Two recent multicenter randomized trials have greatly advanced our understanding of the role of postoperative radiation therapy in operable cervical cancer. In locally advanced cervical cancer, such studies have shown a
resistant to radiation. High initial clinical response rates have been reported with cisplatin-containing regimens in numerous phase II trials, but whether these responses will translate into reproducible improvements in relapse-free and/or overall survival remains to be determined. Sardi et al[4] reported an overall survival advantage for neoadjuvant cisplatin, vincristine, and bleomycin prior to surgery in 209 patients with stage IB disease. Benedetti-Panici et al[5] and Chang et al[6] reported conflicting results with the use of neoadjuvant chemotherapy followed by surgery vs radiation therapy alone.

GOG-141 was a phase III trial designed to assess the role of neoadjuvant chemotherapy in patients with bulky stage IB cervical cancer, who were randomized to primary surgery vs three cycles of cisplatin and vincristine followed by surgery. The study was closed prematurely because the majority of patients needed further therapy (radiotherapy or chemoradiotherapy) despite the use of neoadjuvant chemotherapy prior to surgery. At a future date, with more effective chemotherapy, it might be appropriate to reevaluate this strategy.

• **GOG-109/SWOG/RTOG: Postoperative Chemoradiation** For patients with positive pelvic lymph nodes following radical hysterectomy, pelvic irradiation reduces the pelvic failure rate from approximately 50% to 25% but does not affect survival. This phase III Intergroup trial (conducted by Peters et al for the GOG, Southwest Oncology Group [SWOG], and Radiation Therapy Oncology Group [RTOG]) was initiated to determine whether the efficacy of adjuvant radiotherapy following radical hysterectomy and lymphadenectomy in high-risk early-stage cervical cancer patients might be improved by concomitant chemotherapy.[7] The high-risk group includes one or more of three histologically defined poor prognostic factors (positive pelvic lymph nodes, positive parametrial involvement, and positive surgical margins).

Patients were randomized to receive adjuvant radiotherapy alone or combined concurrent chemoradiotherapy (Figure 2)[7]; 85% had positive pelvic nodes, 34% had positive parametrial involvement, and 5% had positive margins. The estimated 4-year, disease-free survival (81% vs 63%) and overall survival rates were significantly higher with chemoradiotherapy, compared to radiotherapy alone (81% vs 71%).

With its impressive results, combined adjuvant chemoradiotherapy has become the current standard treatment after radical hysterectomy for patients with selected high-risk factors, particularly positive pelvic nodes. Although grade 3/4 toxicity—notably, acute hematologic and gastrointestinal effects—were more common in patients who received combined chemoradiotherapy, these reactions were considered manageable. Because the combination of radical surgery and irradiation is associated with greater morbidity than either modality above, complete preoperative assessment is crucial to minimize the need for both.

**Radiation Therapy**

In the radiotherapeutic management of stage IB cervical cancer, bulky disease (the so-called “barrel shaped” cervix) is associated with a high local failure rate. Definitions of bulky stage IB disease have ranged from greater than 2.0 cm to greater than 6.0 cm; the GOG definition is ≥ 4.0 cm in size. Management of this entity is controversial. Recently, the International Federation of Gynecology and Obstetrics (FIGO) staging system divided stage IB disease into stages IB1 (≤ 4.0 cm) and IB2 (> 4.0 cm). One way to improve definitive radiotherapy is with the use of planned extrafascial hysterectomy after irradiation.[8]

• **GOG-71/GOG-123: Preoperative Radiotherapy** In two studies for the GOG, Keys et al examined the use of preoperative radiotherapy in women with early-stage cervical cancer. GOG-71 compared definitive radiotherapy vs moderate-dose irradiation (75 Gy to point A) followed by extrafascial hysterectomy in 256 patients with stage IB bulky disease.[9] GOG-123 examined whether a regimen of weekly cisplatin (40 mg/m²) during external-beam radiation therapy improved survival compared with that achieved with irradiation alone in 369 patients with stage IB/IIA cervical cancer.[10] Both arms of GOG-123 included completion of extrafascial hysterectomy, because the results of GOG-71 were not yet available when the later study was initiated.

The results of GOG-71 showed that the addition of surgery did not improve survival. In GOG-123, survival was significantly improved in patients who received concurrent cisplatin and radiation, compared with those who received radiation alone prior to extrafascial hysterectomy. At a median follow-up of 36 months, survival rates were 83% and 74% (P = .008) for the chemoradiation arm and the radiotherapy-alone arm, respectively. Although the rate of severe adverse effects was higher in the cisplatin-and-radiotherapy group (35%) compared to the radiotherapy-alone group (13%), no treatment-related deaths occurred. The improved survival associated with the use of concurrent cisplatin and radiation is attributable to a reduction in pelvic recurrence.

