Delaloye *et al*, 1996). Fyles *et al* (1992) reported the influence of treatment duration on local control. Using three statistical methods of analysis in 830 patients, they observed loss of local control of approximately 1% per day when treatment lasted over 30 days, most evident in stage III and IV patients. Girinsky *et al* (1993) also reported decreased rates of local control and survival when the treatment period was longer than 52 days. By multiple regression analysis, they observed loss of 1.1% local control per day when the treatment period was prolonged from 52 days to more than 62 days. All patients in the current study received radiation therapy within 7 weeks, and this yielded a better result. Second, ICBT is divided into many fractions. According to the linear quadratic model, tumour cells sustain more damage than normal cells by a reduction in the exposure dose and fractionation. The cure rate is improved by controlling normal tissue side effects, easing late complications, and maintaining equal doses of radiation. Intracavitary brachytherapy is more difficult than EBRT, but greater efficacy and fewer complications result (Barendsen, 1982; Fowler, 1989; Brenner and Hall, 1992; Dale and Jones, 1998).

Perez *et al* (1999) investigated correlation between irradiation therapy and sequelae. They graded sequelae as follows: grade 2, producing major symptoms, repeated occurrences requiring short-term (less than 4 weeks) hospitalisation for diagnosis and non-surgical management; grade 3, requiring an operative procedure for correction or prolonged hospitalisation (over 4 weeks) or life threatening. For disease stages II or more, they reported grade 2 morbidity of 10–12% and grade 3 morbidity of 10%. The most frequent grade 2 sequelae were cystitis and proctitis (0.7–3%), and the most common grade 3 sequelae were vesicovaginal fistula (0.6–2%), rectovaginal fistula (0.8–3%), and intestinal obstruction (0.8–4%). Nakano *et al* (2005) also reported late toxicity of radiation therapy. The 10-year actuarial grade 3–5 complication rate was 4.4% in the rectosigmoid colon, 0.9% in the bladder, and 3.3% in the small intestine. Considering these data, morbidity after radiotherapy in our patient population was acceptable. However, survival data of a considerable proportion of the study patients were obtained from the family register database. We believe the survival data are accurate. However, radiotherapy-related morbidity might have been underestimated.

An important issue in the treatment of cervical cancer is how to treat advanced-stage disease, which affects the majority of patients. The reported survival of patients with stage III cervical cancer treated with radiation therapy alone is between 30 and 50% (Barillot *et al*, 1997). Perez *et al* (1999) reported 1456 patients given EBRT (whole pelvis and central shielding, total 50–60 Gy, depending on tumour size) and ICBT (80–90 Gy at point A for stage IIb–IV disease). The 10-year survival rate was 65% for patients with stage IIb disease and 40% for patients with stage III disease, but there were no long-term survivors among patients with stage IV disease. Logsdon and Eifel (1999) reported 983 patients with stage IIIb SCC treated with various radiotherapies, including EBRT and ICBT. The overall survival was 32%. Barillot *et al* (1997) reported a large multi-centre study of 1875 patients treated with radiation alone. Specific survival at 5 years was 70% for stage IIb, 55% for stage IIIa, 45% for stage IIIb, and 10% for stage IV disease. Nakano *et al* (2005) also reported long-term follow-up data for 1148 patients treated with EBRT (whole pelvis and central shielding, total 45–50 Gy at 1.8–2 Gy per fraction) and ICBT (24 Gy in four fractions). The 5- and 10-year cause-specific survival rates were 80 and 74%, respectively, for stage II disease and 66 and 59%, respectively, for stage III disease.

Radiation therapy is known to cause various malignancies, including leukaemia, sarcoma, thyroid carcinoma, and lung carcinoma. Boice *et al* (1985) examined data from 15 cancer registries in eight countries and compared the number of second cancers reported for 182 040 women against the number expected had the same risk prevailed as in the general population. They found an increased risk for cancers of the bladder, rectum, vagina, and caecum. Arai *et al* (1991) reported significantly higher incidences of second cancers in the rectum, bladder, and lung as well as leukaemia. Kleinerman *et al* (1995) described a large-scale study of 49 828 patients with cervical cancer treated with radiation therapy and 16 713 matched patients treated without radiotherapy. They reported that most of the second cancers were of the rectum, vagina, vulva, and bladder, and they concluded that radiation is an important cause of the second cancers, with no evidence that the risk returns to a normal level. Second cancers were observed in 13 of our patients (0.87%), most frequently in the rectum (five cases), colon (three cases), and uterine body (two cases). Although there are many reports on radiation-induced cancer, such cancers occurred in less than 1% of our patients. Although our radiotherapy regimen causes some complications, the benefits of the treatment outweigh the disadvantages. Continued improvement in radiotherapeutic techniques, along with diagnosis at younger ages and earlier stages, will result in longer survival times for patients. This may in turn increase the significance of radiation-related second cancers.

