What Is the Role of Cytotoxic Chemotherapy in Advanced Cervical Cancer?

8

Alok Pant, Nobuyuki Susumu, Takafumi Toita, Satoru Sagae, and William Small Jr.

Summary Points

- Adjuvant Chemotherapy after Surgery
- The Role of Neoadjuvant Chemotherapy
- Concurrent Chemotherapy and Radiation for Locally Advanced Disease
- Combining Chemoradiation and Adjuvant Chemotherapy
- The Addition of Chemotherapy to Extended Field Radiation for Patients with Known Para-Aortic Disease
- Chemotherapy for Recurrent or Metastatic Disease
- The Use of Targeted Agents

A. Pant, MD (✉)
Department of Obstetrics and Gynecology, Northwestern Memorial Hospital, 250 East Superior Suite 05-2168, Chicago, IL 60611, USA
e-mail: acpant@gmail.com

N. Susumu, MD, PhD
Department of Obstetrics and Gynecology, School of Medicine, Keio University, 35 Shinanomachi, Shinjyuku-ku, Tokyo, 160-8582, Japan
e-mail: susumu35@a6.keio.jp

T. Toita, MD
Department of Radiology, Ryukyu University Hospital, 207 Uehara, Nishihara, Okinawa, 903-0215, Japan
e-mail: b983255@med.u-ryukyu.ac.jp

S. Sagae, MD, PhD
Department of Obstetrics and Gynecology, JR Sapporo Hospital, North 3 East 1, Chuou-ku, Sapporo, Hokkaido, 060-0033, Japan
e-mail: s-sagae@jrhokkaido.co.jp

W. Small Jr., MD, FACRO, FACR, FASJRO
Chairman of Radiation Oncology, Loyola University Medical Center, 251 E. Huron Street, Galter LC-178, Chicago, IL 60611, USA
e-mail: wsmall@nmff.org

Introduction

Cervical cancer is the second most common cancer of women worldwide, with an estimated 529,000 cases in 2009 [1] and a 5-year prevalence of more than 1.4 million cases. Cervical cancer accounted for approximately 275,100 deaths worldwide in 2009 [1] and is the leading cause of death of women from cancer in developing countries [2]. Treatment outcome and prognosis are highly dependent upon stage at diagnosis. Cervical cancer is clinically staged according to the 2009 FIGO staging system.

Stage IA1 cervical cancer is treated with conization or hysterectomy, and the vast majority of patients are cured with this approach [3]. The standard treatment for stage IA2 squamous cell carcinoma is a modified (type II) radical hysterectomy and pelvic lymphadenectomy. Stage IB is divided into IB1 (lesions less than 4 cm) and IB2 (lesions confined to cervix >4 cm). IB1 lesions can be treated with one of two different regimens. Patients can undergo radical hysterectomy and pelvic lymph node dissection followed by tailored (chemo)radiation as indicated by pathologic results, or primary radiation concurrent with chemotherapy. Both treatment options offer equivalent outcomes, and the decision to proceed with either modality is based on the patient's age, medical comorbidities, and surgical feasibility. This represents the initial opportunity for studies of the additional role of chemotherapy to the treatment paradigm of cervical cancer.

IB2 cervical cancers can either be treated with up-front surgery followed by tailored (chemo)radiation as indicated by pathologic results or chemoradiation with curative intent. A 1999 prospective, randomized Gynecologic Oncology Group (GOG) trial [4] of 374 patients with IB2 cervical cancer randomly assigned patients to be treated with radiation therapy (external beam and intracavitary cesium) and adjuvant extrafascial hysterectomy 3–6 weeks later, with or without weekly intravenous cisplatin at a dose of 40 mg/m^2 for 6 weeks during the external radiation. Residual cancer in the operative specimen was significantly reduced in the group

J.A. Ledermann et al. (eds.), *Controversies in the Management of Gynecological Cancers*,
DOI 10.1007/978-0-85729-910-9_8, © Springer-Verlag London 2014

receiving cisplatin, to 47 % down from 57 %. Survival at 24 months was significantly improved by the addition of cisplatin, being 89 % with and 79 % without chemotherapy. There was also a significant improvement in recurrence-free survival, from 69 % without chemotherapy to 81 % with cisplatin. Grade 3 and 4 hematologic and gastrointestinal toxicities were more frequent in the group receiving cisplatin, whereas other toxicities were equivalent in both treatment arms.

Using this data as a starting point, the role of chemotherapy in the treatment of cervical cancer has undergone a remarkable evolution over the past 15 years. In this chapter we will discuss the role of adjuvant chemotherapy after surgery, the potential use of neoadjuvant chemotherapy, the use of combined chemoradiation, adjuvant chemotherapy after chemoradiation, chemotherapy and biologic agents in the metastatic and recurrent setting, and, finally, potential future directions of treatment.

What Is the Evidence for Adjuvant Chemotherapy After Surgery?

There are limited data and few adequately powered randomized trials regarding the role of adjuvant chemotherapy after radical surgery for the treatment of cervical cancer. The Japanese Gynecologic Oncology Group randomized patients who had undergone surgery ($n=623$) or surgery and radiation therapy ($n=919$) to receive oral 5-FU for 1 year or observation. No benefit for 5-FU was seen in patients who received surgery alone. However, an improved 5-year survival was seen in patients who had surgery, radiation, and 5-FU as compared to those who received surgery and radiation alone [5]. A trial in Thailand randomized 926 patients with stage IIB–IVA cervical cancer to one of four arms: radiation therapy, radiation therapy plus adjuvant (5-FU) chemotherapy, radiation therapy and concurrent (mitomycin C) chemotherapy, and radiation therapy plus concurrent (mitomycin C) and adjuvant (5-FU) chemotherapy. The 5-year disease-free survival was 48.2, 54.1, 64.5, and 59.7 %, respectively, suggesting a benefit from adjuvant chemotherapy [6]. A recent phase II trial of 125 patients with early cervical cancer compared adjuvant paclitaxel/cisplatin (TP) chemotherapy to radiotherapy in patients who had undergone radical hysterectomy. The 3-year recurrence-free survival for chemotherapy-treated patients was 78.1 %, compared to 67.3 % for RT ($p=0.23$). The 3-year overall survival was 93.8 % with TP versus 69.4 % with RT ($p=0.02$). The authors concluded that postoperative chemotherapy using TP may have a survival benefit compared to adjuvant RT for patients with early-stage disease, along with reduced postoperative complications [7]. Japanese investigators reported similar results using adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB–IIA cervical cancer [8]. In 65 consecutive patients with stage IB or IIA cervical cancer who were initially treated with radical hysterectomy and pelvic lymphadenectomy, chemotherapy was administered using three courses of bleomycin, vincristine, mitomycin, and cisplatin for intermediate-risk cases and five courses for high-risk cases. The estimated 5-year disease-free survival was 93.3 % for the 30 patients with intermediate-risk tumors and 85.7 % for the 35 patients with high-risk tumors. These results indicate a potential role for adjuvant chemotherapy on its own for patients with cervical cancer.

Does Neoadjuvant Therapy Have a Place in the Management of Cervical Cancer?

