A regional cooperative clinical study of radiation therapy for stage IIIB carcinoma of the uterine cervix in Asian countries

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Abstract

Objective: International clinical study was undertaken to evaluate the pilot protocol on radiation therapy for stage IIIB carcinoma of the uterine cervix for Asian patients.

Methods: From January 1996 to Sep. 1998, 210 patients with squamous cell carcinoma of stage IIIB uterine cervix treated by standardized protocol were analyzed retrospectively with regard to survival, control rate, possible prognosis factors, and relapse patterns. Patients were treated with combination of external pelvis irradiation and intracavitary radiation therapy. Additionally many problems involving to undertake regional clinical study are discussed.

Results: An average age is 61 ± 13 years (range 35 to 83), varying significant among countries . The 5-years survival rate is 53.7% and the 5-year local control rate is 81.5%. Patients with tumor of small size or medium size showed the 5-year survival rates of approximately 60%, which were significantly better than the 28.8% of those with large tumor. Severe acute reaction was developed for 5 patients including one severe bleeding in the rectum, two sever cystitis and ileus of small intestine. More than 98 % of the patients had minimum and mild acute radiation

reaction. Sever cystitis developed for 4 patients, one of whom had ulceration. 3 patients had severe proctitis and one had severe small intestinitis. More than 95 % of the patients had minimum and mild late radiation reaction.

Conclusion: The present study suggests that the pilot radiation protocol in stage IIIB carcinoma of the cervix is effective in terms of long survival and local control and well tolerated in acceptable acute and late toxicity.

Key Words: Carcinoma , Uterine Cervix , Radiation therapy

Introduction

Incidence of uterine cervix cancer is ranked in the first or second among female cancers in many Asian countries(1). It is, therefore, of major concern for the welfare of the public of the region to develop and establish effective methods of medical care for this disease. Radiation therapy is recognized to play a very important and effective role among many treatment modalities for this cancer(2,3). However, the treatment methods and facilities for radiation therapy are considerably varied among Asian countries due to various technical and socio-economical limitations.

There are many patients with cervical cancer in the region who have not an opportunity to receive appropriate radiation therapy treatment and, resultantly, are treated with compromised treatment method due to machinery shortage. Consequently, clinical results of advanced cervical cancer remained to be poor in many hospitals in Asian countries(1). Radiation oncologists in the region recognized the importance to try to maintain applying optimal treatment methods to overcome these clinical situations. On the other hand, it would be very useful to create suitable treatment protocol for Asian countries under such a socio-economical limitations.

For this purpose, it was proposed, as the first step, for the participating medical institutions of the eight Asian countries, including China, Indonesia, Japan, Korea, Malaysia, Philippines, Thailand, and Vietnam to carry out radiation therapy of cervical cancer according to a unified "Standardized protocol", so that the results of

the treatment from each country can be compiled together for scientific and statistical evaluation.

The proposed cooperative study, which is the first trial in the region, aims to establish the most effective treatment procedures of radiation therapy of stage IIIB carcinoma of the uterine cervix that could be commonly made available to the region. The present study reports clinical outcome including the rate of survival and control, possible prognosis factors and relapse pattern to establish the most effective radiotherapy procedure for advance carcinoma of the cervix in the region. Additionally, many problems involving in undertaking regional cooperative clinical study are discussed.

Materials and Methods

In order to improve our living standard, it is mandatory to foster secure, competitive and reliable energy sources and production that are environmentally and economically sustainable. In this connection, the International Conference for Nuclear Cooperation in Asia (ICNCA) was launched in 1990 and has been promoting peaceful use of atomic energy in Asia. More recently ICNCA was succeeded by the Forum of Nuclear Cooperation in Asia (FNCA). Based on this agreement, since 1993, the seminar on Radiation Oncology has been held annually at the participating countries including China, Indonesia, Japan, Korea, Malaysia, Philippines, Thailand, and Vietnam in turn. At the third Seminar in Thailand in 1994, the clinical study on radiation therapy for locally advanced uterine cervical cancer was chosen as the unique multi-center cooperative study in Asia. The protocol was established as following and the patients were treated according to the protocol.

Patient eligibility

Previously untreated cervical cancer with squamous cell carcinoma of the uterine cervix and stage IIIB (T3BNXM0) with vaginal invasion under 2/3 of vaginal wall were entered in this trial. Additionally, the patients with following criterions were prohibited for inclusion; history of previous irradiation on the treatment field,

poor general conditions expected survival less than 6 months, poor physical condition (Performance status is 3 or 4), presence of active double cancer, and presence of active or persistent infection in the treatment area.

