

Concurrent Chemotherapy for Cervical Cancer Patients Primarily Treated with Radiotherapy: Is It Necessary for All?

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Concurrent cisplatin-based chemotherapy has been strongly recommended in women with cervical cancer requiring radiotherapy (RT). However, our studies have shown a subset of patients can achieve good treatment outcome by RT alone and the benefit of treating them with concurrent chemoradiation (CCRT) is questionable. On the other hand, patients with positive lymph node, squamous cell carcinoma antigen (SCC-ag) level > 10 or stage III/IVA disease have a higher risk of distant metastasis and weekly single-agent cis-platinum might be ineffective in reducing systemic relapse. This review will present our rationales and suggestions for the selection of cervical cancer patients who should receive different forms of CCRT or RT alone. We believe the intensity of CCRT for cervical cancer should vary between patients based on their individual risk for local and distant relapse. (*Chang Gung Med J* 2006;29:550-4)

Key words: cervical cancer, concurrent chemoradiation, radiotherapy, risk factors.

In 1999, four prospective, randomized trials showed that concurrent radiotherapy (RT) with cisplatin-based chemotherapy improved local control and survival rates in patients with advanced cervical cancer. Three of the papers on these trials were published in the *New England Journal of Medicine* and one was published in the *Journal of Clinical Oncology*.⁽¹⁻⁴⁾ Based on these positive results, the American National Cancer Institute (NCI) made a strong recommendation stating, "women with cervical cancer requiring radiotherapy (RT) should be treated concurrently with cisplatin-based chemotherapy". This statement has become the standard of care worldwide for cervical cancer treated with RT. Although the inclusion criteria of patients and treatment methods varied among these studies, in general they showed that the local relapse rates were reduced from 30%-44% in patients treated with RT alone or RT combined with hydroxyurea to 19%-25% in

those treated with concurrent chemoradiation (CCRT) using agents containing cis-platinum. On the other hand, randomized trials conducted by several other groups, including ourselves, did not obtain positive results in favor of using CCRT for advanced cervical cancer patients, even when cis-platinum was included in the regimen of CCRT.^(5,6) The discrepancies in the effects of CCRT between studies with opposing results might be caused by the different inclusion criteria of patients, chemotherapy agents and their intensity and schedule, and the RT protocols. However, the benefit of CCRT has been challenged for patients treated with an optimal RT protocol that had consequential higher local tumor control rates.^(6,7) Questions remain unanswered as to whether certain sub-groups of advanced cervical cancer patients had a greater benefit and the rest had little or no benefit from CCRT.

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Elderly cervical cancer patients in Taiwan achieved good local control from RT alone

We have previously identified several risk factors associated with poor tumor control and survival rate in cervical cancer patients primarily treated with RT, which included advanced stage, high pre-treatment squamous cell carcinoma (SCC) antigen (SCC-ag) levels, positive pelvic nodes shown on imaging studies and adenocarcinoma/adenosquamous carcinoma histology.⁽⁸⁻¹¹⁾ Our studies suggested that not all patients with advanced stage cervical cancers had poor tumor control and survival, and the risk of local relapse and distant metastasis varied widely among patients carrying different risk factors. Instead of using stage/tumor size as the sole factor for decision-making in concurrent use of chemotherapy or inclusion of patients into clinical trials, more detailed stratification of patients' risk should be helpful in estimating the likelihood of benefit from combination treatments.

In a recent study, we retrospectively reviewed 1,031 patients with stage IB-IVA SCC of the cervix, who were treated with RT alone, without any chemotherapy, during the period 1990-1999.⁽⁸⁾ Since the positive effects of CCRT were not established until 1999, only 257 patients received chemotherapy during this period. We found that the independent risk factors for local relapse in patients with SCC of the cervix are advanced stage and age younger than 45 years, and for distant metastasis are advanced stage, positive lymph nodes shown on computed tomography/magnetic resonance imaging (CT/MRI) and high SCC-ag levels. Following risk stratification, a sub-group of patients with bulky stage I/IIA-IIB disease and age > 45 years had 86% 5-year local-relapse free survival, which increased to 90% if the patient was over 65 years of age. The corresponding figure for patients with non-bulky IB/IIA disease was 96%. These two sub-groups comprised 70% of patients primarily treated with RT in our hospital. For distant metastasis, 5-year distant-relapse free survival rate was 83% for patients with bulky IB/IIA disease, SCC-ag < 2 and negative pelvic nodes, and 43% for patients with stage III disease, SCC-ag > 2 and positive pelvic nodes. From this study, we found that age (< 45 years) and stage are two independent prognostic factors for advanced cervical cancer patients treated with RT alone, and elderly patients had a very good local control rate.