Neoadjuvant chemotherapy (NAC) is a potential therapeutic modality prior to radical hysterectomy or radiotherapy for locally advanced cervical cancer (stage IB2, IIB, III, or IV). Neoadjuvant chemotherapy is used to reduce the tumor volume prior to radical surgery or chemoradiation. The goal of NAC is to increase the probability of complete tumor resection with free surgical margins and to optimize the safety of surgery. Additional goals are to increase the effectiveness to radiation and the early treatment of micrometastases and the prevention of distant metastases. Theoretically, NAC has the ability to not disturb the blood supply to the tumor as occurs with surgery or radiation. However, there remains the possibility of delaying the main curative treatment via radical surgery, radiotherapy, or chemoradiotherapy. There also remains the possibility of developing radioresistant cell clones. There are reports of randomized controlled trials utilizing NAC followed by surgery and radiation therapy [9]. In 2003, a meta-analysis was reported involving 872 patients from 5 randomized trials [10]. The combined results from the 5 trials indicated a highly significant reduction in the risk of death with NAC (HR = 0.65, 95 % CI = 0.53–0.80, $p=0.00004$) and also a highly significant reduction in the risk of disease progression or recurrence with NAC (HR = 0.68, 95 % CI = 0.56–0.82, $p=0.0001$). However, as the authors of this study stated, these analyses potentially suffer from selection biases and a significant amount of heterogeneity and are, therefore, inconclusive. The timing and dose intensity of cisplatin-based NAC appears to play an important role in whether or not it benefits women with locally advanced cervical cancer. This meta-analysis included radiation alone, not chemoradiation. Benedetti-Panici et al. reported on 441 patients with stage IB2–III cervical cancer who were randomized to cisplatin-based NAC followed by radical hysterectomy or external beam radiation (45–50 Gy) followed by brachytherapy [11]. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 59 and 55 % for NAC and surgery and 45 and 41 % for radiation ($p=0.007$ and $p=0.02$), respectively.

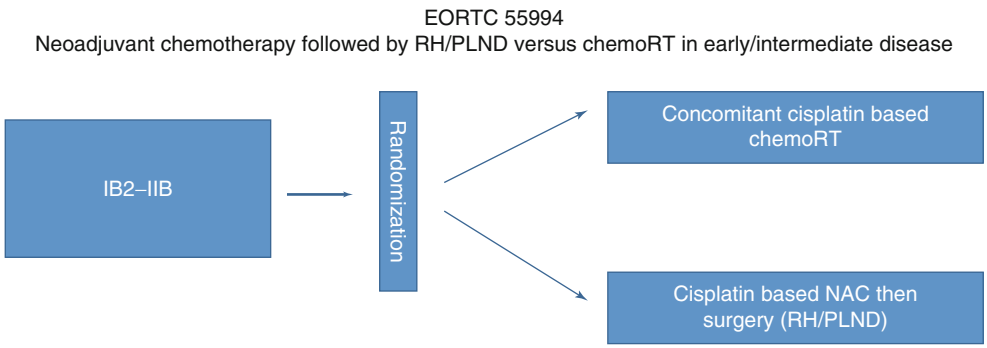

Fig. 8.1 Schema for EORTC 55994, a phase III, randomized controlled trial in patients with early-stage and intermediate-risk disease treated with neoadjuvant chemotherapy followed by either surgical management or combined chemotherapy and radiation

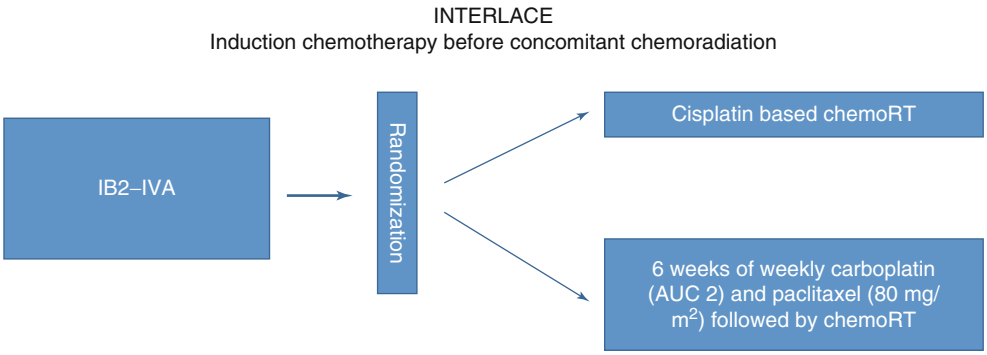

Fig. 8.2 Schema for INTERLACE, a phase III, randomized controlled trial in patients with early stage through locally advanced disease who are randomized to induction chemotherapy or no treatment before definitive combined chemotherapy and radiation

A subgroup survival analysis was undertaken in stage IB2–IIB patients. The subgroup analysis showed an OS and PFS of 65 and 60 % in the NAC and surgery arm compared to 46 and 47 % in the radiation arm ($p=0.005$ and $p=0.02$). NAC followed by radical surgery showed a significant improvement of OS and PFS in this trial. However, Chang et al. showed no significant difference in OS and PFS between NAC (cisplatin, vincristine, bleomycin) followed by radical hysterectomy and radiotherapy in patients with bulky (primary tumor ≥4 cm) stage IB or IIA cervical cancer [12]. Two randomized trials are currently evaluating the role of NAC. The first, EORTC 55994, compares NAC followed by surgery to concomitant radiotherapy and chemotherapy in FIGO IB2, IIA >4 cm, or IIB cervical cancer (Fig. 8.1). The second is a phase III trial in patients with locally advanced disease for whom surgery is not suitable. INTERLACE will compare the survival of patients treated with weekly induction chemotherapy using carboplatin and paclitaxel followed by standard chemoradiation versus standard chemoradiation alone. The trial is currently open in the UK and will include international centers (Fig. 8.2). Sardi et al. reported a randomized trial of 205 patients with stage IB disease comparing NAC (cisplatin, vincristine, bleomycin) followed by radical hysterectomy then pelvic radiation and up-front radical hysterectomy followed by adjuvant whole-pelvic radiation [13]. No statistically significant differences were seen in OS and DFS in patients with tumors with 2–4 cm in diameter, while in patients with tumors greater than 4 cm, they found significantly improved 9-year OS (80 % in the NAC group vs 61 % in the control group, $p<0.01$). There was an increased ability to achieve negative surgical margins in bulky tumors in the NAC group (61/61, 100 %) compared to the control group (48/56, 85 %; $p<0.01$). The authors concluded that NAC improved OS because of the increased ability to achieve a negative surgical margin and a decrease in pathological risk factors such as lymphovascular space invasion, parametrial invasion, and lymph node involvement in stage IB2 patients. Napolitano et al. reported on 192 patients with stage IB–IIB disease who were randomized to either NAC (cisplatin, vincristine, bleomycin) followed by surgery or control conventional surgery or radiotherapy [14]. The authors did not find a statistically significant difference in 5-year OS between the two groups with stage IB–IIA disease. However, they did report an improved 5-year DFS (77 % in the NAC group vs 64 % in the control group, $p<0.05$). Patients with stage IIB disease had no difference in either OS or DFS. In 2007, the GOG reported the results of their trial of 288 bulky stage IB2 patients who were randomized to NAC (cisplatin, vincristine) followed by radical hysterectomy and pelvic/para-aortic lymphadenectomy (RHPPL) or radical hysterectomy with lymph node dissection [15]. Adjuvant radiation therapy was prescribed for specific surgical/pathological risk factors for both regimens. The NAC group had very similar recurrence rates (relative risk, 0.998) and death rates (relative risk, 1.008) when compared to the control group. Chen et al. reported on the use of a modified NAC schema with a short burst of high-dose preoperative chemotherapy followed by surgery compared to surgery alone in 142 patients with locally advanced

cervical cancer. The authors found that on multivariate analysis, there was no survival improvement in the NAC group. However, patients who demonstrated a significant response to up-front chemotherapy had improved survival [16]. In 2006, Cai et al. reported a trial of 106 stage IB patients who were randomized to either NAC (cisplatin, 5-FU) (with or without radiotherapy) or primary surgery (with or without radiotherapy) [17]. The overall 5-year survival rate was significantly higher in the NAC group (85 %) than in the control group (76 %) ($p=0.011$). They also showed decreased rates of pelvic lymph node metastases, LVSI, and parametrial invasion in the NAC group.