**Surgery vs Radiotherapy**
Landoni et al[11] reported the only randomized phase III trial to compare primary radiotherapy alone with radical hysterectomy followed by postoperative pelvic radiotherapy in this setting. A total of 337 high-risk (positive nodal metastases, parametrial involvement, cut-through, and < 3.0 mm of uninvolved cervical stromal margins) stage IB/IIA cervical cancer patients were included in the intention-to-treat analysis. Based on the qualifying pathologic risk factor identified after radical hysterectomy, 62 of 114 (54%) patients with a tumor diameter of 4.0 cm or less, and a remarkable 46 of 55 (84%) patients with a tumor diameter greater than 4.0 cm received postoperative radiotherapy.

The relapse-free and overall survival rates were identical in both groups, but the complication rate was higher among patients undergoing surgery (28% vs 12%, \( P = .0004 \)). Therefore, patients selected for radical hysterectomy should have small-volume disease, to minimize the need for adjuvant pelvic radiation.

**Locally Advanced Cervical Cancer**

Either radical surgery or definitive radiotherapy is an effective treatment for many women with nonbulky, early-stage (IB1/IIA) cervical cancer. However, for women with bulky, early-stage (IB2) or late-stage (IIB/IVA) pelvic disease, treatment results are unsatisfactory.[12-14] The patterns of failure are characterized by an increase in both local and distant metastasis related to increasing tumor size. However, the main cause of failure is uncontrolled disease within the pelvis. Local failure can be reduced with high doses of radiation, although this technique also increases complications. The utility of cytotoxic chemotherapy in conjunction with radiation in patients with locally advanced cervical cancer has been the subject of extensive clinical investigations with variable results. These studies can be categorized as (1) neoadjuvant chemotherapy administered prior to radiation; (2) concurrent chemotherapy, in which chemotherapy and radiation are administered together; and (3) adjuvant chemotherapy, in which radiation is followed by chemotherapy. This option will be mentioned only in passing, since virtually nothing has been published, especially with respect to randomized trials. The lack of relevant studies may reflect, in part, the absence of a highly active regimen in advanced or recurrent disease, especially with respect to previously irradiated sites of disease as well as the recent shift in focus to concurrent therapy, and the recognition that neoadjuvant chemotherapy prior to irradiation, as discussed below, has not improved outcome. When more promising regimens for the neoadjuvant setting or for recurrent disease are identified, this third option might be revisited.

**Neoadjuvant Chemotherapy With Radiotherapy**

At least 10 phase III trials of preirradiation neoadjuvant chemotherapy have been reported.[15-24] Many of the trials were small, with less than 100 patients in each arm. Cisplatin-based chemotherapy was used in all of these trials. In general, two or three courses of chemotherapy were administered prior to radiation treatment. None of the trials demonstrated a significant difference in survival with the use of neoadjuvant chemotherapy compared to radiation therapy alone. Two trials reported a decreased survival rate and an increased treatment complication rate.[17,22] In light of these results, the GOG has never studied the use of neoadjuvant chemotherapy prior to radiotherapy. Clearly, the partial regression after neoadjuvant chemotherapy did not translate into better local control with subsequent radiotherapy. The possibility of cross-resistance between cisplatin-based drugs and radiation has been proposed. Accelerated repopulation of clonogenic cells in the tumor may provide another explanation for the failure of neoadjuvant chemotherapy.

**Concurrent Chemoradiotherapy**

Using chemotherapy during radiation treatment as a radiation "sensitizer" is an attractive approach. With this strategy, the entire treatment course is not prolonged and, thus, the effects of tumor proliferation are minimized. Unfortunately, the same mechanisms apply to normal tissue and result in greater toxicity. Concurrent chemoradiotherapy has proven beneficial in a variety of tumor sites, including the anus, esophagus, bladder, lung, and more recently, head and neck.

