Yonsei Medical Journal
Vol. 38, No. 5, pp. 255~260, 1997

☐ Review Article ☐

Adjuvant Therapy in Cervical Cancer Patients with High Risk Factors

Tchan Kyu Park

Neoadjuvant and adjuvant chemotherapies are used adjunctively with surgery or radiation and are among the treatment options that are now employed for reducing treatment failure in early-stage cervical cancers with high-risk prognostic factors. Adjuvant therapies have been reported to significantly improve survival than would otherwise be possible with surgery or radiotherapy alone. However, for advanced cervical cancers, sequential or concurrent chemo-radiotherapy does not appear to significantly increase survival. The combination of radiotherapy with IFN-α2a and RA in the treatment of patients with locally advanced cervical cancer showed high response rates, however this should be confirmed in larger studies. Recent reports show that postoperative adjuvant radiotherapy has no benefit in survival, but that postoperative adjuvant chemotherapy has improved survival. Toxicities and the optimum number of cycles of neoadjuvant and adjuvant chemotherapy, as well as biologic therapy, will follow along with individualized treatment based on high-risk prognostic factors. Although more comprehensive studies and longer follow up will be required for complete evaluation of these adjuvant therapies, preliminary results are promising.

Key Words: Cervical cancer, high risk factors, adjuvant therapy

Cervical cancer is the most common female malignancy in Korea with an age-adjusted incidence rate of 29.9 per 100,000 women in Seoul, Korea. (International agency for research on cancer, 1992; Korean cancer research foundation, 1993) In developing countries, cervical cancer is a leading cause of cancer mortality in women. Therefore it is a significant world health-care problem.

Received September 26, 1997

Department of Obstetrics and Gynecology, Yonsei University College of Medicine

Presented at the 5th National and International Gynecological Oncology Conference, Beijing, China, October 10-13, 1996

Address reprint request to Dr. T.K. Park, Department of Obstetrics and Gynecology, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea

It is generally accepted that radiotherapy and surgery are both effective techniques in the management of carcinoma of the cervix with small lesions. However, disease control for groups with risk factors such as advanced stage (Perez *et al.* 1983), bulky disease (Piver and Chung, 1975; Sardi *et al.* 1990), lymph node metastasis (Piver and Chung, 1975), or small-cell carcinoma (Van Nagell *et al.* 1977) is difficult even with the use of modern megavoltage equipment and optimal fractionation schemes or improved extensive surgery. The high treatment failure rate and poor survival with conventional treatment have spurred the development of new treatment modalities. With the advent of newer chemotherapeutic agents, chemotherapy has emerged as an additional mode of therapy in these patients. As a result, many investigators have studied the

combined modalities of chemotherapy and radiotherapy. It has been hypothesized that chemical debulking attained with cytotoxic drugs may induce better oxygenation of previously-hypoxic tumor cells, thereby facilitating the response to subsequent radiation and perhaps the control of micrometastasis. (Vermund and Gollin, 1968; Guthrie, 1985)

Numerous reports of locally-advanced cervical cancer comparing the concurrent and the sequential combination of chemotherapy and radiotherapy have been published with conflicting outcomes. Although some studies have shown promising results with the use of radiotherapy in combination with sequential chemotherapy in advanced disease (Symonds *et al.* 1989; Deppe *et al.* 1991; Park *et al.* 1991), there are also some negative reports. (Withers *et al.* 1988; Souhami *et al.* 1991; Tseng *et al.* 1997) Although several studies have documented 90% response rates using radiotherapy with concurrent chemotherapy in poor prognostic cervical cancer patients, this combination can also produce severe synergistic toxic effects. (Cummings, 1982; Thomas *et al.* 1987; Malviya *et al.* 1989) Roverts *et al.* reported a clinical CR rate of 85% among 67 cases of advanced disease treated in this manner. However, survival did not improve due to local recurrence. (Roberts *et al.* 1991) Further prospective randomized trials of concurrent chemotherapy and radiotherapy are currently in progress.