Pretreatment medical evaluation.

Pre treatment diagnosis was made according to FIGO formulation(4). Although CT diagnosis of tumor spread was applied at some hospitals capable of using CT, for clinical staging, local tumor spread was diagnosed by conventional digital examination and IP.

Radiation therapy methods

Patients were treated in combination with external and intracavitary irradiations. External whole pelvic irradiation with antero-posterior and postero-anterior parallel opposing ports by use of Linac X-ray or Tele cobalt γ-ray was performed with a dose of 1.8-2.0 Gy per fraction, 5 times a week, to a total dose of about 30 Gy. Subsequently, a central shielding pelvic field irradiation with a dose of 2 Gy per fraction, 5 times a week was followed to a total dose of 20 Gy. Total dose of external irradiation was requested to fix to be about 50 Gy. Along with the central shielding irradiation, these patients also received intracavitary irradiation by Low dose rate or High dose rate sources which each institution is available.

Regarding intracavitary irradiation, either high dose rate method or low dose rate technique can be used. Combination of tandem and ovoid sources is recommended in order to make the Manchester-like dose distribution. Point A and B doses are to be calculated as reference dose. Standard doses at point A are as following; as for high dose rate treatment, treatment constraints are total point A dose of 20~28 Gy / 4 fractions / 4 wks (once a week, 5~7 Gy / fraction). Total point A dose is allowed to be altered according to tumor volume by altering fraction dose, for example, 5 Gy / fr. for small tumor, 6 Gy / fr. for medium tumor, and 7 Gy / fr. for large tumor. Regarding low (medium) dose rate treatment, treatment constraints are total doses of 30~40 Gy at point A / fractions / 1 wk. Total dose of intracavitary irradiation is allowed to modify according to policy of radiation oncologist. Over all

treatment period is regarded as one of the prognostic factors. Hence, radiation therapy was requested to be accomplished in no longer than 49 days. The treatment schedule is shown in Table 1.

Clinical evaluation

Acute and late radiation effects on tissues and organs for example, rectum and sigmoid colon, urinary bladder and small intestine are assessed and scored according to the RTOG, RTOG/EORTC scoring criteria for acute and late radiation morbidity. Tumor shrinkage was assessed by CT image, ultrasound or digital examination. Tumor control rate and survival rates up to 5 years, and patterns of failures were analyzed. Histological diagnosis had to be made according to the WHO classification. Autopsy was recommended for each case expired as much as possible.

Number of patients to be registerd

At least, 20 patients per one year were obliged to be treated according to the protocol in each country from January first, 1996 to 1998 in order to gather more than160 patients among 8 countries as a minimum requirement. Patients were requested to be followed minimum of 5 years and a maximum of 7 years after radiation therapy.

Registration and evaluation

Registration center at National Institute of Radiological Sciences in Chiba Japan accumulated and analyzed the data of the patients. The results were presented and evaluated at the annual Radiation Oncology Seminar held at regional institutions each year. Data center distributed 'Case Registration Sheets' (Doc.1) with 'Filling Guide' (Doc.2) to project members in duty of all participating countries. Project members in each country fined and sent the sheets to data center. Data center checked the sheets and recorded. After case registration, follow-up data have been collected and recorded every year.

Results

Patient characteristics

The numbers of registration in this project were 210 cases including 34 cases from China, 24 from Indonesia, 33 from Japan, 20 from Korea, 12 cases from Malaysia, 22 from Philippines, 37 from Thailand, and 28 from Vietnam.

In regard to patient characteristics, there was no significant difference in age, tumor size at portio, and the whole pelvis external irradiation dose between the HDR and MDR/LDR treatment.

One hundred patients were treated with HDR brachytherapy and 109 patients were treated with LDR/MDR. However, The rate of follow-up was clearly higher in HDR group than MDR/LDR treatment (Table 2).

As for the age distribution for the case, elderly patients were relatively outnumbered in China(59 years old) and Japan(66 years old), younger patients were outnumbered in Indonesia(47 years old), and most patients were in their fifties in other countries. Patients were consisted with 35% of small tumor (<40mm in diameter), 51% of medium tumor (40mm-60mm), and 14% of large tumor (>60mm). Incidence of large tumor was higher in Korea and Philippine. As for the degrees of tumor infiltration into the parametrium, although it was a subjective classification, there were many slight infiltrations in Indonesia, Malaysia and, in contrast, there were many intensive infiltrations especially in Vietnam and China.