• **GOG Trials** In 1979, the GOG published the results of an initial chemoradiotherapy trial (GOG-4), which favored concurrent hydroxyurea over radiotherapy alone. These results were controversial due to a small patient population and poor survival rates compared to other studies.[25] Nevertheless, based on this study, three subsequent GOG trials of concurrent chemoradiotherapy used hydroxyurea plus radiotherapy as a control arm (Table 1).[25-28]

First, Stehman et al[26] compared hydroxyurea with misonidazole and reported no survival advantage for the nitroimidazole. Next, Whitney et al[27] compared concurrent hydroxyurea with cisplatin-based chemoradiotherapy and showed a survival benefit for the cisplatin combination.
When the GOG was designing their next trial, the results of the hydroxyurea vs cisplatin-based combined chemotherapy trial were not available. Therefore, in a three-arm study, Rose et al.[28] compared treatment with radiation plus hydroxyurea, radiation plus weekly cisplatin, and radiation plus hydroxyurea, cisplatin, and fluorouracil (5-FU). These GOG investigators found that the relapse-free survival rate was significantly higher with both cisplatin regimens. In addition, patients treated with hydroxyurea had significant hematologic toxicity. The frequency of grade 3/4 neutropenia in the group that received radiotherapy combined with cisplatin, fluorouracil, and hydroxyurea was more than double that of the other groups ($P < .001$). Concurrent weekly cisplatin alone was more effective, less toxic regimen than radiation plus hydroxyurea.

**Other Trials** As shown in Table 2, other important prospective randomized trials of concurrent chemoradiotherapy have included an RTOG trial,[29] two Canadian trials,[30,31] and a trial from Thailand.[32] Both Morris et al[29] and Lorvidhaya et al[32] reported that concurrent chemoradiotherapy improved disease-free and overall survival. However, the results of the Thomas[30] and Pearcey[31] trials did not confirm the benefit of concurrent chemoradiotherapy and led people to question the magnitude of the benefits derived from the addition of chemotherapy to optimally delivered radiotherapy. [33]

The Pearcey trial,[31] conducted by the National Cancer Institute (NCI) of Canada, is the only randomized study that directly addressed the question of adding weekly cisplatin (40 mg/m²) to radiotherapy without any other treatments. Thomas et al[30] reported that their trial of concurrent 5-FU and radiotherapy, using an altered radiation fractionation, demonstrated no survival benefit over standard radiotherapy alone. However, subset analysis showed a significant improvement in outcome for patients with bulky stage IB and medial stage IIB disease who received standard radiotherapy and concurrent 5-FU. It is important to note that no survival benefit was found for the stage IIB patients in the RTOG trial and in the Thomas trial. These trials differed in their inclusion criteria, chemotherapy schedules, and radiotherapy doses. The RTOG trial used a higher dose of radiation (85 Gy to point A) than the GOG trials and the NCI-Canada trial. In recent GOG trials, the dose of radiation to point A has been increased by 5 Gy (to 85 Gy). Careful attention to radiotherapy parameters of total dose and treatment duration is important for achieving optimum outcome for patients with this disease. To evaluate the significance of anemia and the potential anemia protective effect of erythropoietin, the GOG is conducting a trial of radiation with weekly cisplatin with or without erythropoietin.

**Optimal Chemotherapy** Taken together, the recent large multiinstitutional, randomized trials,[8,10,27-29,31] (except for the Canadian trials) showed significant improvement in survival with the use of concurrent chemotherapy and radiation in locally advanced cervical carcinoma. When it became apparent in late 1998 that these studies pointed to a major improvement in treatment,[7,10,27-29] the NCI issued a "clinical alert" on the subject, recommending concurrent cisplatin-based chemotherapy plus radiation. Until further data become available, it is reasonable to routinely consider the use of concurrent cisplatin-based chemotherapy for locally advanced cancer of the cervix. The GOG has chosen weekly cisplatin at a dose of 40 mg/m² as the standard to which newer regimens should be compared.

An optimal choice of chemotherapy (drug and schedule), however, has not been determined. Phase I and II chemotherapy trials have been reviewed previously.[34-36] Cisplatin has been regarded as the most active agent in this setting, although its activity is modest and not clearly superior to that of carboplatin (Paraplatin). Various combinations have produced higher response rates but with more toxicity.

Recently, randomized trials have begun to be reported. These have shown higher response rates with cisplatin combinations compared to cisplatin alone but, so far, with no improvement in overall survival and more toxicity.[37-39] Additional studies are ongoing. New drugs and biologic agents, coupled with a better understanding of the biology of the disease, offer the promise of more effective and less toxic treatment options in the future.

**Elective Para-aortic Radiotherapy**

Two randomized studies have addressed elective irradiation of the para-aortic nodes in women with squamous cell carcinoma of the uterine cervix.