While there have been a number of randomized trials examining the use of NAC in locally advanced cervical cancer, the question remains as to the efficacy of such an approach. The majority of the trials indicate a higher rate of margin-free surgery and tumor response, but this does not always translate into improved survival outcomes.

In an effort to examine the use of NAC before surgery or concomitant chemotherapy and radiation, Duenas-Gonzalez et al. performed a nonrandomized comparison of the results of two consecutive phase II studies in stage IB2–IIIB patients. The 41 patients in the NAC arm were treated with three cycles of cisplatin and gemcitabine followed by surgery or chemoradiation for inoperable cases. In a separate trial, 41 patients were treated with standard cisplatin-based chemoradiation. At a median follow-up of 28 and 24 months, respectively, there were no significant differences in PFS or OS in the NAC trial versus the standard chemoradiation trial indicating that either treatment modality may be acceptable [18]. In 2007, the Korean GOG reported a retrospective review of their experience using different treatment modalities for 692 stage IB2 cervical cancer patients treated between 1995 and 2005. They compared primary radical hysterectomy, NAC followed by radiotherapy and/or extrafascial hysterectomy, and, finally, cisplatin-based chemoradiation and/or extrafascial hysterectomy [19]. The surgery group showed the best results, with an 89 % 5-year DFS. However, there was no statistical difference between the surgery, NAC, and chemoradiation groups.

What Drugs Should Be Used for Neoadjuvant Chemotherapy?

No consensus has yet been obtained regarding the ideal, specific chemotherapy regimen for use as neoadjuvant chemotherapy. There are many reports with the PBV (cisplatin, bleomycin, vincristine) regimen that have shown a 70–80 % response rate. Recently, taxanes such as paclitaxel and docetaxel have been used in NAC regimens [20, 21]. Nagao et al. reported that docetaxel and carboplatin as a NAC regimen for patients with stage IB2–IV disease or recurrent cervical cancer had an overall response rate of 76 % (13/17). The five cases of adenocarcinoma in this cohort had a 100 % RR [20]. Yin et al. retrospectively reviewed 252 consecutive patients with locally advanced disease who were treated with NAC. In their review, 104 patients received nedaplatin and paclitaxel (NP) while the others received PC (paclitaxel and cisplatin). The patients treated with NP NAC had a higher response rate (81 %) compared with the chemotherapy regimen of PC (68 %, $p=0.0267$) [21]. The combination of a platinum and taxane agent appears to be most efficacious, but further study is required to determine the most active regimen in the neoadjuvant setting. NAC followed by surgery is thought to be superior to radiotherapy alone; however, at present, there is no compelling evidence to definitively state that NAC followed by surgery is superior to primary radical surgery alone or primary cisplatin-based chemoradiation alone.

What Is the Role for Adjuvant Chemotherapy Following Surgery?

Adjuvant pelvic radiation following radical hysterectomy is currently given for two sets of indications: firstly, for those patients whose pathology shows involved nodes, disease in the parametria, or positive surgical margins and, secondly, for those patients with negative nodes but high-risk features in the primary tumor (this indication not used universally). The Southwest Oncology Group (SWOG) and the GOG reported the results of a randomized study in 2002 of 243 patients with FIGO stages IA2, IB1, IB2, and IIA cervical cancer who were found to have positive pelvic lymph nodes, parametrial involvement, or positive surgical margins at the time of primary radical hysterectomy and pelvic lymph node dissection [22]. In order to enroll in the trial, patients had to have confirmed negative para-aortic nodes. The patients were randomized to two treatment arms. The first arm consisted of external beam whole-pelvic radiation given concomitantly with intravenous cisplatin at a dose of 70 mg/m^2 followed by a 96-h continuous intravenous infusion of 5-FU (1,000 mg/m^2). The treatment was given every 3 weeks for a total of four cycles. The second treatment arm consisted of external pelvic radiation. The radiation technique in both arms delivered 49.3 Gy to the pelvis utilizing a four-field box technique. Patients with known metastatic disease in high common iliac nodes also received 45 Gy to the para-aortic field. A statistically significant improvement in overall survival was noted in the chemoradiation arm. The reported 3-year survival rate for the 127 patients on the concomitant chemotherapy and radiation arm was 87 %, and the 116 women who were treated with adjuvant radiation alone had a 3-year survival of 77 %. The hazard ratio for overall survival was 1.96 for the patients treated with chemoradiation, and

this was a statistically significant improvement. In 2005, an update on the trial was reported [23]. In those women whose tumors were less than 2 cm, a 5-year overall survival of 82 % was noted when they were treated with concurrent chemotherapy and radiation compared to a 77 % when treated with radiation alone. This thus translated to an absolute improvement in 5-year survival for adjuvant chemotherapy of only 5 %. For those women with tumors larger than 2 cm, there was a statistically significant improvement in 5-year survival of 19 % (58 % vs 77 %). Women who were found to have only one positive node had a relatively modest, nonstatistically significant improvement of 4 % in their 5-year survival with chemoradiation, going from 79 % up to 83 %. However, when two or more lymph nodes were positive, there was a statistically significant 20 % improvement in their overall survival when treated with combined chemotherapy and radiation, going from 55 % up to 75 %. Despite the increased rates of grade 3 and 4 hematologic and gastrointestinal toxicity in the chemoradiation arm, these results established concomitant chemotherapy and radiation as the standard of care for patients in this population.

Patients with negative lymph nodes but high-risk tumor features represent a group where controversy still exists in their management. These high-risk features include size greater than 4 cm, lymphovascular space invasion, and deep stromal invasion. Women who have negative nodes have an 85–90 % survival rate after radical hysterectomy and pelvic lymphadenectomy. However, this patient population results in 50 % of treatment failures, with 70 % of the recurrences occurring in the pelvis [24]. In 1999, the GOG reported the results of a trial of 277 patients with high-risk stage IB cervical cancer who underwent radical hysterectomy and were then randomized to adjuvant whole-pelvic radiation at a dose of 50.4 Gy versus no further treatment [25]. In order to participate in the trial, patients had to have certain risk factors that placed them at a high risk for recurrence. For patients with capillary space lymphatic tumor involvement (CLS) and deep 1/3 stromal invasion, any tumor size was allowed. For patients with CLS and stromal invasion to the middle 1/3, the required tumor size was at least 2 cm. In the setting of CLS and superficial 1/3 stromal invasion, a tumor size of at least 5 cm was required for enrollment. Finally, patients without CLS were required to have deep or middle 1/3 stromal invasion and a tumor size of at least 4 cm. Patients treated with adjuvant radiation had a 15 % recurrence rate at 2 years. Those patients that were randomized to observation had a 2-year recurrence rate of 28 %, and the improvement with radiation was statistically significant. The improvement in recurrence rate came at a cost of increased toxicity. Grade 3 and 4 gastrointestinal or genitourinary toxicity occurred in 6.2 % of patients receiving radiation versus 1.4 % in the observation arm. In 2006, an update of this trial was published that included seven additional recurrences and 19 additional deaths [26]. The patients who were randomized to adjuvant radiation therapy continued to show a statistically significant reduction in their recurrence rate, but the improvement in overall survival with radiation did not reach statistical significance (HR = 0.70, 90 % CI 0.45–1.05; $p = 0.074$). GOG 263 is a phase III trial, currently open, that randomizes patients with intermediate-risk stage I/IIA disease to either RT (IMRT or standard pelvic RT) or concurrent cisplatin (40 mg/m^2 given weekly for six cycles) and RT. Patients are required to have undergone a radical hysterectomy with pelvic lymphadenectomy. The aim of this trial is to determine if there is a survival benefit for chemoradiation in patients with intermediate-risk disease.