In recent years, the use of 13-cis-retinoic acid (RA) and interferon-α2a (IFN-α2a) in cancer therapy has stimulated significant interest. Both IFN-α2a and RA are known to possess antiproliferative, immunomodulatory and antineoplastic properties. IFN-α2a has two main mechanisms of action against neoplasia; first, it is directly cytotoxic and second, it is indirectly cytotoxic by immunomodulation. The combination of IFN-α and RA has produced high response rates in patients with cervical squamous-cell carcinoma. (Lippman *et al.* 1993) These compounds may also potentiate radiation cytotoxicity and act as a radiosensitizer.

INDICATION OF ADJUVANT THERAPY

Neoadjuvant, adjuvant chemotherapy & biologic therapy

The current staging classification of cervical carcinoma by the International Federation of Gynaecologists and Obstetricians (FIGO) does not address cell-type or lymph-node status of the cancer being staged. It is likely that stage I and II diseases with bulky tumor (or barrel-shaped lesion) may have a poorer prognosis than the comparable stage diseases with less bulky tumor and that higher-stage diseases harbor metastatic disease foci outside the traditional radiation field used for cervical cancer.

Indeed, this is likely when cervical cancer is associated with any of the following factors. (Park, 1986; Park *et al.* 1991)

- Stage III-IV
- Lesion size ≥ 4 cm
- Stage I-II with lesion ≥ 4cm
- Adeno-squamous or small-cell carcinoma
- Evidence of lymph-node metastasis on lymphography

These high-risk cases deserve adjuvant therapy. Other authors have discussed similar risk factors. (Jampolis *et al.* 1975; Piver and Chung, 1975; Van Nagell *et al.* 1977)

Postoperative adjuvant chemotherapy

Some cervical cancers are apparently understaged. Pretreatment cancer staging, which forms the basis of primary treatment strategy in cervical cancer, does not always account for the entire cancer, which is usually more accurately delineated by surgery. Postoperative adjuvant chemotherapy is suitable for cases associated with any of the following factors documented postoperatively. (Park, 1986)

- Lymph node metastasis
- Lympho vascular space invasion
- Depth of invasion more than 10 mm
- Parametrial invasion

Traditionally, patients with cervical cancer thought

to have been less than adequately treated with surgery have been treated with postoperative radiotherapy. My criteria for postoperative adjuvant chemotherapy are cervical cancers with any one or more of these risk factors.

TYPES OF NEOADJUVANT, ADJUVANT CHEMOTHERAPY & BIOLOGIC THERAPY

Neoadjuvant chemotherapy may be administered sequentially preceding radiotherapy or surgery, or concurrently with radiotherapy. The sequential mode first delivers an average of three courses of chemotherapy at an interval of about three weeks before radiotherapy or surgery. The concurrent mode is the one in which radiotherapy is initiated during the first course of chemotherapy. Biologic therapy was administered with concurrent radiotherapy.

The sequential mode has merits by taking advantage of vascularity remaining undisturbed by radiation, tumor-cell radiosensitization brought about by the decrease in the hypoxic-cell fraction, and the earlier treatment of occult micrometastasis. Chemotherapy in this fashion often allows radical surgery by tumor reduction in inoperable cases.

The concurrent mode has the advantages of:

- not delaying radiotherapy by several courses of chemotherapy;
- shortening the total treatment duration;
- enhancing tumor control by possible synergistic effects of chemotherapeutic drugs with radiation (e.g. radiosensitization of the tumor mass by 5-FU)

Adjuvant chemotherapy, instituted after surgery in cases associated with at least one of the postoperatively documented high-risk factors described, is delivered in the same way as sequential chemotherapy before proceeding on to radiotherapy.

The biologic drugs (IFN-α2a, RA) may also potentiate radiation cytotoxicity by acting as a radiosensitizer. (Chang and Keng, 1987)

REGIMENS AND ADMINISTRATION

Quite a few regimens are being employed for neoadjuvant or adjuvant chemotherapy for cervical cancer. The most effective regimens, evaluated in the form of shrinkage of the tumor mass, are cisplatin-based. (Thigpen *et al.* 1981)

Cisplatin is present in almost all drug regimens currently being used in this mode of chemotherapy.