Treatment evaluations

Twenty eight percent of the patients received Co-60 X-ray for external radiotherapy. The others were treated by 4MV(4%), 6MV(8%) or 10MV (56%) photon beam from linear accelerator. Histogram of various doses of Whole pelvis field (WP), central shielding pelvis field(CS), HDR and LDR/MDR are shown in Figure 1. WP irradiation was delivered ranging from 1750 to 5250 cGy, an average dose was 3399 ± 309. An average central shielding pelvis(CS) irradiation dose was 1657± 444 cGy (ranging from 250 to 3250 cGy). The dose delivered to the point A by HDR brachytherapy was 2486 ± 432 cGy (ranging from 1200 to 3200 cGy). The dose delivered to the point A by LDR/MDR brachytherapy was 3240 ±

432 cGy (ranging from 2600 to 5000 cGy). Total treatment time was a median of 55 days.

Figure 2 shows the distribution of WP dose and CS dose according to tumor size. Although the doses vary widely among patients, as the tumor size became bigger, the dose was getting higher in the whole pelvis external irradiation. As far as radiation doses are concerned, the patients seemed to be treated with individualized policy of participating doctors for the benefit of patients.

Figure 3 shows the correlation between intracavitary irradiation dose and whole pelvic dose. The distribution of point A dose in the HDR scattered toward low dose side of whole pelvis dose, and, in contrast, that of MDR/LDR scattered toward high dose side.

Regarding the distribution of the over all treatment period, approximately 72 % of all patients finished radiation therapy within 50 days and 28 % of the patients were treated with prolonged treatment time (maximum of 100 days).

Follow-up status

Most of the surviving patients were followed more than 5 years. The follow up rates at 5 years after radiation therapy in China, Indonesia, Japan, Korea, Malaysia, Philippines, Thailand, Vietnam, and total were 94%, 29%, 100%, 100%, 50%,96%,73%,11%, and 71%, respectively. In Japan, Korea, and Philippines, the follow-up was excellent and it to be favorable in China, Thailand. However, in Indonesia, Malaysia and Vietnam, the follow up rate were poor for clinical analysis. For five countries having rather favorable follow-up including Japan, Korea, Philippines, China, and Thailand, the follow-up rate was 91.1%.

Clinical Results

Figure 4 shows overall survival rates and local control rates for all of 210 patients. As a whole, the 5-years survival rate was 53.7% and the local control rate was 81.5 %, the rates of which were similar to that of the standard treatment in Japan. For five countries having accumulated follow-up rate being 91.1%, the 5-years

survival rate was 54.3% and the local control rate was 82.3%. Additionally, there was a wide difference in survivals according to country, one of the reason of which seems to be difference in follow-up aspects in each country.

Figure 5 shows overall survival rate according to tumor size. Patients with tumor of small size or medium size showed the 5-year survival rates of 60.7%, and 55.8%,respectively, which were significantly better than the 28.8% of the patients with large tumor($p<0.05$).

Among 74 patients(35.2%) died from various causes, 57 patients (27.1%) of the dead patients died from primary disease, including 28 (13.3%) having local recurrence, 29 (13.8%) having distant metastases. Two patients(0.95%) died from complication caused by radiation. Five patients(2.4%) died from intercurrent disease. Among them, approximately, a half of the deaths were caused by primary tumor and the later half were by metastasis of the tumor. It is noteworthy that 10 patients(4.8%) died from unknown reason. The 5 year survival rates according to the overall treatment periods below 50 days and over 50 days were 77.6% and 32%, respectively, which was significant difference.

Table 3 shows acute radiation morbidity according to RTOG scouring system. Severe acute reaction was developed for 5 patients including one severe bleeding in the rectum, two sever cystitis and ileus of small intestine. More than 98 % of the patients had minimum and mild acute radiation reaction.

Table 4 shows late radiation morbidity according to RTOG scouring system. Sever cystitis developed for 4 patients, one of whom had ulceration. 3 patients had sever proctitis and one had sever small intestinitis. More than 95 % of the patients had minimum and mild late radiation reaction. Eleven to thirteen percent of patients lost their information of late morbidity.

Discussion

The objectives of our study was to define and improve the quality and accessibility of radiation therapy care for stage IIIB uterine cervix cancer in Asian

countries. To accomplish this goal, it is necessary to examine radiation therapy as it is presently practiced in various settings in Asian countries and to develop treatment protocol for optimal radiation therapy care. Through these procedure, the needs of radiation therapy in the region would be identified in its scientific and operational aspects.

It has already been 5 years since the pilot study on the standardization of radiation therapy for uterine cervix cancer have been initiated in eight Asian countries, including Japan, Korea, China, Vietnam, Thailand, Malaysia, Indonesia and Philippines.