The group from Leiden University in the Netherlands identified 51 patients who had two of the three high-risk factors identified by the GOG, among 402 patients who underwent radical hysterectomy for early-stage cervical cancer [27]. They compared 34 patients (66 %) who received postoperative pelvic radiation with 17 patients (33 %) who underwent observation. A statistically significant improvement was noted in 5-year cancer-specific survival in the group treated with pelvic radiation (86 % vs 57 %). Patients with lymph node involvement, parametrial invasion, or positive surgical margins were excluded from the study. There remains no definitive evidence that chemotherapy in addition to radiation therapy improves outcomes in patients with large tumor size, lymphovascular space invasion, and/or deep stromal invasion. Those patients with involved nodes, disease in the parametria, or positive surgical margins derive a survival benefit from concomitant chemotherapy and radiation.

Encouraging results have been reported for women with intermediate and high-risk cervical cancer treated with adjuvant chemotherapy alone following radical hysterectomy. In one report from Japan published in 2006 of 65 consecutive patients with stage IB or IIA disease, intermediate-risk disease was defined as greater than 50 % stromal invasion while high-risk disease was defined as positive surgical margins, parametrial invasion, or lymph node metastases. Three cycles of bleomycin (5 mg in 500 mL of saline administered via continuous infusion for 7 days), vincristine (0.7 mg/m^2 given on day 7), mitomycin C (7 mg/m^2 on day 7), and cisplatin (10 mg/m^2 given on day 1 through 7 over 4 h) were given for patients with intermediate-risk disease while patients with high-risk disease were treated with five cycles. Five-year progression-free survival was 93.3 % for the 30 patients with intermediate-risk tumors and 85.7 % for the 35 patients with high-risk tumors. The locoregional recurrence rate was 3.3 % in the intermediate-risk group and 8.6 % in the high-risk group. The authors of this study argued that the use of adjuvant chemotherapy alone for intermediate and high-risk cervical cancer would allow for the use of higher doses of chemotherapy than would be used with concurrent radiation and also result in lower rates of distant metastasis.

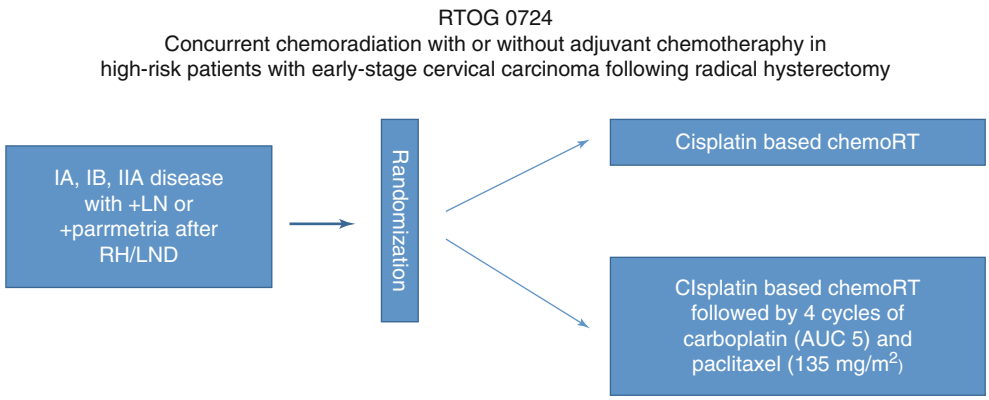

Fig. 8.3 Schema for RTOG 0724, a phase III, randomized controlled trial in early-stage, high-risk patients treated with combined chemotherapy and radiation with or without adjuvant chemotherapy

Chemotherapy alone would also incur less toxicity than concurrent chemoradiation. Additionally, pelvic radiation could then be utilized in the recurrent setting. This approach has not been validated in a prospective, randomized fashion. The RTOG currently is enrolling high-risk early-stage patients in a randomized, phase III trial comparing chemoradiation with or without adjuvant chemotherapy. High risk is defined as positive nodes or positive parametria following radical hysterectomy and the chemotherapy regimen consists of carboplatin and paclitaxel (Fig. 8.3).

Evidence for the Role of Chemoradiation Compared to Radiation Alone in the Treatment of Locally Advanced Cervical Cancer

Locally advanced cervical cancer is not effectively treated with surgery. The usual treatment in these situations is radiation. Three large randomized prospective trials reported in 1999 established concomitant chemotherapy and radiation as the treatment of choice for patients with locally advanced cervical cancer. The GOG reported the results of a phase III randomized study of external beam pelvic radiation and intracavitary radiation combined with concomitant hydroxyurea (3 g by mouth twice weekly) versus weekly cisplatin (40 mg/m^2 for 6 weeks) versus 5-FU (1,000 mg/m^2/day as a 96-h infusion on days 1 and 29)-cisplatin (50 mg/m^2 days 1 and 29) and hydroxyurea (2 mg/m^2 twice weekly for 6 weeks) [HFC] in 526 patients with stages IIB, III, and IVA cervical cancer who had undergone extraperitoneal surgical sampling of the para-aortic lymph nodes. Women with intraperitoneal disease or disease metastatic to the para-aortic lymph nodes were ineligible [28]. The median follow-up was 35 months. The two arms with platinum-containing regimens had statistically improved progression-free survival compared to the regimen with hydroxyurea alone. Seventy percent of the patients in the weekly cisplatin group and 67 % of the patients in the HFC arm were recurrence-free at 2 years. Only 50 % of the patients treated with hydroxyurea alone arm were recurrence-free at 2 years. Grade 3 or 4 hematologic and grade 4 gastrointestinal toxicities were significantly increased with HFC compared with weekly cisplatin or hydroxyurea. While both platinum-containing regimens improved outcomes compared to hydroxyurea alone in patients with locally advanced cervical cancer, the weekly cisplatin arm was better tolerated than HFC. In 2007, the authors published their long-term follow-up from the trial that confirmed the statistically significant improved outcomes with the platinum-containing regimens [29]. The relative risk of progression of disease or death was 0.57 with weekly cisplatin and 0.51 with HFC chemotherapy compared with hydroxyurea alone.

