*Anti-Cancer Drugs 2001,* **12,** pp. 853–858

## Report

# Phase I–II study of neoadjuvant chemoradiotherapy followed by radical surgery in locally advanced cervical cancer

**Hiroshi Tsuda,[1] Masahiro Tanaka,[2] Takao Manabe,[2] Shinichi Nakata,[1] Osamu Ishiko[3] and Kumio Yamamoto[1]**

Departments of [1]Obstetrics and Gynecology, [2]Radiology, Osaka City General Hospital, Miyakojima, Osaka 534-0021, Japan. [3]Department of Obstetrics and Gynecology, Osaka City University Medical School, Osaka, Japan.

**The usefulness of neoadjuvant chemotherapy (NAC) regimens has been reported; however, the effect of NAC for advanced stages (especially stage III–IVA) is thought to be insufficient. We conducted a phase I–II study of neoadjuvant chemoradiotherapy consisting of intra-arterial (i.a.) infusion of carboplatin and intracavitary brachytherapy in patients with locally advanced cervical cancer to achieve the new NAC method. Sixteen eligible patients included those with previously untreated stage IIB, III or IVA cancer with bulky tumor. Brachytherapy using iridium-192 was performed with concurrent i.a. chemotherapy with carboplatin (200, 300 and 400 mg/m$^2$). Treatment was repeated every 4 weeks for a total of two cycles. Both hematologic and non-hematologic toxicities were generally mild. Grade 4 hematologic toxicity was observed in 12.5% and there were no grade III or IV non-hematologic toxicities. The optimal dose of carboplatin was determined to be 400 mg/m$^2$. Among 16 patients, six showed complete response (37.5%) and nine showed partial response (56.3%), for an overall response rate of 93.8%. All 15 responding patients underwent radical surgery with a pelvic lymphadenectomy and postoperative radiotherapy. The combination of brachytherapy and i.a. chemotherapy with carboplatin is a promising regimen for NAC in locally advanced cervical cancer. [© 2001 Lippincott Williams & Wilkins.]**

*Key words*: Brachytherapy, carboplatin, cervical cancer, chemoradiation, neoadjuvant chemotherapy.

## Introduction

Advanced cervical cancer is a common cancer worldwide and it is the second major cause of death in women.[1] Specifically, the survival rate of patients with stage IIIB cervical cancer has been consistently lower than 50%.[2] Radiation therapy is a standard treatment for women with locally advanced cervical cancer. The bulk of disease is a major factor limiting the curative probability of pelvic radiation therapy.[3–5] Recently, the concurrent use of cisplatin and pelvic irradiation in patients with advanced disease seemed to improve local control and overall survival in phase II trials, as well as in reported phase III trials.[6–9] However, Morris reported that the overall survival had not been improved in stage III–IVA patients.[8] In Keys's report, only patients with stage 1B were included.[7] In another two reports, the number of stage III–IVA patients was small and the results of these patients were unclear. The benefit of chemoradiation for stage III–IVA patients is thought to be controversial.

Recently, platinum compound-based chemotherapy has been used as neoadjuvant chemotherapy (NAC) to treat patients with locally advanced cervical cancer and it is presently the most effective single agent against carcinoma of the cervix. Many pilot studies indicate increased tumor-free survival by NAC followed by surgery.[10–16] NAC followed by radical surgery may be an alternative modality in the management of locally advanced disease. The usefulness of NAC regimens has been reported; however, the effect of NAC for advanced stages (especially stage III–IVA) is thought to be insufficient.[16–19] Carboplatin can interact with ionizing radiation, resulting in a potentiation of radiation-induced cell kill.[20] More than 40% of the total tumor dose is given directly with intracavitary applicators in an attempt to reduce the dose to normal tissues (rectum and bladder). The combination of

Correspondence to H Tsuda, Department of Obstetrics & Gynecology, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima, Osaka 534-0021, Japan.
Tel: (+81) 6 6929 1221; Fax: (+81) 6 6929 2041;
E-mail: tsud777@ocgh.hospital.city.osaka.jp

carboplatin and intracavitary brachytherapy may have a synergistic effect in cervical cancer. In this study, we conducted a phase I–II trial of radical surgery following neoadjuvant chemoradiotherapy consisting of intra-arterial (i.a.) infusions of carboplatin and intracavitary brachytherapy in patients with locally advanced cervical cancer.