The present study demonstrated the 5-year survival rate of 58% for all cases, and the 5-year local control rate of 83%, which seems to be relatively better results in comparison with the reported 5 year survival rate of 40-60% and the pelvic recurrence rate of 30-40% for stage III disease documented by clinical results on radiation therapy for cervical cancer(2,3,5,6,7,8). There was a wide difference in survival rate among participating countries. Some of the reason may be difference in accuracy of follow-up rate, treatment variations and variations of tumor volume among the countries.

The correlation between intracavitary irradiation dose and whole pelvic dose showed that the distribution of point A dose in the HDR scattered toward low dose side of whole pelvis dose, and, in contrast, that of MDR/LDR scattered toward the high dose side. This trend may be due to the fact that the former resulted from the difficulty of insertion of tandem applicator for bigger tumor cases that required with higher external doses for substitution. One of the reasons of the LDR latter may be due to different understanding of optimum doses at point A in each doctor for large tumors.

Perez et al. reported the 5-year major complication rates of 2.3% in the rectum, 2.6% in the urinary tract, and 3.9% in the small bowel in patients with cervical cancer(9). In the Patterns of Care Studies (PCS) in the US, the 5-year overall major complication rates ranged from 7% to 15%, and about 70% were bowel

complications(7). In the HDR series, the 5-year major complication rates of 2-5 % in the rectum, 3-5% in the bladder, and 2-3% in the small bowel in patients treated with the similar doses and fractionation schedules to ours(2,3,10). Compared with these data, the patients of the present study had minimal severe complications to be admitted. Hence, our study suggests that the pilot radiation protocol in stage IIIB carcinoma of the cervix is effective and well tolerated, with acceptable acute and late toxicities.

However, about 30% of lost follow-up cases and 10 patients of unknown death impaired accuracy of the clinical results because the better 5-year local control rate may be strongly influenced by the poor follow-up as well as for 5-year survival. Hence, data of the five countries having accumulated follow-up rate being 91.1% was assessed and showed the 5-years survival rate of 54.3% and the local control rate of 82.3%, representing our data are effective.

Comparing relatively better survival rate for patients with tumor of small size or medium size, the patients with large tumor showed significantly poorer survival rate in the present study. The strong correlation between tumor size and treatment outcome is well documented(6-10). As concurrent chemoradiotherapy proved improvement of survival for advanced cervical cancer recently(11-13), the concurrent chemoradiotherapy should be applied at least for patients with bulky cervical tumors.

The present study demonstrated that there was significant difference in the 5 year survival according to treatment time. Several studies demonstrated a significant decrease in pelvic tumor control and survival rates when overall treatment time increased beyond 6 weeks (14,15). In the conventional LDR treatment, the overall treatment time is usually 7 to 9 weeks (6,7,8). In some HDR series, the overall treatment time was over 8 weeks, because 4-5 fractions of HDR-ICBT were performed only after delivering 40-45 Gy of EBRT(10).However, comparing to treatment protocol in USA, most of our patients still accomplished within shorter period than that in the USA. Hence, the fact that overall treatment time of our range

period may affect survival rate and relatively better survival rate of our study was achieved may be due to relatively shorter treatment period.

Regarding follow-up status, the follow-up rate of 71 % really resulted from the elaborate efforts of the participating doctors trying best to select and enter patients who can be followed for over 5 years. Taking into account that the follow-up rate in some countries of this Asian region usually is around 50% of all patients treated for various cancers, our follow-up rate may be significantly higher than the usual and regarded to be rather positive improvement in the follow-up rate. Even though the deficits of the present study, it was very important that it was the first time for some radiation oncologists that they confirmed quality of their own treatment by relatively reliable clinical results of their own. Many of the radiation oncologists in the region are too busy for their routine clinic to chase patients for follow-up and to confirm their own treatment results. Even if they would try to follow them, it is very much difficult to chase patients for several years because of difficulty in communicate with patients. For further organization of international clinical study in this region, establishment of accurate follow-up system for patients treated is urgent matter to be solved. One of the clues may be that patients to be enrolled into a controlled clinical trial should be chosen in terms of accessibility of the patients, for example, city resident, those having telephone, etc.

This kind of international cooperative clinical study in radiation oncology field has never been performed in Asia, although the uterine cervix cancer occupied the major proportion of cancers in the radiation treatment in the region. This trial provided important opportunity of comparing the present status of radiation therapy being performed among various Asian countries as well as to successfully achieve international clinical study.