Between 1990 and 1997, the Radiation Therapy Oncology Group (RTOG) randomized 403 patients with locally advanced cervical cancer (stages IIB through IVA or stage IB or IIA with a tumor diameter of at least 5 cm or involvement of pelvic lymph nodes) between 45 Gy of pelvic plus para-aortic radiation and 45 Gy of pelvic radiation with concomitant cisplatin (75 mg/m^2 over 4 h on day 1) and 5-FU (4,000 mg/m^2 over 96 h) [30]. Para-aortic lymph nodes were evaluated by bipedal lymphangiography or retroperitoneal surgical exploration, and if positive, then the patient was excluded. At a median follow-up of 43 months, there were 193 patients in each group eligible for evaluation. There was a statistically significant improvement in 5-year overall and progression-free survival in the chemoradiation arm. The overall survival at 5 years was 73 % among patients undergoing chemoradiation compared to 58 % in the group of patients treated with radiation alone. Progression-free 5-year survival was 67 % in the chemoradiation arm and 40 % in the radiation alone arm. The rates of distal metastases and locoregional recurrences were significantly higher among patients treated with radiation alone. While there was a higher rate of acute grade 3 and 4 toxicities in the combined therapy group, these side effects were usually self-limited. Additionally, there was no significant difference in the rates of late toxicities. In 2004, an update of the trial was published. Patients with stage IB–IIB disease continued to

demonstrate a statistically significant improvement in overall survival and progression-free survival when treated with combined chemotherapy and radiation versus radiation alone. Patients with stage III–IVA disease continued to have a statistically significant improvement in their progression-free survival and a trend towards an improved overall survival. Similar to the initial publication, there were no significant differences in the toxicity profile between the different treatment arms [31].

The GOG, in collaboration with the SWOG, randomized 388 women with stage IIB, III, or IVA disease and negative para-aortic nodes based on surgical sampling to two different treatment arms. The first arm was treated with pelvic radiation with hydroxyurea (80 mg/kg given twice weekly), and the second arm was treated with standard pelvic radiation with 5-fluorouracil (4,000 mg/m^2 total dose each cycle) and cisplatin (50 mg/m^2) [32]. While the rate of severe leucopenia was higher in the hydroxyurea group, both progression-free survival and overall survival were significantly higher in the group treated with cisplatin and 5-FU in addition to radiation.

The three trials described above helped to bring about a sea change in the management of locally advanced cervical cancer. However, two other randomized trials did not show a benefit for concomitant chemotherapy and radiation in these patients. In 2002, the National Cancer Institute of Canada published their results of 259 patients with stage IB–IVA cervical SCC who were randomly assigned to external beam radiation plus brachytherapy or radiation and concurrent cisplatin (40 mg/m^2 weekly) [33]. While the 5-year survival of the patients in the chemoradiation arm was 62 % and the survival rate was 58 % in the radiation alone arm, this difference failed to reach statistical significance. In 1997, investigators from Taiwan published the results of their randomized trial of 122 patients with bulky IIB or IIIB cervical cancer [34]. Patients were randomized to treatment with pelvic radiation with or without a multi-agent chemotherapy regimen. The chemotherapy consisted of a combination of cisplatin, vinblastine, and bleomycin given on days 1 through 4 and then days 22 through 25 of the radiation course followed by two additional cycles of chemotherapy. At a median follow-up of 47 months, the arm treated with concomitant chemotherapy and radiation did not have a significant improvement in their 3-year progression-free (52 vs 53 %) or overall survival (62 vs 65 %) compared to the arm treated with radiation alone.

An individual patient data Cochrane meta-analysis, which was published in 2010, included 13 trials that randomly assigned women with cervical cancer confined to the pelvis to concurrent chemotherapy and radiation versus radiation alone following hysterectomy [35]. Combined chemotherapy and radiation was associated with a statistically significant 19 % reduction in the risk of death as compared to radiation alone. This significant decrease in the risk of death translated into an absolute improvement in 5-year survival from 60 to 66 %, a 22 % improvement in progression-free survival, and a significant decrease in both local and distant recurrence rates. Clinical benefit was demonstrated across all disease stages; however, the most dramatic survival benefit was noted in stages IA–IIA. The absolute survival improvement was 6 % and relapse-free survival improvement 8 %, and also showed efficacy of non-cisplatin-based regimens [36].

To optimize the safety and efficacy of cisplatin-based chemoradiation, two strategies are being actively investigated. The first is to increase the intensity of concurrent chemotherapy. To address this, Umayahara et al. performed a phase I study evaluating chemoradiation that included the combination of cisplatin and paclitaxel [37]. These researchers concluded that weekly administration of cisplatin 30 mg/m^2 and paclitaxel 50 mg/m^2 with definitive radiotherapy is tolerable and safe. A multi-institutional phase II study utilizing the above doses is currently under way in Japan. The second strategy is to deliver an additional systemic chemotherapy regimen in addition to concomitant chemotherapy and radiation.

The GCIG and Korean Gynecologic Oncology Group are currently investigating the effect of triweekly cisplatin delivered at a dose of 75 mg/m^2 with concurrent radiation versus 40 mg/m^2 weekly in patients with locally advanced disease in a randomized, phase III trial (Fig. 8.4). The impetus for this trial comes from a recently reported randomized, phase II study of 102 patients comparing the same treatment arms from the same group of investigators. Triweekly cisplatin was found to improve the 5-year overall survival compared

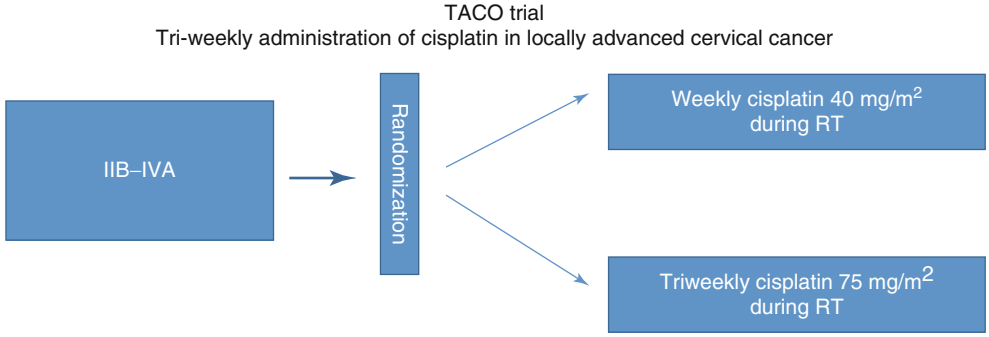

Fig. 8.4 Schema for TACO trial, a phase III, randomized controlled trial in patients with locally advanced disease randomized to receive either weekly or triweekly cisplatin as concomitant chemotherapy with radiation

to weekly cisplatin (89 % vs 66 % [$p=0.03$]). This survival improvement came with the added benefit of significantly lower rates of grade 3/4 neutropenia (22 % vs 40 % [$p<0.05$]) [38]. Treatment delivered every 3 weeks compared to weekly is, obviously, less expensive and easier to administer, and this is significant in settings where resources are limited.

Combining Chemoradiation and Adjuvant Chemotherapy

Investigators from Mexico have recently published the results of a phase III trial comparing the effect of the addition of gemcitabine to cisplatin during chemoradiation and then the addition of gemcitabine to cisplatin for adjuvant chemotherapy on PFS in patients with stage IIB–IVA disease. The experimental arm consisted of patients treated with cisplatin 40 mg/m^2 and gemcitabine 125 mg/m^2 weekly for 6 weeks with concurrent external beam radiotherapy (50.4 Gy in 28 fractions), followed by brachytherapy (30–35 Gy in 96 h), and then two adjuvant 21-day cycles of cisplatin (50 mg/m^2 on day 1) plus gemcitabine (1,000 mg/m^2 on days 1 and 8). The control arm consisted of patients treated with cisplatin and concurrent XRT followed by brachytherapy with the same dose schedule as in the experimental arm. A total of 515 patients were enrolled. Patients in the experimental arm had a significant improvement in their 3-year PFS (74.4 % vs 65.0 %, $p=.029$), but this improvement came at the expense of a dramatic increase in the rates of grade 3 and 4 toxicities (86.5 % vs 46.3 %, $p<.001$) along with two likely treatment-related deaths in the experimental arm [39].