## Materials and methods

### Patient selection

Patients with histologically documented, surgically unresectable stage IIB, IIIA, IIIB or IVA cancer with bulky tumor were enrolled in this study. Bulky cervical tumor was defined as a visible cervical tumor with the largest diameter $\geqslant 4$ cm. None of the patients was previously treated with any treatment and all patients were required to have measurable disease. The nature and purpose of the study were fully explained to each patient. All patients signed an informed consent approved by the institutional review boards of Osaka City General Hospital. Pretreatment evaluation included history and physical examination, biopsy and evaluation of tumor extent, complete hematology and chemistry profiles, chest X-ray, i.v. pyelography, barium enema examination, and tumor imaging by means of contrast-enhanced computerized tomography (CT) of the pelvis and abdomen. Criteria for admission were as follows: biopsy-proven cervical carcinoma, age $<75$ years, an Eastern Cooperative Oncology Group performance status of 0–2 and no distant metastases. Patients were also required to meet all of the following laboratory criteria: WBC count $\geqslant 3000/mm^3$ or absolute neutrophil count $\geqslant 1500/mm^3$, platelet count $\geqslant 100\,000/mm^3$, serum transaminase levels $\geqslant 60$ IU/ml, total serum bilirubin level $\geqslant 1.5$ mg/dl, serum creatinine level $\geqslant 1.5$ mg/dl and blood urea nitrogen level $\geqslant 20$ mg/dl. Also deemed necessary were adequate cardiopulmonary function that could tolerate radical hysterectomy and the absence of concurrent malignancy or history of other cancer. The patients who had grossly positive nodes on CT were excluded.

### Brachytherapy regimen

All patients received two iridium-192 (Micro Selectron-HDR) applications 4 weeks apart. A standard applicator set (modified Fletcher-Suit applicator using non-shielded Manchester ovoids) was used. The total dose calculated to point A was 7 Gy. Concomitant i.a. chemotherapy with carboplatin was given. All patients underwent brachytherapy and chemotherapy on day 1.

### Chemotherapy regimen

All patients received arterial infusion chemotherapy using a totally implantable catheter port system. Using femoral artery access, the catheter (Anthron P-U catheter; Toray Medical, Tokyo, Japan) was placed in both internal iliac arteries. Each catheter was connected with an implantable port (Bard MRI Port; Bard Access Systems) which was placed s.c. at the bilateral inguinal region. Both superior and inferior gluteal arteries had been embolized using metallic coils. Pelvic arteriography was performed during catheterization procedures to assess catheter position and tumor perfusion. This procedure was performed by an experienced radiologist.

Carboplatin was prepared by diluting in 200 ml saline. After a 5-$HT_3$ serotonin receptor antagonist was administered, carboplatin was given as a 30-min i.a. infusion simultaneously with brachy-therapy using the infusion pump, followed by a post-hydration of 1000 ml saline. Dose escalation was performed. The starting dosage was 200 $mg/m^2$ every 4 weeks. At least three new patients were to be recruited for each dose level. If all three patients at any dose level developed dose-limiting toxicities (DLT), the study was terminated. Three additional patients were treated at a dose level if one of the first three patients exhibited DLT. If at least four of six patients developed DLT at this level, then a maximum tolerated dose (MTD) was said to have been reached. The following dose levels were evaluated: 200, 300 and 400 $mg/m^2$. Several reports demonstrated that the MTD of carboplatin was 440–550 $mg/m^2$.[21–24] In this study, the maximum dose level was determined to be 400 $mg/m^2$. DLTs were defined as: (i) non-hematological toxicities grade 3 or 4 (excluding nausea, vomiting and alopecia) and (ii) hematological toxicity grade 4 (excluding anemia). The phase II study was performed one level below the MTD. The primary endpoint of the phase II study was response rate and toxicity. The phase II study was designed to detect a response rate (partial plus complete response) of 90% compared with a minimal, clinically meaningful response rate of 50%. The designed protocol study specified that the total accrual goal would be at least 10 assessable patients. This study design provided a statistical power of at least 90% to detect a response rate of 90%. The primary statistical analysis consisted of an estimation of the complete and partial response rates. The response rate was calculated as the ratio of the number of complete and partial responders to the total number of assessable patients. A 95% confidence interval for the response was computed based on the binomial distribution function. We also tested the hypothesis

that the response rate was greater than 50% by means of an exact test based on the binomial distribution function.

### Operative treatment and postoperative irradiation

The two courses of combined chemo-brachytherapy was followed, when feasible, by radical hysterectomy (type III hysterectomy) with lymphadenectomy. All patients underwent postoperative external beam irradiation (1.8 Gy per fraction, Box technique, four fields treated daily, 5 days a week) up to 50.4 Gy with mid-line block at 36 Gy.