In recent years, several groups have reported concurrent chemoradiation to improve the survival of patients with locally advanced cervical carcinoma (Keys *et al*, 1999; Morris *et al*, 1999; Rose *et al*, 1999; Whitney *et al*, 1999; Peters *et al*, 2000). Cisplatin is the most active cytotoxic agent against cervical cancer. Questions pertaining to treatment of cervical cancer are focused mainly on chemotherapy regimens, so there is a tendency to ignore the radiotherapy method.

In 1999, the National Cancer Institute (USA) published an announcement stating that cisplatin-based chemotherapy should be used concomitantly with radiation therapy in cases of cervical cancer. However, there were not an adequate numbers of patients with advanced cancer in the studies published, particularly patients with pelvic and/or para-aortic lymph node metastasis. We know from surgical series that the incidence of positive para-aortic nodes is less than 10% for stage II, 20% for stage II, 30% for stage III, and 40% for stage IV disease (Berman *et al*, 1984). Although the current study is a retrospective one, it involved a purely consecutive series of patients regardless of pelvic and/or para-aortic lymph node status before treatment, so the data may be of great value.

In conclusion, long-term results of our ICBT/EBRT regimen for cervical cancer are reviewed herein. Our method of irradiation is unique, but it provides a good result and a decreased incidence of complications. Our study is one of only a few long-term follow-up studies involving a large number of patients, and it yielded valuable data pertaining to the incidence of second cancers following radiation therapy for cervical cancer. The standard treatment for locally advanced cervical cancer is gradually changing to concurrent chemoradiation. The main issue in the treatment of cervical cancer is how chemotherapy is used, but we believe the radiation methodology needs further discussion.

REFERENCES

Arai T, Nakano T, Fukuhisa K, Kasamatsu T, Tsunematsu R, Masubuchi K, Yamauchi K, Hamada T, Fukuda T, Noguchi H, Motoi M (1991) Second cancer after radiation therapy for cancer of the uterine cervix. *Cancer* 67: 398–405

Barendsen GW (1982) Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Int J Radiat Oncol Biol Phys* 8: 1981–1997

Barillot I, Horiot JC, Pigneux J, Schraub S, Pourquier H, Daly N, Bolla M, Rozan R (1997) Carcinoma of the intact uterine cervix treated with

radiotherapy alone: a French cooperative group study: update and multivariate analysis of prognostic factors. *Int J Radiat Oncol Biol Phys* **38:** 969–978

Berman ML, Keys H, Creasman W, DiSaia P, Bundy B, Blessing J (1984) Survival and patients of recurrence in cervical cancer metastatic to periaortic lymph nodes (a gynecology oncology group study). *Gynecol Oncol* **19:** 8–16

Boice Jr JD, Day NE, Andersen A, Brinton LA, Brown R, Choi NW, Clarke EA, Colemen MP, Curtis RE, Flannery JT (1985) Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. *J Natl Cancer Inst* **74:** 955–975

Boice Jr JD, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, Moloney WC, Austin DF, Bosch A, Cookfair DL (1988) Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res* **116:** 3–55

Brenner DJ, Hall EJ (1992) The origins and basis of the linear-quadratic model. *Int J Radiat Oncol Biol Phys* **23:** 252–253

Coia L, Won M, Lanciano R, Marcial VA, Martz K, Hanks G (1990) The patterns of care outcome study for cancer of the uterine cervix. Results of the second national practice survey. *Cancer* **66:** 2451–2456

Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Phys* **31:** 1341–1346

Dale RG, Jones B (1998) The clinical radiobiology of brachytherapy. *Br J Radiol* **71:** 465–483

Delaloye JF, Coucke PA, Pampallona S, De Grandi P (1996) Effect of total treatment time on event-free survival in carcinoma of the cervix. *Gynecol Oncol* **60:** 42–48

Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* **62:** 679–694

Fyles A, Keane TJ, Barton M, Simm J (1992) The effect of treatment duration in the local control of cervix cancer. *Radiother Oncol* **25:** 273–279

Girinsky T, Rey A, Roche B, Haie C, Gerbaulet A, Randrianarivello H, Chassagne D (1993) Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. *Int J Radiat Oncol Biol Phys* **27:** 1051–1056

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

Kleinerman RA, Boice Jr JD, Storm HH, Sparen P, Andersen A, Pukkala E, Lynch CF, Hankey BF, Flannery JT (1995) Second primary cancer after treatment for cervical cancer. An international cancer registries study. *Cancer* **76:** 442–452

Komaki R, Brickner TJ, Hanlon AL, Owen JB, Hanks GE (1995) 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* **31:** 973–982

Lanciano RM, Pajak TF, Martz K, Hanks GE (1993) 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* **25:** 391–397

Logsdon MD, Eifel PJ (1999) 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 Phy* **43:** 763–775

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

Nakano T, Kato S, Ohno T, Tsujii H, Sato S, Fukuhisa K, Arai T (2005) Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* **103:** 92–101

Perez CA, Grigsby PW, Castro-Vita H, Lockett MA (1995) Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys* **32:** 1275–1288

Perez CA, Grigsby PW, Lockett MA, Chao KS, Williamson J (1999) Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. *Int J Radiat Oncol Biol Phys* **44:** 855–866