The Australia New Zealand Gynaecological Oncology Group (ANZGOG) is currently leading the OUTBACK trial that is designed to evaluate the therapeutic value of adding an adjuvant chemotherapy regimen to standard cisplatin-based chemoradiation (Fig. 8.5). Concern has been raised regarding the additional toxicity from the additional chemotherapy and if the additive toxicity would preclude patients from receiving the appropriate treatment. A phase I study designed to determine the optimal dose of adjuvant chemotherapy will begin soon in Japan. Finally, the third strategy is to evaluate chemotherapy options associated with less toxicity. Nedaplatin (cis-diammine-glycoplatinum) is a derivative of cisplatin developed in Japan. Different small series have demonstrated that this agent appears to have similar efficacy with lower renal and gastrointestinal toxicities compared to cisplatin [40]. Performance of non-inferiority randomized trial with nedaplatin could help identify less toxic chemoradiation regimens.

Is There Benefit of Adding Chemotherapy to Extended Field Radiation for Patients with Known Para-Aortic Disease?

An additional area of controversy is the appropriate treatment of patients with para-aortic nodal metastases. The three previously discussed landmark randomized trials regarding chemoradiation for locally advanced disease specifically excluded these patients from their analysis. Three cooperative group trials have been published examining the effect of extended field radiation in addition to chemotherapy in women with positive para-aortic nodes. In 1998, the RTOG published the results of their phase II trial of 30 patients with clinical stage I through IV disease and positive para-aortic nodes who received twice daily extended field radiation in addition to intracavitary brachytherapy with two to three cycles of concomitant chemotherapy [41]. The chemotherapy regimen consisted of cisplatin (75 mg/m^2 given on days 1 and 22) and 5-FU (1,000 mg/m^2 daily on days 1 through 4 and days 22 through 25). The total external radiation doses were 24–48 Gy to the whole pelvis, 12–36 Gy parametrial boost, and 48 Gy to the para-aortics with an additional boost to a total dose of 54–58 Gy to the known metastatic para-aortic site. One or two intracavitary applications were performed to deliver a total minimum dose of 85 Gy to point A. The long-term follow-up to this trial was published in 2001, and the overall survival estimates were 46 % at 2 years and 29 % at 4 years. The probability of local-regional failure was 40 % at 1 year and 50 % at 2 and 3 years [42]. However, there were unacceptably high rates of acute and late grade 3 or 4 gastrointestinal toxicity (50 and 34 %, respectively). Unacceptably high rates of both acute and late toxicity were

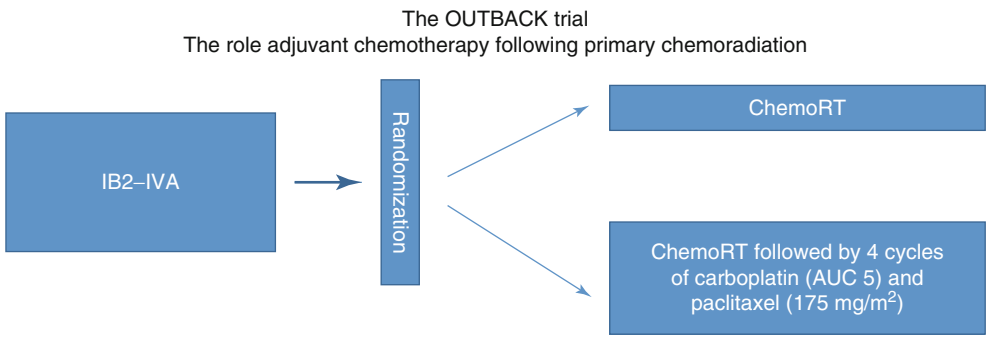

Fig. 8.5 Schema for the OUTBACK trial, a phase III, randomized controlled trial in patients with locally advanced disease treated with combined chemotherapy and radiation and then randomized to receive either adjuvant chemotherapy or no further treatment

also noted in a subsequent phase II, two-arm RTOG trial published in 2007 in which 26 women with para-aortic or high common iliac nodes were treated with extended field radiation delivered at a dose of 45 Gy with 1.8 Gy per fraction in addition to intracavitary radiation and concomitant weekly cisplatin (40 mg/m^2) [43]. Patients in the second treatment arm also received amifostine before each fraction of radiation in an effort to reduce toxicity. In a report of results from the arm with patients who were not treated with amifostine, rates of acute and late grade 3 or 4 gastrointestinal and hematologic toxicity were 81 and 40 %. In the second arm of the study, after a median 23-month follow-up, 87 % of patients experienced grade 3 or 4 acute toxicities and 20 % experienced grade 3 or 4 late toxicities [44]. Similar oncologic outcomes were noted in a GOG study of radiation delivered with standard fractionation and concomitant chemotherapy consisting of 5-FU (1,000 mg/m^2/day for 96 h) and (cisplatin 50 mg/m^2 in weeks 1 and 5) in 95 women with positive para-aortic nodes [45]. The 3-year overall and progression-free survival rates for the entire group were 39 and 34 %, respectively. Survival rates for those with stage I and II disease were 50 and 39 %, respectively. The dose to the para-aortic nodes was lower than the dose in the previously discussed RTOG study (45 Gy delivered daily at 1.5 Gy per fraction), resulting in lower rates of gastrointestinal toxicity. While increased rates of acute toxicity have been consistently demonstrated in regimens utilizing concomitant chemotherapy and radiation, the survival advantage shown in the majority of randomized trials argues in favor of this treatment modality in this high-risk subset.

Chemotherapy for Recurrent or Metastatic Cervical Cancer

Women with widely metastatic and/or recurrent cervical cancer represent a difficult group of patients to treat. This treatment dilemma often arises in the setting of recurrent disease, especially given the lower response rate in those patients previously treated with concurrent chemotherapy. It is unclear if treatment with chemotherapy offers any meaningful survival advantage when compared to supportive care. There are no randomized trials that have demonstrated overwhelming survival benefit for chemotherapy in this setting. Chemotherapy is most often given with a palliative intent in this situation. Fifty-eight cytotoxic agents have been tested in recurrent or advanced cervical cancer, and 21 of them have had clinical activity as defined by a response rate of 15 % or greater [46]. The most active single agents have been cisplatin, paclitaxel, topotecan, vinorelbine, and ifosfamide [47]. Multiple platinum-based regimens have been tested, and improved response rates have been demonstrated for the combinations of cisplatin and ifosfamide (31 %) and for cisplatin and paclitaxel (36 %) [48, 49]. The only trial that has shown a statistically significant improvement in survival for multi-agent chemotherapy over cisplatin alone was published by the GOG in 2005 [50]. This trial randomly assigned 356 women with stage IVB recurrent or persistent cervical cancer to treatment with three different chemotherapy protocols. The treatment arm consisting of methotrexate, vinblastine, doxorubicin, and cisplatin was closed early due to four treatment-related deaths in the 63 patients that had been treated. Compared to cisplatin alone (50 mg/m^2 given on day 1 every 3 weeks), the group treated with a combination of cisplatin and topotecan (0.75 mg/m^2 days 1–3 every 3 weeks) had a statistically significant improvement in response rate (27 vs 13 %), progression-free survival (4.6 vs 2.9 months), and median overall survival (9.4 vs 6.5 months). Rates of grade 3 and 4 hematologic and gastrointestinal toxicities were overwhelmingly higher in the group treated with cisplatin and topotecan.