### Evaluation of response and toxicity

Cervical tumor measurements using contrast-enhanced CT were obtained at the completion of every treatment cycle. Measurement of response was based on the product of the two largest perpendicular diameters. Criteria for tumor response were as follows: complete response (CR) was defined as the complete disappearance of all known disease with no development of new disease. Partial response (PR) was defined as a $\geqslant$50% reduction of the sum of products of measurement of new lesions. Progressive disease (PD) was defined as a $\geqslant$25% increase in the sum of the products of all indicator lesions, or reappearance of any lesion that had disappeared, or appearance of any new lesion. Stable disease (SD) was defined as any situation that did not quality as response or progression. Measurements were performed by an experienced radiologist who was not aware of patient s information.

Toxicity evaluation was based on WHO criteria. Complete blood cell counts were performed at least twice weekly. Serum chemistries and liver function tests were obtained before every treatment cycle.

## Results

### Patient characteristics

From March 1996 to August 2000, 16 consecutive patients with stage IIB–IVA bulky cervical carcinoma were admitted to the study (IIB, 5; IIIB, 10; IVA, 1; squamous cell carcinoma, 15; adenocarcinoma, 1). The stage IV patient was proven to have bladder invasion by bladder biopsy. The median tumor diameter was 5.0 cm (range 4.0–8.6) and median age was 60 years (range 36–74). All patients had an ECOG performance status of 0 or 1.

### Toxicity

A total of 32 cycles of chemotherapy were given during this study. The schedule of i.a. carboplatin infusion and intracavitary brachytherapy was well tolerated. The major toxicity was neutropenia; however, it was mild (Table 1). From the phase I study, the dose of carboplatin used for the phase II study was 400 mg/m$^2$. Hematologic toxicity at each dose level is listed in Table 1 and ranked according to WHO toxicity using the worst toxicity on record for individual patients. Hemoglobin counts ranged from 75 to 110 g/dl (median 90). White blood cell nadirs ranged from 1380 to 5400/$\mu$l (median 2760). Absolute neutrophil counts ranged from 392 to 3024/$\mu$l (median 1242), with the median day of nadir being day 23 (range 6–36). The platelet counts ranged from 34 000 to 230 000/$\mu$l (median 156 000). The grade 4 hematologic toxicities excluding anemia of level 1, 2 and 3 were each 0, 0 and 20.0% (two of 10). There were no episodes of infection.

Non-hematologic toxicity was very mild. There were no grade 3 and no 4 non-hematologic toxicities excluding vomiting. All patients received prophylactic antiemetics; however, the major non-hematologic toxicity was nausea and vomiting (seven of 16; grade 1, 4; grade 2, 1; grade 3, 2), which was frequently reported with carboplatin administration. Diarrhea (grade 1) was observed in four patients and hematouria (grade 1) was observed in four patients. Five patients had mild elevation of transaminase (grade 1, 4; grade 2, 1). There was no renal toxicity. Arterial catheter toxicity was acceptable without major complications.

Mean intervival of chemotherapies of level 1, 2 and 3 were each $30.3\pm4.9$, $37.0\pm7.5$ and $32.2\pm6.4$ days, respectively, for an overall mean of $32.8\pm6.4$ days. Ten of 16 patients had no delays for treatment. In three of six patients, treatment delays were for less than 1 week. Treatment was delayed for 14 days in three patients.

### Response

Sixteen patients were assessable for response; six (37.5%) had a CR and nine (56.3%) a PR, for an overall response rate of 93.8%. The CR rate of dose levels 1, 2 and 3 were 33.3% (one of three), 33.3% (one of three) and 40.0% (four of 10), respectively. In three patients, pathological CR was achieved. Three pathological CR patients were IVA (4.5 cm), IIB (5.0 cm) and IIIB (4.9 cm). For 11 stage III–IVA patients, three (27.3%) had a CR and seven (63.6%) a PR, for an overall response rate of 90.9%. In the 15 responders, nine (60%) patients achieved PR after the first course of

**Table 1.** Worst toxicity observed

| Carboplatin dose ($m^2$) | | Patients (*n*) | WBC | | | | | Neutrophil | | | | | Platelet | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 | 0 | 1 | 2 | 3 | 4 |
| Phase I | 200 | 3 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 |
| | 300 | 3 | 0 | 2 | 0 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 3 | 0 | 0 | 0 | 0 |
| | 400 | 3 | 0 | 1 | 2 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 |
| Phase II | 400 | 7 | 1 | 1 | 3 | 2 | 0 | 1 | 1 | 2 | 1 | 2 | 2 | 4 | 0 | 1 | 0 |