Peters III WA, Liu PY, Barrett II RJ, Stock RJ, Monk BJ, Berek JS, Souhami L, Grigsby P, Gordon Jr W, Alberts DS (2000) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* **18:** 1606–1613

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

Schonberg B, Myer M (1972) Statistical methods for studying multiple primary malignant neoplasms. *Cancer* **40:** 1892–1898

Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler Jr WC, Clarke-Pearson DL, Liao SY (1999) Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: gynecologic oncology group and southwest oncology group study. *J Clin Oncol* **17:** 1339–1348

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 2, pp. 485–490, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.12.013

PRACTICE PATTERNS OF RADIOTHERAPY IN CERVICAL CANCER AMONG MEMBER GROUPS OF THE GYNECOLOGIC CANCER INTERGROUP (GCIG)

DAVID K. GAFFNEY, M.D., PH.D.,* ANDREAS DU BOIS, M.D.,† KAILASH NARAYAN, M.D.,‡ NICK REED, M.D.,§ TAKAFUMI TOITA, M.D.,‖ SANDRO PIGNATA, M.D.,¶ PETER BLAKE, M.D.,# LORRAINE PORTELANCE, M.D.,** AZMAT SADOYZE, M.D.,†† RICHARD PÖTTER, M.D.,‡‡ ALESSANDRO COLOMBO, M.D.,§§ MARCUS RANDALL, M.D.,¶¶ MANSOOR R. MIRZA, M.D.,‖‖ AND EDWARD L. TRIMBLE, M.D.##

*Radiation Therapy Oncology Group, Salt Lake City, UT; †Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom, Weisbaden, Germany; ‡Australia & New Zealand Gynecological Oncology Group, Melbourne, Australia; §European Organization for Research and Treatment of Cancer, Glasgow, Scotland; ‖Japanese Gynecologic Oncology Group, Okinawa, Japan; ¶Multicenter Italian Trials in Ovarian Cancer, Naples, Italy; #Royal Marsden Hospital, London, England; **National Cancer Institute of Canada, Montreal, Canada; ††Scottish Gynaecological Cancer Trials Group, Glasgow, Scotland; ‡‡Arbeitsgemeinschaft Gynaekologische Onkologie Austria, Vienna, Austria; §§Mario Negri Gynecological Oncology Group, Lecco, Italy; ¶¶Gynecological Oncology Group, Lexington, KY; ‖‖Nordic Society of Gynecological Oncology, Odense, Denmark; ##National Cancer Institute, Baltimore, MD

Purpose: The aim of this study was to describe radiotherapeutic practice of the treatment of cervical cancer in member groups of the Gynecologic Cancer Intergroup (GCIG).

Methods and Materials: A survey was developed and distributed to the members of the GCIG focusing on details of radiotherapy practice. Different scenarios were queried including advanced cervical cancer, postoperative patients, and para-aortic–positive lymph node cases. Items focused on indications for radiation therapy, radiation fields, dose, use of chemotherapy, brachytherapy and others. The cooperative groups from North America were compared with the other groups to evaluate potential differences in radiotherapy doses.

Results: A total of 39 surveys were returned from 13 different cooperative groups. For the treatment of advanced cervical cancer, external beam pelvic doses and total doses to point A were 47 + 3.5 Gy (mean + SD) and 79.1 + 7.9 Gy, respectively. Point A doses were not different between the North American cooperative groups compared with the others ($p = 0.103$). All groups used concomitant chemotherapy, with 30 of 36 respondents using weekly cisplatin. Of 33 respondents, 31 intervened for a low hemoglobin level. For a para-aortic field, the upper border was most commonly (15 of 24) at the T12-L1 interspace. Maintenance chemotherapy (after radiotherapy) was not performed by 68% of respondents. For vaginal brachytherapy after hysterectomy, 23 groups performed HDR brachytherapy and four groups used LDR brachytherapy. In the use of brachytherapy, there was no uniformity in dose prescription.

Conclusions: Radiotherapy practices among member groups of the GCIG are similar in terms of both doses and use of chemotherapy. © 2007 Elsevier Inc.

Cervix, Chemoradiation, Cooperative group.

INTRODUCTION

The Gynecologic Cancer Intergroup (GCIG) is a global association of cooperative groups involved in research and treatment of gynecologic neoplasms. International collaboration began in 1991 in the treatment of ovarian cancer, and regular meetings were initiated between cooperative groups in 1995 (1). By 1997 a more formal structure was adopted for cooperation among cooperative groups in gynecologic cancers, and the GCIG was created. The GCIG represents cooperative groups from Europe, Asia, Australia, and North America. There is no representation from Africa or South America. The GCIG currently represents 15 cooperative groups and receives partial administrative support from the National Cancer Institute (NCI) in the United States. The member groups of the GCIG are as follows: AGO-Austria, AGO-OVAR (Germany), ANZGOG (Australia, New Zea-

Reprint requests to: David K. Gaffney, M.D., Ph.D., Department of Radiation Oncology, Huntsman Cancer Hospital, 1950 Circle of Hope, Rm 1570, Salt Lake City, UT 84112; Tel: (801) 581-2396; Fax: (801) 585-2666; E-mail: david.gaffney@hci.utah.edu

Conflict of interest: none.