In general, reports from hospitals in Taiwan, including ours, Tri-Service General Hospital, China Medical College Hospital and Chang Gung Memorial Hospital-Kaohsiung, showed a much better local control rate by using RT alone for advanced cervical cancer than those reported from the control (RT alone) arm of randomized trials published from the USA.⁽¹²⁻¹⁴⁾ After comparing patients' characteristics between the USA and Taiwan, we found the median age of our patients was much older than that of those in the USA, and the difference, in general, was around 15 years. The median age in our study was 64 years and only 10% of patients were younger than 45 years. In contrast, patients in trials in the USA had a median age between 40 and 50 years.^(2,3,15) The reason for this difference can be partially illustrated from epidemiology data. The Surveillance, Epidemiology and End Results (SEER) showed that the age-specific incidence rate of invasive SCC of the cervix in white women was rather stable, ranging from 40 to 70 years of age.⁽¹⁶⁾ In Taiwan, there is a positive association between age-specific incidence rate and age; women aged seventy years had a 2.8 times higher incidence rate when compared to those aged 40 years.⁽¹⁷⁾ However, the possibility that a higher percentage of younger cervical cancer patients in Taiwan being treated with radical surgery cannot be ruled out. Our retrospective studies and results from Hong Kong by Wong *et al.*⁽¹⁸⁾ showed age to be an important independent prognostic factor for advanced cervical cancer, and we therefore consider that the older age of our patients is the major reason for better treatment results.

The effectiveness of chemotherapy in reducing systemic metastasis, except to the lungs, is still uncertain

Since our study has clearly shown that elderly stage I/IIA-B cervical cancer patients have a very good local control rate, comparable to or even better than those in the CCRT arm of randomized trials favoring CCRT, the possibility of improving local control by concurrent chemotherapy in elderly patients is expected to be limited or even non-existent. Our previous studies also showed that, except for younger patients (< 45 years), distant metastasis is a more common relapse pattern than local failure.^(8,19) Although a combination of chemotherapy with RT seems to be the treatment of choice for

reducing distant metastasis, its effectiveness in reducing systemic metastasis, except to the lungs, is still uncertain. The Radiation Therapy Oncology Group Trial (RTOG) 90-01 showed that patients who received 3 cycles of cisplatin (75 mg/m²), fluorouracil (4,000 mg/m²) and pelvic RT had significantly less local as well as distant relapses when compared with those who received pelvic and para-aortic lymph node (PALN) irradiation; the distant relapse rate was reduced from 32% to 18% by chemotherapy.⁽¹⁵⁾ A Gynecologic Oncology Group (GOG) trial showed lung metastasis to be reduced in patients receiving either cisplatin alone or cisplatin plus fluorouracil.⁽²⁾ Another trial, GOG protocol 85 and Southwest Oncology Group protocol 8695, showed cisplatin plus fluorouracil reduced lung metastasis but did not decrease metastasis in other sites.⁽³⁾ A phase III trial from Canada also showed concurrent RT with single agent cisplatin (40 mg/m² weekly) decreased lung metastasis but did not improve local control and other metastasis.⁽⁶⁾ Our previous CCRT trial, using cisplatin, oncovin and bleomycin, did not show any therapeutic improvement in survival and relapse rates.⁽⁵⁾ Most of the current CCRT protocols in Taiwan use single agent cisplatin, which is mainly used as a radiosensitizer, instead of a strong chemotherapy agent for systemic metastasis. We, therefore, believe that this protocol will not reduce distant metastasis, except in the lungs, and believe that omitting single agent cisplatin in patients with good local control will not compromise disease control rates.

CCRT and Toxicities

Several prospective, randomized trials in advanced cervical cancer have shown that CCRT with a cisplatin-containing agent increased grade 3-4 acute toxicities, especially hematological and gastrointestinal (GI) toxicities.^(1,4,6) When these trials were carefully reviewed, only a study reported by *Pearcey et al.* from Canada used pelvic RT as the control arm and weekly cis-platinum as the experimental arm;⁽⁶⁾ the other studies included patients concurrently treated with hydroxyurea, irradiated with the pelvis plus para-aortic field or combination therapy with adjuvant hysterectomy as the control arm.^(4,15,20) The chemotherapy protocol used in this Canadian study has now been adopted by most of the hospitals in Taiwan, including ourselves, with minor

modification in dosages. The acute grade 3-5 toxicity in this study was 40% for patients treated with CCRT vs. 4% for patients treated with RT alone. The increase of acute toxicities in the CCRT group is very obvious and its effects on elderly patients are expected to be much less tolerable.