**Table 2.** Clinical response

| Carboplatin dose ($m^2$) | | Patients (*n*) | Clinical response | | | | Response rate (%) | CR rate (%) |
|---|---|---|---|---|---|---|---|---|
| | | | CR | PR | NC | PD | | |
| Phase I | 200 | 3 | 1 | 2 | 0 | 0 | 100 | 33.3 |
| | 300 | 3 | 1 | 2 | 0 | 0 | 100 | 33.3 |
| | 400 | 3 | 1 | 2 | 0 | 0 | 100 | 33.3 |
| Phase II | 400 | 7 | 3 | 4 | 1 | 0 | 85.8 | 42.9 |
| Overall | | 16 | 6 | 9 | 1 | 0 | 93.8 | 37.5 |

chemoradiotherapy. There was only one non-responder. This case was stage IIIB and had a bulky tumor of 8.6 cm.

All the 15 responding patients underwent radical surgery with pelvic lymphadenectomy and postoperative adjuvant radiotherapy. Radiotherapy was performed on the non-responder. Pathologic examination of surgical specimens revealed lymph node involvement in two (40.0%) of five patients with stage IIB disease and in three (30.0%) of 10 patients with stage IIIB–IVA disease. Parametrial involvement was found in two (40.0%) of five patients with stage IIB disease and in four (40%) of 10 patients with stage IIIB disease. All patients had tumor-free resection margins.

Three patients died at 17, 31 and 41 months. TNM classification of these patients was T2BX0M0 (pT2BN1M0), T3BX0M0 (pT2BN1M0) and T3BX0M0 (pT1BN0M0). The second patient had adenocarcinoma. These three patients were administered carboplatin at dose level 1. Two had recurrent tumor in the pelvic cavity and one had recurrent tumor in the lung. Median survival time was 41 months (range 8–57 months).

## Discussion

In this phase I study, the MTD was not reached. However, we determined the optimal dose of carboplatin to be 400 mg/$m^2$ for the following reasons. (i) Four reports demonstrated that the MTD of carboplatin was 440–550 mg/$m^2$.[21–24] (ii) The good clinical response rate could be obtained at a dose of 400 mg/$m^2$ of carboplatin. (iii) The goals of this study were to determine the optimal dose of carboplatin at neoadjuvant setting and it is thought to be very important to treat patients without treatment delay.

In general, the response rate has been reported to be around 70% for NAC with a cisplatin-based regimen.[10,14,16–19,25–29] In particular, NAC for stage III–IA patients is thought to have a limited effect. Eddy reported that there was a significant relationship between response rate and clinical stage,[30] indicating that the bulk of the tumor might be a major factor limiting the curative probability of pelvic cancer. Response rates for stage III–IA patients were reported to be 47–77%.[16–19,29,30] Scarabelli reported that NAC induced response in 33 of the 36 patients with stage IIIB–IVA (response rate, 91.7%; CR rate, 13.9%).[14] However, in their series, 19.4% (seven of 36) of patients discontinued chemotherapy because of hematologic toxicity. In our series, all patients completed the planned two courses of treatment; toxicity was mild and the response rate for stage IIIB–IVA was 90.9% (CR 27.3%). In addition, 60% (nine of 15) of patients achieved PR after only the first course of chemotherapy. The sole non-responder had the largest mass (8.6 cm) in this study.

According to NAC studies, the frequency of lymph node involvement in stage IIIB patients was around 30%.[14,16,17] These data were expected for the same

stage, when compared with the incidence in cervical cancer patients.[31] In our series, lymph node involvement in stage IIB and IIIB–IVA patients was 40.0% (two of five) and 30.0% (three of 10), respectively. Platinum-based NAC may have a limited effect on lymph node involvement because of drug delivery. It was reported that platinum accumulation in lymph nodes was low by both i.a. and i.v. platinum compound administration.[32,33] However, in our series, lymphadenectomy was could be performed in most of patients (15 of 16). Koumantakis reported that concurrent brachytherapy and chemotherapy with platinum compounds was well tolerated and effective in reducing tumor bulk in patients with locally advanced carcinoma of the uterine cervix.[34] The overall response rate was 91.7% (33 of 36); 86.1% (31 of 36) of patients had radical surgery. However, in their study, most of patients were stage II (IIA, 14; IIB, 19; IIIA, 3) and the response rate for stage IIIA was 33.3% (one of three). In our series, most of the patients (11 of 16) were stage III. In addition, their chemotherapy regimen was i.v. It was reported that platinum accumulation in the cancer tissue and myometrium was significantly higher following i.a. infusion than i.v. infusion.[32]