Received Oct 9, 2006, and in revised form Nov 10, 2006. Accepted for publication Dec 7, 2006.

land), EORTC (Europe), GEICO (Spain), GINECO (France), GOG (USA), JGOG (Japan), MANGO (Italy), MITO (Italy), MRC/NCRC (Great Britain), NCIC (Canada), NSGO (Scandinavia), Radiation Therapy Oncology Group (RTOG, US), and SGCTG (Scotland).

Cervical cancer is the second most common cancer diagnosed in women worldwide after breast cancer, with more than 493,000 new cases in 2002 (2). Similarly, cervical cancer is the third most common cause of death from cancer in women after breast and lung cancer. More than 273,000 women die annually of cervical cancer. Eastern and southern Africa record the highest incidence and mortality rates from cervical cancer. In the developed world the rates are markedly lower. Screening programs are responsible for the lower incidence rates in the developed countries (3).

Surgery is widely used for early cervical cancers (International Federation of Gynecology and Obstetrics [FIGO] I–IIA), whereas radiotherapy is the standard management for larger tumors or more advanced FIGO stages. Radiotherapy practice patterns of the treatment of cervical cancer have been studied in different countries over the past several decades (4–14). In the United States, practice patterns in the treatment of cervical cancer have been documented systematically through a funded mechanism (4, 10–12, 14). These studies have revealed the importance of limiting the overall treatment time, necessity of brachytherapy, institutional volume on improving umor control, and the superiority of fractionated low-dose-rate (LDR) brachytherapy over a single insertion. In Japan, Patterns of Care Studies have revealed a 20% lower dose than practiced in the United States (13). Brachytherapy practice patterns have been specifically studied in the Patterns of Care studies (5, 7, 14). In the United States between the years 1996 and 1999, 94% of patients received curative-intent brachytherapy. Of patients receiving brachytherapy in that report 77.8% received LDR and 13.3% received HDR brachytherapy (14).

In 1999 the NCI of the United States published a clinical alert indicating a survival benefit for the addition of cisplatin-based chemotherapy to radiotherapy in FIGO stages IB2–IVA (15–21). Meta-analyses have confirmed the survival advantage of chemoradiotherapy over radiotherapy alone (22). Some studies have documented the rapid incorporation of cisplatin-based chemoradiotherapy as standard treatment within a short period after the NCI 1999 clinical alert (9, 23).

In this study we describe the radiotherapeutic practice of the treatment of cervical cancer in member groups of the GCIG. We also describe the use of chemotherapy in the treatment of advanced cervical cancer.

METHODS AND MATERIALS

A survey was developed by multiple members of the GCIG and was distributed to the members of the GCIG. This survey focused on the treatment of locally advanced cervical cancer and the adjuvant, post-operative treatment (see Appendix). The use of concurrent and sequential chemotherapy was queried also.

Table 1. Radiotherapy doses posthysterectomy

Area/dose	Mean (SD)(Gy)
Pelvic	47.9 (1.8)
Vaginal cuff brachytherapy	19.1 (8.4)
Vaginal cuff dpf brachytherapy	6.4 (1.6)
Para-aortic	45.6 (2.7)
Dpf (pelvis)	1.84 (0.08)
Dpf (para-aortic)	1.81 (0.06)

Abbreviation: Dpf = dose per fraction.

Each cooperative group was asked to submit four questionnaires from separate, representative centers. Centers chosen were required to have a large volume of cancer cases within that specific cooperative group. If the cooperative group had published or written guidelines then a single questionnaire was sufficient. A total of 39 questionnaires were returned. The number of respondents per GCIG member group were AGO-Austria, three; AGO-OVAR (Germany), three; ANZGOG (Australia, New Zealand), one; EORTC (Europe), two; GOG (USA), two; JGOG (Japan), four; MANGO (Italy), four; MITO (Italy), five; MRC/NCRC (Great Britain), one; NCIC (Canada), eight; NSGO (Scandinavia), one; RTOG (US), four; and SGCTG (Scotland), one. GEICO (Spain) is a medical oncology–only group and does not perform radiation oncology. Descriptive statistics were used and the Student's *t* test was used to compare differences between groups. The three groups from North America (GOG, NCIC, RTOG) were compared with the other groups to evaluate potential differences in radiotherapy doses.

RESULTS

Doses

A total of 39 surveys were returned from 13 different cooperative groups. For the treatment of locally advanced cervical cancer external beam pelvic doses, total doses to point B and point A were 48.0 Gy, 57.9 Gy, and 79.2 Gy, respectively (Table 1). The doses to point A and B were crude sums of the external beam and brachytherapy doses. There was very little variation in dose per fraction with a mean (± standard deviation [SD]) of 1.85 Gy ± 0.10 Gy with a range of 1.8 to 2.15 Gy. Similarly, for the treatment of the para-aortic chain there was little difference in prescribed dose, with a mean of 46.9 Gy ± 5.0 Gy. Point A doses were compared between the North American cooperative groups (GOG, NCIC, and RTOG) compared with the other groups, and no statistical difference was noted (p = 0.103). In North America the mean point A dose was 81.8 Gy ± 6.0 Gy, compared with a mean point A dose in the other cooperative groups of 77.4 Gy ± 8.6 Gy.