**RTOG Study** The RTOG study[40] randomized 367 patients to receive either pelvic irradiation or pelvic plus para-aortic irradiation for stage IB/IIA disease with the primary tumor measuring 4.0 cm or greater, and for stage IIB disease. Patients with clinically apparent or histologically involved para-aortic nodes were excluded from this study. The difference in absolute survival was statistically significant: The 5-year survival rate was 66% in the para-aortic group and 55% in the pelvic group.
The differences in 2- and 5-year survival were more pronounced among patients with stage IB/IIA cervical cancer.

**EORTC Study** The recently published study conducted by the European Organization for Research and Treatment of Cancer (EORTC)[41] is the only other randomized study that compared pelvic irradiation alone vs pelvic plus elective para-aortic irradiation in stage I (with positive pelvic lymph nodes), IIB, and III cancer of the cervix. It should be emphasized that the EORTC trial included stage III patients, whereas the RTOG trial did not. In the EORTC trial, there was a significant reduction in clinically evident para-aortic node metastases in the group that received elective para-aortic irradiation. However, no statistical difference in disease-free survival at 4 years was found between these two groups for any of these stages.

**Conclusions About Para-aortic Irradiation** These studies strongly support the theory that extended-field radiation is of greatest benefit when administered to patients with stage I/II disease who are at increased risk for microscopic deposits within regional lymph nodes. When the primary tumor burden is increased, the risk/benefit ratio of extended-field radiation declines. Although the morbidity of extended-field radiotherapy is no longer prohibitive because of multiple-field techniques and modest doses, it is still greater than that of standard pelvic field irradiation.

Further definition of the patients most likely to benefit from elective para-aortic radiotherapy would improve the therapeutic ratio of such treatment. However, the role of the extended-field strategy needs to be clarified in light of the success seen with standard-field (pelvic only) radiation with concurrent chemotherapy in the recent RTOG trial.[29] The use of extended-field radiation in combination with chemotherapy has not been widely studied in the adjuvant setting, but has been found to be tolerable in patients with proven para-aortic nodal metastases in a GOG phase II trial.[42]

**Early-stage vulvar cancer**

Epidermoid (squamous cell) carcinoma of the vulva is an uncommon tumor, comprising only 3% to 4% of all genital neoplasms in women. Despite the rarity of cancer at this site, optimization of therapy is important not only to improve local control and cure rates, but also to minimize the attendant morbidity of radical surgery. In recent years, the surgical trend has moved away from the classic radical vulvectomy with en bloc bilateral inguinal node dissections through "butterfly" incisions. New approaches involve less extensive vulvar surgery, separate groin incision with preservation of the skin bridge, and less radical inguinal node surgery.

The most important modification has been the use of separate groin incisions. Wound healing is superior when groin dissections are performed through separate incisions, and the results are not inferior. Another recent modification is the performance of a wide local excision rather than a radical vulvectomy for a smaller lesion.

The role of radiotherapy in the management of vulvar cancer has not been explored in a systematic fashion. Radiation therapy fell into disrepute in this setting because of reports of severe necrosis of the vulva associated with its use. The GOG is beginning to explore the use of chemoradiotherapy as adjuvant treatment.

**Surgical/Pathologic Studies**

- **GOG-36** Histologic groin node status is the most important independent prognostic factor when assessing risk of death due to recurrent vulvar cancer. Thus, it is critical to accurately assess all independent variables for prediction of histologic groin node status. In GOG-36, Sedlis et al conducted a prospective clinical and surgical-staging study of squamous cell cancer of the vulvar in 558 women, 272 (48.2%) of whom had superficial (\( \leq 5 \) mm) tumors, 20% of which had metastasized to the lymph nodes. Patients with minimal tumor thickness (\( \leq 1 \) mm) had positive groin nodes in 2.7% of cases, whereas those with a 1- to 2-mm thick lesion had positive groin nodes in 8.9% of cases.[43]

  The significant predictors of groin node metastasis in patients with superficial vulvar cancer were tumor thickness, histologic grade, capillary-like space involvement, clitoral or perineal location, and clinically suspicious nodes. The most accurate and reproducible method for assessment of lymph node metastases was best determined by simultaneous evaluation of all risk factors rather than a single factor.

- **GOG-37** Homesley et al conducted a prospective trial in 114 patients with squamous cell cancer of the vulva who were found to have groin node metastasis after radical vulvectomy and bilateral groin node dissection.[44] Although all patients in this study had at least one groin node metastasis,
nearly half (49%) had clinically negative findings. Patients were randomized to undergo either radiation therapy to the pelvis and groin (45 to 50 Gy) or pelvic node dissection. Pelvic node dissection was usually performed if groin nodes were positive for metastasis. Adjuvant radiation therapy to the groin and deep pelvic nodes decreased the incidence of inguinal node failure (5.1% vs 23.6%) and significantly improved 2-year survival in those with clinically involved groin nodes or more than one pathologically involved groin node (68% vs 54%, \( P = .03 \)). Survival for all patients is related to the number of positive groin nodes.