The effects of CCRT on late complications are less well documented than acute toxicities. In the RTOG 90-01 CCRT trial for advanced cervical cancer, *Eifel et al.* reported that concurrent chemotherapy and pelvic irradiation induced grade 3-5 late toxicities in 13% of patients, which is similar to that of 12% found in patients treated with whole pelvis plus para-aortic irradiation.⁽¹⁵⁾ However, the treatment field was extended to the para-aortic region for patients in the RT alone arm and 27% of them had retroperitoneal lymph node dissection; both extended field RT and lymph node dissection were expected to increase the risk of bowel complications. In a study most similar to our present practice and reported by *Pearcey et al.* from Canada, the late grade 3-5 complication rate was 33% for the CCRT group vs. 25% for the RT group ($p > 0.05$).⁽⁶⁾ After a thorough search, we did not find any report showing the effects of CCRT on the acute and late toxicities in an elderly population. Our clinical observation did find some elderly patients had worse tolerance to CCRT and the treatment had to be interrupted or mortality occurred due to acute toxicities. The potential risk of complications from CCRT should be of more concern in elderly patients.

CCRT for cervical cancer patients: who and how?

Based on our own data and a literature review, cervical cancer patients primarily treated with RT may be divided into three groups by potential benefit from concurrent chemotherapy. This division is according to patients' risk factors for local and distant relapse. Patients with adenocarcinoma/adenosquamous carcinoma histology are excluded from this analysis because they have a much higher local relapse rate than those with SCC⁽⁸⁾ and should be considered separately from SCC.

Group I are patients who have a good treatment outcome from RT alone and have only minimal benefit from concurrent chemotherapy. For those with non-bulky stage I-IIA disease and negative pelvic nodes, our data showed their 5-year local control and

relapse-free survival rate was 96% and 88%, respectively. Patients with these characteristics were not included in any prospective, randomized CCRT trials published in the literature and the recommendation from the American NCI to include this group of patients was not evidence-based. In contrast to the NCI recommendation, we suggest routine use of concurrent chemotherapy for these patients is not indicated, except for those being included in a clinical trial. For patients with bulky stage IB-IIA and IIB disease, aged > 45 years and with no lymph node metastasis, the 5-year local control and relapse-free survival rate was 86% and 77%, respectively. Also, the local control rate was even higher, up to 90%, for those over 65 years of age. The benefit of concurrent chemotherapy for these patients needs further clinical trials to verify it. However, the benefit, if it does exist, is expected to be minimal to modest. In consideration of potential toxicity, we suggest patients with these clinical characteristics and who are over 65 years of age should be treated with RT alone, and the rest could be either treated with RT alone or entered into clinical trials to verify the effects of CCRT (as in group III).

Group II are patients who have a high risk of distant metastasis, in addition to local failure, and need more than single-agent cis-platinum for improvement of their risk of distant metastasis. Weekly infusion of single agent cis-platinum mainly works as a radiation sensitizer for local disease and is not expected to be an effective regimen for systemic metastasis. Patients with specific clinical parameters had high 5-year distant relapse rates. For example, the distant relapse rate was 33% for those with positive lymph node involvement shown on CT/MRI, 27% for those with an SCC-ag level >10 and 30% for those with stage III/IVA disease. Although the general consensus is that cis-platinum is an essential element for chemotherapy, the best combination regimen is still being developed and patients with one or more of these clinical characteristics are good candidates for clinical trials to test the efficacy of a new regimen.

Group III are patients who do not belong to group I or II and for whom concurrent single-agent cis-platinum treatment is appropriate by present standards. For patients who have higher than stage IB1 and non-bulky IIA disease, and do not have the risk factors listed in group II, CCRT with weekly cis-plat-

inum is an acceptable regimen for those under 45 years of age. For those with the same clinical characteristics but aged between 45 and 65 years, either RT alone or concurrent weekly cis-platinum (preferably within a clinical trial) is an acceptable treatment.

Conclusion

The American NCI recommended concurrent chemotherapy for "all" women with cervical cancer primarily treated with RT. However, our results have shown that some subsets of patients, especially those with stage IB1 disease and elderly patients with stage IB2 and II, can achieve good treatment outcomes with RT alone, and the benefit of treating them with CCRT is questionable. Prospective studies or meta-analysis are necessary to establish the role of CCRT in these good prognosis patients. Furthermore, instead of single-agent cis-platinum, more intensive combination chemotherapy should be developed for patients who have a high risk of distant relapse.

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