The impact on survival of NAC followed by radical surgery is still a matter of discussion.[35] Some authors have reported that NAC followed by surgery may improve survival in locally advanced cervical cancer.[15,16,36] Some authors have observed that NAC has no survival benefit.[37] To our knowledge, there have been no randomized studies of NAC for stage III–IV patients. Phase III study is required to solve this problem.

In conclusion, concurrent platinum chemotherapy and intracavitary brachytherapy for locally advanced cervical cancer is well tolerated and effective in reducing tumor bulk before surgery. Further examination is required to evaluate its effect of extending the survival time in advanced cervical cancer.

## Acknowledgments

We are grateful to Kathrine Allikian of Enzyme Bio-Systems, Ltd for her critical review of the manuscript.

## References

1. Parkin DM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. *Int J Cancer* 1998; **41**: 184–97.
2. FIGO. Annual report on the results of treatment in gynecological cancer. *Int J Gynecol Obstet* 1991; **36**(suppl): 38–9.
3. Mendenhall WM, Thar TL, Bova FJ, Marcus Jr RB, Morgan LS, Million RR. Prognostic and treatment factors affecting pelvic control of stage IB and IIA–B carcinoma of the intact uterine cervix treated with radiation therapy alone. *Cancer* 1984; **53**: 2649–54.
4. Kovalic JJ, Perez CA, Grigsby PW, Lockett MA. The effect of volume of disease in patients with carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys* 1991; **21**: 905–11.
5. Perez CA, Grigsby PW, Chao KSC, Mutch DG, Lockett MA. Tumor size, irradiation dose, and long-term outcome of carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys* 1998; **41**: 307–11.
6. 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**: 1144–53.
7. 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**: 1154–61.
8. 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**: 1137–43.
9. Wong LC, Ngan HYS, Cheung ANY, Cheng DKL, Ng TY, Choy DTK. Chemoradiation and adjuvant chemotherapy in cervical cancer. *J Clin Oncol* 1999; **17**: 2055–60.
10. Benedetti-Panici P, Greggi S, Scambia G. High-dose cisplatin and bleomycin neoadjuvant chemotherapy plus radical surgery in locally advanced cervical carcinoma: a preliminary study. *Gynecol Oncol* 1991; **41**: 212–6.
11. Giaroli A, Sananes C, Sardi JE, *et al*. Lymph node metastases in carcinoma of the cervix uteri: response to neoadjuvant chemotherapy and its impact on survival. *Gynecol Oncol* 1990; **39**: 34–9.
12. Dottino P, Plaxe S, Beddoe AM, Johnson C, Cohen CJ. Induction chemotherapy followed by radical surgery in cervical cancer. *Gynecol Oncol* 1991; **4**: 7–11.
13. Namkoong SE, Park JS, Kim JW, *et al*. Comparative study of the patients with locally advanced stages I and II cervical cancer treated by radical surgery with and without preoperative adjuvant chemotherapy. *Gynecol Oncol* 1995; **59**: 136–42.
14. Scarabelli C, Zarrelli A, Gallo A, Visentin MC. Multimodal treatment with neoadjuvant intraarterial chemotherapy and radical surgery in patients with stage IIIb–IVA cervical cancer. A pilot study. *Cancer* 1995; **76**: 1019–26.
15. Sardi JE, Giaroli A, Sananes C, *et al*. Long-term follow-up of the first randomized trial using neoadjuvant chemotherapy in stage Ib squamous-cell carcinoma of the cervix: the final results. *Gynecol Oncol* 1997; **67**: 61–9.
16. Benedetti-Panici P, Greggi S, Scambia G, *et al*. Long-term survival following neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. *Eur J Cancer* 1998; **34**: 341–6.
17. Minagawa Y, Kigawa J, Irie T, Okada M, Kanamori Y, Terakawa N. Radical surgery following neoadjuvant chemotherapy for patients with stage IIIB cervical cancer. *Ann Surg Oncol* 1998; **5**: 539–43.