Vulvar irradiation was not administered in this study. The local vulvar recurrence rate was only 8.8% in both groups. Compared to the results of pelvic node dissection, these data strongly support the use of postoperative nodal radiation, at least for the identified patient subsets. In this study, 28% of patients with groin node metastasis had positive pelvic lymph nodes, and the estimated 2-year survival rate for this subgroup was only 23%. The frequency of positive pelvic nodes was 14% for patients with N0/1 disease and 45% for those with N2/3 disease and two or more positive groin nodes.

GOG-185 is an ongoing randomized study evaluating the effects of cisplatin in conjunction with local radiotherapy in the same patient populations as those in GOG-37.

• **GOG-88**—Given that radical vulvectomy with bilateral groin lymph node dissection has been the standard therapy for carcinoma of the vulva, Stehman et al sought to determine whether groin irradiation is superior to and less morbid than groin dissection in patients with squamous cell carcinoma of the vulva and nonsuspicious (N0/1) inguinal nodes.[45] Patients were randomized to undergo groin dissection or groin irradiation to a depth of 3.0 cm below the anterior skin surface. The groins were treated daily to a total dose of 50 Gy over 5 weeks, and it was recommended that 50% of the prescribed dose be given with 12 to 13 MeV electrons to reduce the dose to the femoral heads.

The study closed prematurely when interim monitoring revealed an excessive number of groin relapses associated with the groin irradiation regimen. There were five (18.5%) groin relapses among the 27 patients who received radiation and none among those who underwent groin dissection.

The criticism of groin irradiation in GOG-88 focused on the fixed depth of 3.0 cm used for localization of femoral nodes. Koh et al[46] demonstrated that femoral vessel depths, measured on computed tomography (CT) scan, varied from 2.0 to 18.5 cm, with a mean of 6.1 cm. In a series of 100 CT scans of the inguinal region, McCall et al[47] showed that a 3.0-cm depth of radiation would cover inguinal nodes in only 18% of women. These data suggest that the role of inguinal radiotherapy has not been properly studied. The RTOG tried to repeat this study with accurate radiation doses to inguinal nodes using CT scans. However, that trial was discontinued due to poor accrual.

**Locally Advanced Vulvar Cancer**

When the disease involves the anus, rectum, rectovaginal septum, proximal urethra, or bladder, adequate surgical resection is possible only by pelvic exenteration combined with radical vulvectomy. In selected patients, 5-year survival is about 50%. However, the postoperative physical and psychological morbidity is substantial. Radiation therapy has traditionally been considered to have a limited role in primary management of vulvar cancer. In 1973, Boronow[48] advocated a combined radiation-surgical approach as an alternative to pelvic exenteration.

• **GOG-101**—Reported by Moore et al[49] and Montana et al[50], GOG-101 was a phase II study of preoperative chemoradiotherapy for advanced vulvar cancer. A total of 73 patients with unresectable T3/4 primary vulvar tumor with N0/1 groin nodes (50 patients) or N2/3 groin nodes (23 patients) were enrolled in this study. Treatment consisted of a planned split course of concurrent cisplatin/5-FU and radiation therapy followed by surgical excision of the residual primary tumor plus bilateral inguinal-femoral lymph node dissection. Radiation therapy was delivered to the primary tumor volume in 1.7-Gy fractions to a total dose of 47.6 Gy.

Following chemoradiotherapy, 34 (48%) of 71 patients had no visible cancer, and three of these patients did not undergo surgery. Of the remainder, 22 (70%) of 31 had no residual microscopic disease. With the use of preoperative chemoradiotherapy, only 2 (2.8%) of 71 had residual unresectable disease. It was not possible to preserve urinary and/or gastrointestinal continence in only three patients. Twenty-four women (32.9%) developed recurrent vulvar cancer. The vulva was the initial site of recurrence in eight patients, and three additional patients had vulvar recurrence along with recurrence in the groin or pelvis in follow-up ranging from 22 to 72 months.

Toxicity was acceptable, although an acute cutaneous reaction was the most common adverse effect
and early postoperative surgical wound healing was a frequent problem (15%). Two patients developed fatal treatment-related complications (femoral artery necrosis and septicemia). This study used the planned split-course chemoradiotherapy and multiple daily fraction radiation therapy. However, optimal radiation dose fractionation has not been determined.

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