I have been using the cisplatin and 5-FU combination in patients associated with any of the high-risk prognostic factors described above. Cisplatin, 100 mg/m^2 IV, is followed by 5-FU 1000 mg/m^2 as a 24-hour IV infusion for five days. Carboplatin, a drug similar to cisplatin but with lower bone marrow toxicity, in a dose of 400 mg/m^2 may be used instead of cisplatin. A different regimen is used for adenocarcinoma. Interested readers are referred to regimens used by other authors. (Thigpen *et al.* 1981; Drescher *et al.* 1989; Zanetta *et al.* 1993) All patients are prehydrated for about 10 hours before receiving cisplatin or carboplatin and premedicated with metoclopromide and lorazepam.

The biologic therapy consisted of a IFN-α2a subcutaneous injection of 6 million units (MU) per day for the first 3 days, followed by 3 MU per day for 81 days and then RA orally 1mg/kg/day in 2 divided doses for 84 days with concurrent radiotherapy.

It is important that patients should be maintained to have at least 12 g/dl of hemoglobin level and the absence of other intercurrent diseases which may contraindicate chemotherapy. A guideline like 'Common Toxicity Criteria of Gynaecologic Oncology Group (October 1988)' may be followed for monitoring the toxicity of chemotherapy and biologic therapy during and after adjuvant therapy.

OUTCOME

Neoadjuvant, adjuvant chemotherapy & biologic therapy

Many authors including myself have reported favorable results of neoadjuvant chemotherapy administered to invasive cervical cancer patients. (Friedlander *et al.* 1984; Kim *et al.* 1989; Sardi *et al.* 1990; Panici *et al.* 1991; Park *et al.* 1991) In

my series (Park *et al.* 1991), the survival of patients with high-risk factors was significantly better after neoadjuvant chemotherapy followed by surgery or radiotherapy than it was after surgery or radiotherapy alone. For example, with a lesion of more than 4cm, the five-year survival was 67% after sequential chemoradiotherapy, significantly higher than the 53% obtained after radiotherapy alone.

After sequential chemoradiotherapy, stage III-IV diseases, adeno-squamous or small-cell carcinomas, stage I-II diseases having lesions greater than 4cm, and diseases with evidence of lymph-node metastasis on lymphography all showed significantly higher five-year survivals of 69, 68, 78, and 80%, respectively when compared to the radiotherapy-alone group, which showed survival rate of 57, 55, 48, and 49%, respectively.

Concurrent chemoradiotherapy did not appear to be superior to sequential chemoradiotherapy in the patients we treated. (Park *et al.* 1993) In bulky tumors of more than 4cm, however, its effects may be better than the sequential mode. (Kersh *et al.* 1990; Thomas *et al.* 1990)

IFN-α2a, RA and radiotherapy resulted in a 47% response rate (33% complete resonse) while concurrent chemoradiotherapy resulted in a 42% response rate (17% complete response) in locally advanced squamous carcinoma of the cervix. (Park *et al.* in press)

Postoperative adjuvant chemotherapy

This mode of chemotherapy followed by radiotherapy may improve the survival of patients showing postoperatively documented high-risk factors (Park, 1986) compared with postoperative radiotherapy, which according to many previous studies did not benefit the overall survival outcome.

TOXICITY OF ADJUVANT CHEMOTHERAPY & BIOLOGIC THERAPY

As is the case with chemotherapy of other malignancies, nausea and vomitting, elevation of liver transaminases, decreased creatinine clearance, and neutropenia were the frequently encountered drug toxicities from neoadjuvant and adjuvant chemotherapy.