In 2009, the GOG published the results of a phase III trial comparing four different cisplatin-containing doublets in stage IVB, recurrent or persistent cervical cancer. There were 513 enrolled patients who were randomized to therapy with cisplatin (50 mg/m^2 given on day 1 every 3 weeks) along with either paclitaxel (135 mg/m^2 given on day 1 every 3 weeks), vinorelbine (30 mg/m^2 given on day 1 and day 8), topotecan (0.75 mg/m^2 given on day 1, 2, and 3 every 3 weeks), or gemcitabine (1,000 mg/m^2 given on day 1 and 8 every 3 weeks). While there was a trend towards an improved RR, PFS, and OS for the cisplatin and paclitaxel doublet, there was no significant difference among the four arms. The toxicities in the four different arms were comparable, and the authors note that the different dosing schedules should be taken into account when deciding on the individual regimen [51]. The GOG has recently closed a phase III trial (GOG 240) of 452 advanced and recurrent cervical cancer patients randomized to treatment with paclitaxel and cisplatin, with and without bevacizumab, or topotecan and paclitaxel, with and without bevacizumab. Those patients who were treated with chemotherapy alone had a median overall survival of 13.3 months, and the patients who were treated with a combination of chemotherapy and bevacizumab had a median overall survival of 17 months, and this improvement was statistically significant. The Japanese GOG is currently enrolling a similar group of patients in a trial comparing cisplatin and paclitaxel to carboplatin and paclitaxel.

What Is the Evidence Supporting the Use of Targeted Therapy and Chemotherapy for Recurrent Cervical Cancer?

Numerous agents that target the vascular endothelial growth factor (VEGF) pathway are in clinical development, including agents targeting the VEGF ligand and agents targeting the

VEGF receptor. Among them, bevacizumab is the most promising drug in gynecologic cancer. A phase II trial from the GOG of bevacizumab in the treatment of 46 patients with persistent or recurrent cervical cancer was reported in 2009. Median PFS was 3.4 months and median OS was 7.3 months. These results compare favorably with historical controls. Bevacizumab seems to be well tolerated and active in second and third line treatment with recurrent cervical cancer [52]. RTOG 0417 was a phase II study of 49 patients treated with bevacizumab in combination with concurrent radiotherapy and cisplatin in stage IIB–IIIB disease or IB–IIA disease with biopsy-proven pelvic nodal metastasis and/or tumor size of at least 5 cm [53]. Bevacizumab was administered intravenously every 2 weeks during treatment at a dose of 10 mg/kg. The primary endpoint of the trial was toxicity, and per the preliminary results, reported in 2012, there were no serious adverse effects of treatment. Survival data has not yet matured.

The GOG reported a phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer in 2010. These agents are tyrosine kinase inhibitors that target the VEGF receptor, platelet-derived growth factor receptor, and epidermal growth factor receptor. In this randomized trial of 230 patients, pazopanib monotherapy demonstrated improved progression-free survival and a favorable toxicity profile [54].

Conclusions and Future Directions

In summary, while the use of chemotherapy in the management of cervical cancer has undergone a significant evolution over the past 15 years, many questions remain and are the subject of current randomized trials. International collaboration remains a focus for the completion of these trials. It is hoped that definitive results will answer questions regarding the efficacy of neoadjuvant and adjuvant chemotherapy, concurrent chemotherapy in intermediate-risk disease, and alternative dosing strategies for concurrent cisplatin and radiation. Current trials focus on pelvic-confined disease, and specific investigations of therapies directed at para-aortic positive patients are needed. Future directions should also include the continued exploration of the biology of cervical cancer with the hope of identifying targets for therapeutic agents.

Concluding Comments

- International collaboration to complete current randomized trials.
- Develop innovative trials for patients with para-aortic lymph node metastasis.
- Continue research to develop targeted agents.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. 2011;61(4):212.
2. Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2000: cancer incidence, mortality, and prevalence worldwide. Version 1.1, IARC Cancer Base No. 5. Lyon: IARC Press; 2001.
3. Kolstad P. Follow-up study of 232 patients with stage IA1 and 411 patients with stage IA2 squamous cell carcinoma of the cervix (microinvasive carcinoma). Gynecol Oncol. 1989;33:265–72.
4. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe EW, Suggs CL, et al. *Cisplatin*, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med. 1999;340:1154–61.
5. Yamamoto K, Izumi R, Hasegawa K. Adjuvant oral 5-fluorouracil for cervical cancer: Japanese gynecologic oncology group report. Int J Oncol. 2004;24:1175–9.
6. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys. 2003;55:1226–32.
7. Hosaka M, Watari H, Kato T, et al. Clinical efficacy of paclitaxel/cisplatin as an adjuvant chemotherapy for patients with cervical cancer who underwent radical hysterectomy and systematic lymphadenectomy. J Surg Oncol. 2012;105:612–6. doi:10.1002/jso.22136.
8. Takeshima N, Umayahara K, Fujiwara K, et al. Treatment results of adjuvant chemotherapy after radical hysterectomy for intermediate- and high-risk stage IB-IIA cervical cancer. Gynecol Oncol. 2006;103:618–22.
9. Matsumura M, Takeshima N, Ota T, et al. Neoadjuvant chemotherapy followed by radical hysterectomy plus postoperative chemotherapy but no radiotherapy for stage IB2-IIB cervical cancer–irinotecan and platinum chemotherapy. Gynecol Oncol. 2010;119:212–6.
10. Tierney J, Neoadjuvant Chemotherapy for Cervical Cancer Meta-analysis Collaboration. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. Eur J Cancer. 2003;39:2470–86.
11. Benedetti-Panici P, Greggi S, Colombo A, Amoroso M, Smaniotto D, Giannarelli D, Amunni G, Raspagliesi F, Zola P, Mangioni C, Landoni F. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. J Clin Oncol. 2002;20:179–88.
12. Chang TC, Lai CH, Hong JH, Hsueh S, Huang KG, Chou HH, Tseng CJ, Tsai CS, Chang JT, Lin CT, Chang HH, Chao PJ, Ng KK, Tang SG, Soong YK. Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. J Clin Oncol. 2000;18:1740–7.
13. Sardi JE, Giaroli A, Sananes C, Ferreira M, Soderini A, Bermudez A, Snaidas L, Vighi S, Gomez Rueda N, di Paola G. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous carcinoma of the cervix: the final results. Gynecol Oncol. 1997;67:61–9.
14. Napolitano U, Imperato F, Mossa B, Framarino ML, Marziani R, Marzetti L. The role of neoadjuvant chemotherapy for squamous cell cervical cancer (Ib-IIIb): a long-term randomized trial. Eur J Gynaecol Oncol. 2003;24:51–9.
15. Eddy GL, Bundy BN, Creasman WT, Spirtos NM, Mannel RS, Hannigan E, O'Connor D. Treatment of ("bulky") stage IB cervical cancer with or without neoadjuvant vincristine and cisplatin prior to radical hysterectomy and pelvic/para-aortic lymphadenectomy: a phase III trial of the gynecologic oncology group. Gynecol Oncol. 2007;106:362–9.