In the post-hysterectomy setting the mean pelvic dose was also 47.9 Gy ± 1.8 Gy. When a vaginal cuff boost was used the mean total dose was 19.1 Gy, delivered on average with 6.4 Gy ± 1.6 Gy fractions. For vaginal brachytherapy after hysterectomy, 23 groups performed HDR brachytherapy and four groups used LDR brachytherapy.

Table 2. Clinical parameters for locally advanced cervical cancer

Definitive RT	No. (%)
Pelvic field Size	
Large L4/5	17 (50)
Small L5/S1	4 (11.8)
NOS	5 (14.7)
CT planned	8 (23.5)
Type of simulation	
CT	33 (94.3)
Fluoroscopic	1 (2.9)
MR fusion	1 (2.9)
Implant device	
Tandem and ovoid	25 (86.2)
Tandem and ring	1 (3.4)
Either	3 (10.3)
Normal tissue points recorded	
Bladder and Rectum	20 (66.7)
Rectum	2 (6.7)
Bladder, Rectum and VSD	8 (26.7)
Intervene for low Hb	
Yes	31 (93.9)
no	1 (3)
Maybe	1 (3)
Type of chemo (concomitant)	
CDDP	30 (81.1)
5FU/CDDP	2 (5.4)
5FU/Nedaplatin	1 (2.7)
CDDP/Taxol	4 (10.8)
Indication for PA RT	
+ lymph nodes	14
+ para-aortic nodes	20
+ common iliac nodes	18
+ ext iliac nodes	1
Not performed	1
Upper border of PA field	
T10/11	4 (12.9)
T11/12	5 (16.1)
T12/L1	15 (48.4)
CT planned	7 (22.6)

Abbreviations: CDDP = cisplatin; CT = computed tomography; Hb = hemoglobin; MR = magnetic resonance; NOS = not otherwise specified; RT = radiotherapy; VSD = vaginal surface dose; PA = para aortic. Plus sign (+) denotes positive. In the CT-planned cases the upper border was not explicitly stated. When more than one response is indicated, a percentage is not given.

Locally advanced cervical cancer

For locally advanced cervical cancer the upper border of the pelvic field was set at L4/5, L5/S1, and not specifically stated for 17, 4, and 13 respondents, respectively (Table 2). Of the 35 respondents, 33 used computed tomographic simulation. A tandem and ovoid device was used exclusively in 25 of 29 respondents. For brachytherapy treatment planning, bladder and rectal points were recorded in 28 of 30 respondents. For locally advanced cervical cancer, all groups used concomitant chemotherapy, with 30 of 37 respondents using weekly cisplatin (CDDP). The dose of CDDP was 40 mg/m^2 in 27 respondents, 30 mg/m^2 in 1 respondent, 8 mg daily in one respondent, and 20 mg/m^2 times 5 days every 21 days in one respondent. Of 33 respondents, 31 intervened for a low hemoglobin level. For a para-aortic field, the upper border was most commonly at the T12 to L1 interspace (15 of 24 respondents).

Adjuvant treatment after a radical hysterectomy

In the adjuvant treatment after a radical hysterectomy multiple factors were used as indications to deliver radiotherapy or brachytherapy (Table 3). A large pelvic field (upper border at the junction of L4–L5) was most commonly prescribed (18 of 39 respondents, 46%). Concomitant chemotherapy was routinely used 28 of 36 respondents. Maintenance chemotherapy (after radiotherapy) was not performed in 68% of respondents. For vaginal brachytherapy after hysterectomy, 23 groups performed HDR brachytherapy and four groups used LDR brachytherapy. For brachytherapy the prescription point was at the vaginal surface, 0.5 cm, and 1 cm in eight, 18, and one respondent, respectively. In terms of length of the vagina treated, 13 groups prescribed treatment to a fraction of the vagina and 9 prescribed treatment to a definitive length in centimeters. A vaginal cylinder was used in 25 of 30 respondents, and 5 respondents used either a cylinder or ovoids.

DISCUSSION

Overall, this international collaborative study sponsored by the GCIG reveals very similar practice patterns in member groups of the GCIG. No serious impediments to international collaboration were identified. External beam and intracavitary doses were similar (Table 1). The SD in external beam doses for the definitive cases and postoperative treatment were 3.5 and 1.8 Gy, respectively. The SD in the daily dose per fraction was only 0.10 Gy. A previous report indicated a 20% lower dose prescribed in Japan compared with the US (13). Differences in doses practiced in North America compared with elsewhere were not documented in this study. This series also demonstrated that 97% (34 of 35 respondents) used either computed tomographic or magnetic resonance simulation. Field sizes were also similar among respondents (Tables 2 and 3).