Although some countries have domestic limitations by economically underdevelopment and socio-political status, these problems cannot be obstacles to prohibit the improvement of radiation therapy techniques academically, if Asian countries including well-developed and developing countries cooperate each other. To do it, above all, it was very important that participating scientists understood the

present status and circumstance of radiation oncology in each country one another through the annual radiation oncology study meeting. When it came to analysis of our research data, it was also to be admitted that we are facing some difficulties in analyzing them because of the difference of treatment techniques and treatment facilities among various countries. Furthermore, when we are trying to report our results to the international journals, these difficulties may induce more serious problems, because this trial has some deficits from scientific viewpoint and we cannot draw a reliable conclusion. However, because these data are for pilot study on the standardization of radiation treatment methods in Asian countries, there seems no problem in reporting to the international journals, unless we make an unreasonable analysis and make misunderstanding conclusions.

In conclusion, the pilot radiation protocol in stage IIIB carcinoma of the cervix was effective and well tolerated, with acceptable acute toxicity. The participants confirmed that the proposed protocol may be one of the most effective treatment procedures of radiation therapy of stage IIIB cervical cancer in Asian region for the first time. Our study must continue to monitor the practice of radiation oncology on Asian basis, observing areas needing improvement and directing educational interventions to improve treatment results or care. To accomplish this objective, we have to do (1) the continued monitoring of our Asian treatment outcomes with long-term follow up, (2) the continued assessment of efficacy of new technologies as they become active in clinical practice, and (3) monitoring the penetration of positive new clinical trials into the Asian practice. This joint international endeavor will not only contribute to the improved treatment of patients in the region but also to the advancement of medical science, radiation oncology in particular, through the exchange and sharing of valuable information and experiences among participating institutions.

References

1. Tatsuzaki H, Levin CV.Quantitative status of resources for radiation therapy in

Asia and Pacific region.Radiother Oncol. 2001 Jul;60(1):81-9.

2. Arai T, Nakano T, Morita S, Sakashita K, Nakamura YK, Fukuhisa K.,. High dose rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. A 20-year experience. Cancer 69,175-180, 1992.

3. Teshima T, Inoue T, Ikeda H, Miyata Y, Nishiyama K, Inoue T, Murayama S, Yamasaki H, Kozuka T.. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital.Cancer 1993 Oct 15;72(8):2409-14

4. Annual report on the results of treatment in carcinoma of the uterus, vagina and ovary. Radiumhemmet, Sweden, 1979, Vol 16:FIGO.

5. Sakurai H, Mitsuhashi, N, Takahashi M, et al. Analysis of recurrence of squamous cell carcinoma of the uterine cervix after definitive radiation therapy alone -patterns of recurrence, latent periods and prognosis- Int. J. Radiat. Oncol. Biol. Phys. 50(5):1136-1144, 2001.

6. Perez CA, Grigsby PW, Chao C, 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: 307-317.

7. Komaki R, Brickner TJ, Hanlon AL, Owen JB, Hanks GE. Long-term results of treatment of cervical carcinoma in the United States in 1973, 1978, and 1983: Patterns of care study (PCS). Int J Radiat Oncol Biol Phys 1995; 31: 973-982.

8. Logsdon MD, Eifel PJ. FIGO IIIB squamous cell carcinoma of the cervix: An analysis of prognostic factors emphasizing the balance between external beam and

intracavitary radiation therapy. Int J Radiat Oncol Biol Phys 1999; 43: 763-775.

9. Perez CA, Beaux S, Bedwinek JM, et al. Radiation therapy alone in treatment of the uterine cervix. II. Analysis of complications. Cancer 1984; 54: 235-246.

10. Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer 2002; 94: 117-124.

11. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, Rotman M, Gershenson DM, Mutch DG.: Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340: 1137-1143, 1999

12. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL 3rd, Walker JL, Gersell D.: Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 340: 1154-1161, 1999

13. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, Clarke-Pearson DL, Insalaco S.: Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340: 1144-1153, 1999

14. Lanciano RM, Pajak TF, Martz K, Hanks GE. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: A patterns-of-care study. Int J Radiat Oncol Biol Phys 1993; 25: 391-397.

15. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. 1. Impact of prolongation of overall treatment time and timing of

brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995; 32: 1275-1288.

Legends for figures

Figure 1. Histograms of intensities of various type of irradiation. a, Whole pelvis dose. b, Central shielding dose. c, point A dose of HDR brachytherapy. d, point A dose of LDR/MDR brachytherapy

Figure 2. Correlation between whole pelvis dose and tumor size.

Figure 3. Scatter gram between point A dose of brachytherapy and whole pelvis dose.

Figure 4. Over all survival and local control rates of the patients treated with radiation therapy.

Figure 5. Over all survival rates of the patients treated with radiation therapy according to tumor size.