18. Sugiyama T, Nishida T, Hasuo Y, Fujiyoshi K, Yakushiji M. Neoadjuvant intra-arterial chemotherapy followed by radical hysterectomy and/or radiotherapy for locally advanced cervical cancer. *Gynecol Oncol* 1998; **69**: 130–6.
19. Sugiyama T, Nishida T, Kumagai S, *et al*. Combination therapy with irinotecan and cisplatin as neoadjuvant chemotherapy in locally advanced cervical cancer. *Br J Cancer* 1999; **81**: 95–8.
20. O'Hara JA, Douple EB, Richmand RC. Enhancement of radiation-induced cell kill by platinum complexes (carboplatin and iproplatin) in V79 cells. *Int J Radiat Oncol Biol Phys* 1986; **12**: 1419–22.
21. Calvert AH, Harland SJ, Newell DDR, *et al*. Early clinical studies with *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II. *Cancer Chemother Pharmacol* 1982; **9**: 140–7.
22. Joss RA, Kaplan S, Goldhirsch A, Sessa C, Brunner KW, Cavalli F. A phase I trial of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (Carboplatin, CBDCA, JM-8) with a single dose every five week-schedule. *Invest New Drugs* 1984; **2**: 297–304.
23. Leyvraz S, Ohnuma T, Lassus M, Holland JF. Phase I study of carboplatin in patients with advanced cancer, intermittent intravenous bolus, and 24-hour infusion. *J Clin Oncol* 1985; **3**: 1385–92.
24. Koeller JM, Trump Dl, Tutsch KD, Earhart RH, Davis TE, Tormey DC. Phase I clinical trial and pharmacokinetics of carboplatin (NSC 241240) by single monthly 30-minute infusion. *Cancer* 1986; **57**: 222–5.
25. Souhami L, Gil RA, Allan SE, *et al*. A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. *J Clin Oncol* 1991; **9**: 970–7.
26. Vermorken JB. The role of chemotherapy in squamous cell carcinoma of the uterine cervix: a review. *Int J Gynecol Cancer* 1993; **3**: 129–42.
27. Sundfor K, Trope CG, Hogbert T, *et al*. Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage 3B and 4A. *Cancer* 1996; **7**: 2371–8.
28. Zanetta G, Lissoni A, Pellegrino A, *et al*. Neoadjuvant chemotherapy with cisplatin, ifosfamide and paclitaxel for locally advanced aquamous-cell cervical cancer. *Ann Oncol* 1998; **9**: 977–80.
29. Yamakawa Y, Fujimura M, Hidaka T, Hori S, Saito S. Neoadjuvant intraarterial infusion chemotherapy in patients with stage IB2–IIIB cervical cancer. *Gynecol Oncol* 2000; **77**: 264–70.
30. Eddy GL. Neoadjuvant chemotherapy before surgery in cervical cancer. *J Natl Cancer Inst* 1996; **14**: 93–9.
31. van Nagell JR. Invasive cervical cancer. In: Knapp RC, Berkowitz R, eds. *Gynecologic oncology*. New York: McGraw-Hill 1993: 192–221.
32. Ishikawa H, Kikkawa F, Tamakoshi K, *et al*. Distribution of platinum in human genecologic tissues and lymph nodes after intravenous and intraarterial neoadjuvant chemotherapy. *Anticancer Res* 1996; **16**: 3849–53.
33. Tsuda H, Yamamoto K, Kawabata M, Lee T, Hidaka A. Continuous local injection of carboplatin into the uterine cervix for cervical and endometrial cancer: preliminary study. *Gynecol Obstet Invest* 1997; **44**: 196–9.
34. Koumantakis E, Haralambakis Z, Koukourakis M, *et al*. A pilot study on concurrent platinum chemotherapy and intracavitary brachytherapy for locally advanced cancer of the uterine cervix. *Br J Radiol* 1998; **71**: 552–7.
35. Tierney JF, Stewart LA, Parmar MKB. Can the published data tell us about the effectiveness of neoadjuvant chemotherapy for locally advanced cancer of the uterine cervix? *Eur J Cancer* 1999; **35**: 406–9.
36. Serur E, Mathews RP, Gates J, Levine P, Maiman M, Remy JC. Neoadjuvant chemotherapy in stage IB2 squamous-cell carcinoma of the cervix. *Gynecol Oncol* 1997; **65**: 348–56.
37. Chang TG, Lai CH, Hong JH, *et al*. Randomized trial of neoadjuvant cisplatin, vincristen, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. *J Clin Oncol* 2000; **18**: 1740–7.

*(Received 25 June 2001; accepted 20 August 2001)*