In the use of brachytherapy after hysterectomy, HDR was most commonly used. Of the respondents, 23 used HDR and four used LDR. In the postoperative setting, there was no uniformity in the fraction of the vagina treated or in the doses and schedules used. The method of prescription varied, with nine centers prescribing to a specific length and 13 centers prescribing a dose to a specific fraction of the vagina with 1 of 3 being reported most frequently. For the definitive radiotherapy cases, the tandem and ovoid device was used exclusively in 86% of centers, either a tandem and ovoid or tandem and ring in 10% of cases, and a tandem and ring in only 3% of cases. Bladder and rectal dose points were recorded for 28 of 30 respondents.

For the definitive radiotherapy cases, there was high concordance in the use of chemotherapy, with all respondents using concurrent chemotherapy and with 30 of 33 respondents

Table 3. Clinical parameters for posthysterectomy cervix cancer

Adjuvant RT	No. (%)
RT Indications	
+ lymph nodes	32
+ margins	28
Deep stromal invasion	22
> 4 cm	14
Parametrial involvement	9
LVSI	22
Close margins	9
≥T2	7
≥IB2	5
Unfavorable histology	1
Pelvic field size	
LargeL4/5	18 (46.2)
Small L5/S1	9 (23.1)
NOS	9 (23.1)
CT planned	3 (7.7)
Concomitant chemotherapy	
Yes	28 (77.8)
No	1 (2.8)
Varies	7 (19.4)
Type of chemotherapy(concomitant)	
CDDP	28 (80.0)
5FU/CDDP	3 (8.6)
5FU/Nedaplatin	1 (2.9)
CDDP/Taxol	3 (8.6)
Dose of CDDP	
40 mg/m2 q wk	25 (89.3)
45 mg/m2 q wk	1 (3.6)
30 mg/m2 q wk	1 (3.6)
8 mg/m2 qd	1 (3.6)
Adjuvant chemotherapy after RT	
Yes	2 (5.9)
No	23 (67.6)
Varies	9 (26.5)
Indication for PA RT	
+ lymph nodes	12
+ para-aortic nodes	17
+ common iliac nodes	14
+ ext iliac nodes	1
No LN dissection	1
Not performed	3
Upper border of PA field	
T10/11	3 (9.7)
T11/12	7 (22.6)
T12/L1	18 (58.1)
CT planned	3 (9.7)
Vaginal cuff RT Indications	
Positive margins	26
Vaginal involvement	2
Close margins	7
≥TIB	3
LVSI	1
Deep stromal invasion	1
T2	1
Proportion of vagina treated	
1/3	6 (24)
	4 (16)
2/3	1 (4)
Whole	2 (8)
2 cm	1 (4)
4 cm	6 (24)
5 cm	2 (8)
	Varies 2 (8)
	Ovoids only 1 (4)
Normal tissue points recorded	
Bladder and rectum	23 (44.2)
Rectum	2 (3.8)
Prescription point	
cm	18 (34.6)
Vaginal surface	8 (15.4)
1 cm	1 (1.9)

Abbreviations: CDDP = cisplatin; LN = lymph node; LVSI = lymph vascular space invasion; NOS = not otherwise specified; PA = para aortic. RT = radiotherapy. Plus sign (+) denotes positive. When more than one answer is recorded then a percentage is not given.

using single-agent CDDP. Previous studies have indicated rapid incorporation of chemoradiotherapy as standard practice (9, 23). In patients treated with a radical hysterectomy, concomitant chemotherapy was routinely used in 28 of 36 respondents. Maintenance chemotherapy (after radiotherapy) was not performed by 23 of 34 respondents (68%).

This study was not documentation of radiotherapy delivered. This was a survey of best practice by select member groups of the GCIG. Also, this study is not a population average of radiotherapy practice. Some groups had higher numerically representation. It may or may not be representative of typical practice patterns within the country of the GCIG member. However, it does likely reflect best practice patterns, as institutions participating have express interest in clinical research in gynecologic cancers. In addition, in attempts to cover many aspects of cervical cancer treatment including concomitant and maintenance chemotherapy, we did not specifically enquire about LDR of HDR doses in the definitive cases. Thus, the doses reported here should not be used as justification of the appropriate LDR or HDR dose. The data do indicate that there are little differences in doses used by different groups in different countries. It is also the first global survey that we are aware of in radiotherapy for cervical cancer. In addition, the survey was a broad overview of radiotherapy practice for the international community. It did not include many details of prescriptive brachytherapy practice as have been documented previously (14).

Radiotherapy practices among member groups of the GCIG are similar in terms of fields and doses. For definitive radiotherapy cases, the predominant brachytherapy device is a tandem and ovoid; and after hysterectomy, a vaginal cylinder. At this time there is no uniformity in vaginal brachytherapy prescription after hysterectomy. All respondents used concomitant chemotherapy in definitive radiotherapy cases, and 83% used weekly cisplatin. Radiotherapy practices should not be a limitation to international participation in cervical cancer clinical trials.