Neutropenia occurred in 36% of all drug cycles administered in our series. (Park *et al.* 1991; Park *et al.* 1993) Neutropenia usually causes no serious infection when patients are carefully monitored, since many patients with neutropenia of less than 1000/μl will remain afebrile. Thus, unless fever is associated with neutropenia, antibiotics were not always administered. However, it should be remembered that once fever of even a mild degree occurs in the neutropenic patient, combination antibiotic therapy should be initiated. Hepatotoxicity, though demonstrated by increased transaminases, was rarely symptomatic and was short-lived without any treatment. In the face of decreased creatinine clearance, doses of cisplatin or carboplatin, the drugs chiefly cleared through the kidney, are usually reduced to diminish the potential nephrotoxicity.

The major toxicity of IFN-α2a , RA and radiotherapy was fever (60%). There was no grade 3 or 4 toxicity. (Park *et al.* in press)

CONCLUSION

Neoadjuvant and adjuvant chemotherapy in cervical cancer is a method of treatment aimed at increasing the chance for longer survival in a set of patients with high risk factors for treatment failure after conventional surgery or radiotherapy alone. It is a form of treatment that is one step closer to achieving individualized treatment. As more experience with this mode of therapy is gained, it will become clearer what regimens and how many drug courses are the optimum for patients. The combination of systemic IFN-α2a, RA and radiotherapy is an active, well-tolerated therapy for locally-advanced cervical cancer. Further studies are required to define its role in the treatment of advanced cervical cancer.

REFERENCES

Chang AYC, Keng PC: Potentiation of radiation cyto-

toxicity by recombinant interferons, a phenomenon associated with increased blockage at the G2-M Phase of the cell cycle. *Cancer Res 47: 4338-4341, 1987*

Cummings BJ: The place of radiation therapy in the treatment of carcinoma of the anal cancer. *Cancer Treat Rev 9: 125-147, 1982*

Deppe G, Valviya V, Han I, Christensen CW, Malone Jr JM, Kim Y, Ahmed K: A preliminary report of combination chemotherapy with cisplatin and mitomycin C followed by radical hysterectomy or radiation therapy in patients with locally advanced cervical cancer. *Gynecol Oncol 42: 178-181, 1991*

Drescher CW, Reid GC, Terada K, Roberts JA, Hopkins MP, Schoeppel SL: Continuous infusion of low-dose 5-fluorouracil and radiation therapy for poor prognosis squamous cell carcinoma of the uterine cervix. *Gynecol Oncol 33: 225-230, 1989*

Friedlander M, Atkinson K, Coppleson VM, Elliot P, Green D, Houghton R, Solomon H, Russell P: The integration of chemotherapy into the management of locally advanced cervical cancer: A pilot study. *Gynecol Oncol 19: 1-7, 1984*

Guthrie D: Chemotherapy of cervical cancer. *Clin Obstet Gynecol 12: 229-246, 1985*

International agency for research on cancer: *Cancer Incidence in Five Continents. vol VI(Lyon : IARC Scientific Publications), 1992*

Jampolis S, Andras EJ, Fletcher GH: Analysis of sites and causes of failure of irradiation in invasive squamous carcinoma of the cervix. *Radiology 115: 681-685, 1975*

Kersh CR, Constable WC, Hahn SS, Andersen WA, Talor PT: A phase I-II trial of multimodality management of bulky gynecologic malignancy. *Cancer 38: 446-451, 1990*

Kim DS, Moon H, Kim KT, Hwang YY, Cho SH, Kim SR: Preoperative adjuvant chemotherapy in the treatment of cervical cancer stage IB and II with Bulky tumor. *Gynecol Oncol 33: 225-230, 1989*

Korean cancer research foundation: *Implantation Study of Seoul Cancer Registry(Seoul: KCRF Publication), 1993*

Lippman SM, Kavanagh JJ, Paredes-Espinoza M, Hong WK, Massimini G, Krakoff IH: 13-cis-retinoic acid plus interferon-α2a in locally advanced squamous cell carcinoma of the cervix. *J Natl Cancer Inst 85: 499-500, 1993*

Malviya VK, Deppe G, Kim Y, Gove N: Concurrent radiation therapy, cisplatin and mitomycin C in patients with poor prognosis cancer of the cervix: a pilot study. *Am J Clin Oncol 12: 434-437, 1989*

