [abstract].** *Gynecol Oncol* 1999,**72:**443.

In this study, patients with stage IIB to IVA cervical cancer, negative para-aortic lymph nodes, and pelvic washings were randomized to receive pelvic radiotherapy concurrently with either hydroxyurea or combined 5-FU and cisplatin. The relative risk of both progression-free survival and overall survival was significantly in favor of the group receiving cisplatin. Sites of progression were not significantly different between the two groups, and toxicity was acceptable.

35. Stehman FB, Bundy BN, DiSaia PJ, *et al.*: **Carcinoma of the cervix treated with irradiation therapy I: a multivariate analysis of prognostic variables in the Gynecologic Oncology Group.** *Cancer* 1991, **67:**2776–2785.