REFERENCES

1. Vermorken JB, Avall-Lundqvist E, Pfisterer J, Bacon M. The Gynecologic Cancer Intergroup (GCIG): History and current status. *Ann Oncol* 2005;16(Suppl 8):viii39–viii42.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global Cancer Statistics, 2002. *CA Cancer J Clin* 2005;55:74–108.
3. Bray F, Loos AH, McCarron P, *et al.* Trends in cervical squamous cell carcinoma incidence in 13 European countries: Changing risk and the effects of screening. *Cancer Epidemiol Biomarkers Prev* 2005;14:677–686.
4. Hanks GE, Herring DF, Kramer S. Patterns of Care outcome studies. Results of the national practice in cancer of the cervix. *Cancer* 1983;51:959–967.
5. Jones B, Tan LT, Blake PR, Dale RG. Results of a questionnaire regarding the practice of radiotherapy for carcinoma of the cervix in the UK. *Br J Radiol* 1994;67:1226–1230.
6. Teshima T, Abe M, Ikeda H, *et al.* Patterns of care study of radiation therapy for cervical cancer in Japan: The influence of the stratification of institution on the process. *Jpn J Clin Oncol* 1998;28:388–395.
7. Potter R, Van Limbergen E, Gerstner N, Wambersie A. Survey of the use of the ICRU 38 in recording and reporting cervical cancer brachytherapy. *Radiother Oncol* 2001;58:11–18.
8. Denton AS, Bond SJ, Matthews S, *et al.* National audit of the management and outcome of carcinoma of the cervix treated with radiotherapy in 1993. *Clin Oncol (R Coll Radiol)* 2000; 12:347–353.
9. Haie-Meder C, Fervers B, Fondrinier E, *et al.* SOR guidelines for concomitant chemoradiotherapy for patients with uterine cervical cancers: Evidence update bulletin 2004. *Ann Oncol* 2005;16:1100–1108.
10. 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 Biol Phys* 1993;25:391–397.
11. Komaki R, Brickner TJ, Hanlon AL, *et al.* 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 Biol Phys* 1995;31:973–982.
12. Eifel PJ, Moughan J, Erickson B, *et al.* Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: A patterns of care study. *Int J Radiat Biol Phys* 2004;60: 1144–1153.
13. Teshima T. Patterns of care study in Japan. *Jpn J Clin Oncol* 2005;35:497–506.
14. Erickson B, Eifel P, Moughan J, *et al.* Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996–1999): A patterns of care study. *Int J Radiat Oncol Biol Phys* 2005;63:1083–1092.
15. 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: 1137–1143.
16. Eifel PJ, Winter K, Morris M, *et al.* 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;22:872–880.
17. Rose PG, Bundy BN, Watkins EB, *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;340:1144–1153.
18. Whitney CW, Sause W, Bundy BN, *et al.* Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: A Gynecol Oncol Group and Southwest Oncology Group study. *J Clin Oncol* 1999;17:1339–1348.
19. Peters WA III, Liu PY, Barrett RJ, *et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606–1613.
20. 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;340:1154–1161.
21. Pearcy T, Brundage M, Drouin P, *et al.* 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;20:966–972.
22. Green JA, Kirwan JM, Tierney JF, *et al.* Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: A systematic review and meta-analysis. *Lancet* 2001;358:781–786.
23. Barbera L, Paszat L, Thomas G, *et al.* The rapid uptake of concurrent chemotherapy for cervical cancer patients treated with curative radiation. *Int J Radiat Oncol Biol Phys* 2006; 64:1389–1394.

APPENDIX

Gynecologic Cancer Intergroup radiation oncology standard clinical practices survey

(Please single-click on each field to answer)

Cervical cancer

Post–radical hysterectomy adjuvant pelvic radiotherapy (RT)
- Indications: []
- Dose/fractions: []
- Field (provide borders): []
- Concomitant chemotherapy: []
  - Drug (s) (List if more than one; e.g. TIP, Carbo taxol, cis taxol): []
  - Dose: []
  - Schedule: []
  - Additional chemotherapy after radiation therapy: []

Post–radical hysterectomy adjuvant para-aortic RT
- Indications: []
- Dose/fractions: []
- Field (provide borders): []

Post–radical hysterectomy vaginal cuff RT
- Indications: []
- Total dose (brachytherapy): []
- Dose per fraction: []
- Number of insertions: []
- LDR: []
- HDR: []
- Device: []

Prescription point: []
Vaginal length: []
Normal tissue points recorded: []
Primary radiation for locally advanced disease
External pelvic dose/fractions: []
Field (provide borders): []
Method of planning/simulation: []
Computed tomographic simulation: []
Intensity-modulated radiotherapy: []
Conventional simulation: []
Do you routinely shield? []
Total pelvic dose: []
Total dose to point A: []
Total dose to point B: []
Device: []
Normal tissue points recorded: []
Hemoglobin/hematocrit goal: []
At start of RT: []
During RT: []
Do you intervene during RT and what is your target level? []
Concomitant chemotherapy: []
Drugs: []
Dose: []
Schedule: []
Indications for para-aortic RT: []
Dose/fractions: []
Field (provide borders): []

Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 107 (2007) 469–473
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary

Yutaka Nagai [a,*], Morihiko Inamine [a], Makoto Hirakawa [a], Kazuya Kamiyama [a], Kazuhiko Ogawa [b], Takafumi Toita [b], Sadayuki Murayama [b], Yoichi Aoki [a]

[a] *Department of Obstetrics and Gynecology, Faculty of Medicine, University of the Ryukyus, 207 Uehara, Nishihara, Okinawa 903-0215, Japan*
[b] *Department of Radiology, Faculty of Medicine, University of the Ryukyus, Okinawa, Japan*

Received 8 May 2007
Available online 31 August 2007

Abstract

Objectives. The aim of this study was to clarify the efficacy of postoperative whole abdominal radiotherapy (WAR) for ovarian clear cell adenocarcinoma (OCCA).