Panici BP, Scambia G, Greggi S, Gallo A: Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer: Prognostic factors for response and survival. *Cancer 67: 372-379, 1991*

Park TK: Carcinoma of the uterine cervix in Korea: an analysis of treatment failures and suggested therapeutic strategies. *Korean J Obstet Gynecol 29: 617, 1986*

Park TK, Choi DH, Kim SN, Lee CH, Kim YT, Kim GE, Suh CO, Loh JK: Role of induction chemotherapy in invasive cervical cancer. *Gynecol Oncol 41: 107-112, 1991*

Park TK, Lee JP, Kim SN, Choi SM, Kudelka AP, Kavanagh JJ: Interferon-α2a, 13-cis-retinoic acid and radiotherapy for locally advanced carcinoma of the cervix: a pilot study. Eur J Gynecol Oncol, accepted

Park TK, Lee SK, Kim SN, Hwang TS, Kim GE, Suh CO, Loh JK: Combined chemotherapy and radiation for bulky stages I-II cervical cancer: Comparison of concurrent and sequential regimens. *Gynecol Oncol 50: 196-201, 1993*

Perez CA, Breaux S, Madoc-Jones H, Bedwine KJM, Camel HM, Walz BJ: Radiation therapy alone in the treatment of carcinoma of the cervix. 1. Analysis of tumor recurrence. *Cancer 51: 1393-1402, 1983*

Piver MS, Chung WS: Prognostic significance of cervical lesion size and pelvic node metastasis in cervical carcinoma. *Obstet Gynecol 46: 507-510, 1975*

Roberts WS, Hoffman MS, Kavanagh JJ, Fiorica JV, Greenberg H, Finan MA, Cavanagh D: Further experience with radiation therapy and concomitant intravenous chemotherapy in advanced carcinoma of the lower female genital tract. *Gynecol Oncol 43: 233-236, 1991*

Sardi J, Sananes C, Giaroli A, Maya G, DiPaola G: Neoadjuvant chemotherapy in locally advanced carcinoma of the cervix uteri. *Gynecol Oncol 38: 486-493, 1990*

Souhami L, Canary PC, Araujo CM, Pinto LH, Silveira TR: A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. *J Clin Oncol 9: 970-977, 1991*

Symonds RP, Burnett RA, Habeshow T, Kaye SB, Snee MP, Watson ER: The prognostic value of a response to chemotherapy given before radiotherapy in advanced cancer of cervix. *Br J Cancer 59: 473-475, 1989*

Thigpen T, Shingleton H, Homesley H, Lagasse L, Bressing J: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix. A phase II study of the Gynecologic oncology group. *Cancer 481: 899-903, 1981*

Thomas GM, Dembo AJ, Black B, Bean HA, Beale FA, Pringle JR, Radwing G: Concurrent radiation and chemotherapy for carcinoma of the cervix recurrent after radical surgery. *Gynecol Oncol 27: 254-260, 1987*

Thomas G, Dembo A, Fyles A, Gadalla T, Beale F, Bean H, Bush R, Balck B: Concurrent chemoradiation in advanced cervical cancer. *Gynecol Oncol 38: 446-451, 1990*

Tseng CJ, Chang CT, Lai CH, Soong YK, Hong JH, Tung SG, Hsueh S : A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix. *Gynecol*

Oncol 66: 52-58, 1997

Van Nagell JR Jr, Donaldson ES, Parker JC, Van Dyke AH, Wood EG: Prognostic significance of pelvic node morphology in carcinoma of the uterine cervix. *Cancer 39: 2624-2632, 1977*

Vermund H, Gollin FF: Mechanism of action of radiotherapy and chemotherapeutic adjuvants-A review. *Cancer 21: 58-76, 1968*

Withers HR, Talor JM, Maciejewski B: The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol 27: 131-146, 1988*

Zanetta G, Landoni F, Colombo A, Maneo A, Leventis C: Three-year results after neoadjuvant chemotherapy, radical surgery and radiotherapy in locally advanced cervical carcinoma. *Obstet Gynecol 82: 447-450, 1993*