16. Chen H, Liang C, Zhang L, Huang S, Wu X. Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: randomized study. Gynecol Oncol. 2008;110:308–15.
17. Cai HB, Chen HZ, Yin HH. Randomized study of preoperative chemotherapy versus primary surgery for stage IB cervical cancer. J Obstet Gynaecol Res. 2006;32:315–23.
18. Duenas-Gonzalez A, Lopez-Graniel C, Gonzalez-Enciso A, Mohar A, Rivera L, Mota A, Guadarrama R, Chanona G, De La Garza J. Concomitant chemoradiation versus neoadjuvant chemotherapy in locally advanced cervical carcinoma: results from two consecutive phase II studies. Ann Oncol. 2002;13:1212–9.
19. Ryu HS, Kang SB, Kim KT, Chang KH, Kim JW, Kim JH. Efficacy of different types of treatment in FIGO stage IB2 cervical cancer in Korea: results of a multicenter retrospective Korean study (KGOG-1005). Int J Gynecol Cancer. 2007;17:132–6.
20. Nagao S, Fujiwara K, Oda T, Ishikawa H, Koike H, Tanaka H, Kohno I. Combination chemotherapy of docetaxel and carboplatin in advanced or recurrent cervix cancer. A pilot study. Gynecol Oncol. 2005;96:805–9.
21. Yin M, Zhang H, Li H, Li X, Liu Y, Chen X, Lou G, Li K. The toxicity and long-term efficacy of nedaplatin and paclitaxel treatment as neoadjuvant chemotherapy for locally advanced cervical cancer. J Surg Oncol. 2012;105:206–11.
22. Peters 3rd WA, Liu PY, Barrett RJ, Gordon Jr W, Stock R, Berek JS, et al. *Cisplatin* and 5-FU plus radiation therapy are superior to radiation therapy as adjunctive in high- risk early-stage carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: report of a phase III intergroup study. J Clin Oncol. 2000;18:1606–13.
23. Monk BJ, Wang J, Im S, Stock RJ, Peters III WA, Liu PY, et al. Rethinking the use of radiation and chemotherapy after radical hysterectomy: a clinical-pathologic analysis of a Gynecologic Oncology Group/Southwest Oncology Group/Radiation Therapy Oncology Group trial. Gynecol Oncol. 2005;96:721–8.
24. Thomas GM, Dembo AJ. Is there a role for adjuvant pelvic radiotherapy after radical hysterectomy in early stage cervical cancer? Int J Gynecol Cancer. 1991;1:1–8.
25. Sedlis A, Bundy BN, Rotman M, Lentz S, Muderspach LI, Zaino R. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecol Oncol. 1999;73:177–83.
26. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys. 2006;65:169–76.
27. Pieterse QD, Trimbos JBMZ, Dijkman A, Creutzberg CL, Gaarenstroom KN, Peters AAW, Kenter GG, et al. Postoperative radiation therapy improves prognosis in patients with adverse risk factors in localized, early-stage cervical cancer: a retrospective comparative study. Int J Gynecol Cancer. 2006;16:1112–8.
28. Rose PG, Bundy B, Watkins EB, Thigpen T, Deppe G, Maiman MA, et al. Concurrent *cisplatin*-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med. 1999;340:1144–53.
29. Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, et al. Long term follow-up of a randomized trial comparing concurrent single agent *cisplatin* or *cisplatin*-based combination chemotherapy for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol. 2007;25:1–7.
30. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and paraaortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340:1137–43.
31. Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, Rotman M, Gershenson D, Mutch DG. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90–01. J Clin Oncol. 2004;22:872–80.
32. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler Jr WC, et al. Randomized comparison of *fluorouracil* plus *cisplatin* vs *hydroxyurea* as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative paraaortic nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol. 1999;17:1339–48.
33. Pearcey R, Brundage M, Drouin P, Jeffrey J, Johnston D, Lukka H, MacLean G, Souhami L, Stuart G, Tu D. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. J Clin Oncol. 2002;20(4):966.
34. Tseng CJ, Chang CT, Lai CH, Soong YK, Hong JH, Tang SG, Hsueh S. A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix. Gynecol Oncol. 1997;66(1):52.
35. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010;(1):CD008285.
36. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol. 2008;26:5802–12.
37. Umayahara K, Takeshima N, Nose T, Fujiwara K, Sugiyama Y, Utsugi K, Yamashita T, Takizawa K. Phase I study of concurrent chemoradiotherapy with weekly cisplatin and paclitaxel chemotherapy for locally advanced cervical carcinoma in Japanese women. Int J Gynecol Cancer. 2009;19(4):723–7.
38. Ryu SY, Lee WM, Kim K, Park S, Kim BJ, Kim MH, Choi SC, Cho CK, Nam BH, Lee ED. Randomized clinical trial of weekly vs triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2011;81(4):e577–81.
39. Dueñas-González A, Zarbá JJ, Patel F, Alcedo JC, Beslija S, Casanova L, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol. 2011;29(13):1678–85.
40. Mabuchi S, Ugaki H, Isohashi F, Yoshioka Y, Temma K, Yada-Hashimoto N, Takeda T, Yamamoto T, Yoshino K, Nakajima R, Kuragaki C, Morishige K, Enomoto T, Inoue T, Kimura T. Concurrent weekly nedaplatin, external beam radiotherapy and high-dose-rate brachytherapy in patients with FIGO stage IIIb cervical cancer: a comparison with a cohort treated by radiotherapy alone. Gynecol Obstet Invest. 2010;69:224–32.
41. Grigsby PW, Lu JD, Mutch DG, Kim RY, Eifel PJ. Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: Phase II study of the Radiation Therapy Oncology Group 92–10. Int J Radiat Oncol Biol Phys. 1998;41(4):817.
42. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92–10: cervical cancer with positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys. 2001;51(4):982.
43. Small Jr W, Winter K, Levenback C, Iyer R, Gaffney D, Asbell S, Erickson B, Jhingran A, Greven K. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. Int J Radiat Oncol Biol Phys. 2007;68(4):1081.

44. Small Jr W, Winter K, Levenback C, Iyer R, Hymes SR, Jhingran A, Gaffney D, Erikson B, Greven K. Extended field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of Arm II of RTOG 0116. Int J Gynecol Cancer. 2011;21(7):1266–75.
45. Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG, Connelly P. Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group study. Int J Radiat Oncol Biol Phys. 1998;42(5):1015.
46. Thigpen T. The role of chemotherapy in the management of carcinoma of the cervix. Cancer J. 2003;9:425–32.
47. Long III HJ. Management of metastatic cervical cancer: review of the literature. J Clin Oncol. 2007;25:2966–74.
48. Omura GA, Blessing JA, Vaccarello L, Berman ML, Clarke-Pearson DL, Mutch DG, Anderson B. Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol. 1997; 15(1):165.
49. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF, Rocereto TF. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2004;22(15):3113.
50. Long 3rd HJ, Bundy BN, Grendys Jr EC, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA, Fiorica JV, Gynecologic Oncology Group Study. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol. 2005;23(21):4626.
51. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of 4 Cisplatin containing doublet combinations in stage IVb, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2009;27:4649–55.
52. Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol. 2009;27:1069–74.
53. Schefter TE, Winter K, Kwon JS, et al. A phase II study of bevacizumab in combination with definitive radiotherapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma: preliminary results of RTOG 0417. Int J Radiat Oncol Biol Phys. 2012;83:1179–84.
54. Monk BJ, Mas Lopez L, Zarba JJ, et al. Phase II, open-label study of pazopanib or lapatinib monotherapy compared with pazopanib plus lapatinib combination therapy in patients with advanced and recurrent cervical cancer. J Clin Oncol. 2010;28:3562–9.