Methods. Between 1996 and 2004, 16 patients with OCCA underwent initial debulking surgery and received postoperative WAR. Indications for WAR were as follows: OCCA, International Federation of Gynaecology and Obstetrics (FIGO) stage Ic–III, no macroscopic residual disease in the upper abdomen and residual disease in the pelvic cavity ≤2 cm. The planned WAR comprised external beam radiotherapy (EBRT) to the entire abdominal cavity with 22.0–24.0 Gy/22–24 fractions followed by EBRT to the pelvis with 23.4–21.6 Gy/12–13 fractions. Overall survival (OS) and disease-free survival (DFS) were compared with 12 historical control (HC) patients treated with initial debulking surgery followed by platinum-based chemotherapy.

Results. The FIGO stage in the WAR group was stage Ic in 11 patients, stage II in 3, and stage III in 2. Fifteen of the 16 patients (94%) completed the planned WAR. Two patients developed radiation enterocolitis and required bowel surgery. Five-year OS and DFS in the WAR/HC group were 81.8%/33.3% and 81.2%/25.0% ($p=0.031$ and $p=0.006$), respectively.

Conclusions. This study suggests that postoperative WAR may be effective in selected patients with OCCA. Prospective randomized trials should be considered to assess postoperative WAR for OCCA.

Keywords: Ovarian cancer; Whole abdominal radiotherapy; Clear cell adenocarcinoma

Introductions

Postoperative whole abdominal radiotherapy (WAR) has been performed worldwide for many decades. Dembo and colleagues reported the efficacy of WAR as a postoperative treatment for ovarian cancer in the 1970s [1]. Two large randomized controlled trials (RCT) comparing WAR with chemotherapy were conducted. The first, reported by the MD Anderson Cancer Center, compared WAR+pelvic radiotherapy (PR) with PR+melphalan and showed no improvement in 5-year disease-free survival (DFS) or overall survival (OS) [2]. The second, reported by the Princess Margaret Hospital, compared WAR+PR with PR+chlorambucil, and showed a 27% improvement in survival in patients who underwent complete surgical resection followed by WAR+PR [1]. The first report was criticized for the use of liver shielding, inadequate irradiation to the diaphragm, and an imbalanced stage distribution between the two treatment arms [3]. The study of MD Anderson Cancer Center (MDACC) had a great impact on most institutions in the United States to abandon postoperative WAR for ovarian cancer [4]. Worldwide, most gynecologists changed the postoperative treatment to platinum-based chemotherapy without RCT, comparing WAR with platinum-based chemotherapy. Now, postoperative WAR for ovarian cancer is performed in only a few centers around the world.

Historically, ovarian clear cell adenocarcinoma (OCCA) was termed "mesonephroid" because it was believed to originate from mesonephric structures and resembled renal carcinoma [5]. Since 1973, OCCA has been recognized as a distinct histological type of epithelial ovarian neoplasia in the World Health Organization classification of ovarian tumors [6]. Many gynecologic oncologists seem to believe that OCCA has different clinical charac-

* Corresponding author. Fax: +81 98 895 1426.
E-mail address: ynagai@med.u-ryukyu.ac.jp (Y. Nagai).

0090-8258/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2007.07.079

teristics, such as insensitivity to platinum-based chemotherapy. Several studies have demonstrated that platinum-based chemotherapy did not improve the survival of patients with OCCA [7]. The authors showed that OCCA had a poorer prognosis than other subtypes of epithelial ovarian cancer, such as serous and endometrioid adenocarcinoma.

The pelvis or abdomen is the initial recurrence site in around 85% of ovarian cancers. Radiotherapy can produce a response in chemo-resistant ovarian cancer. To date, none of the published trials has compared WAR with platinum-based chemotherapy following initial surgery. In this study, to evaluate the clinical efficacy of WAR as a postoperative treatment in OCCA, we compared the clinical results of patients who underwent platinum-based chemotherapy after initial debulking surgery. This is the first study to evaluate the efficacy of postoperative WAR in a platinum-resistant ovarian cancer such as OCCA.

Patients and methods

Patients

This study was a non-randomized trial. From January 1985 to December 2004, 35 women with OCCA were treated at the University of the Ryukyus Hospital. Between January 1985 and September 1996, we performed postoperative platinum-based chemotherapy after initial debulking surgery. We changed our method of postoperative treatment in OCCA to postoperative WAR in October 1996, due to a lower survival rate of patients undergoing platinum-based chemotherapy. The indications for postoperative WAR were as follows: (1) OCCA; (2) International Federation of Gynaecology and Obstetrics (FIGO) stage Ic, II, or III; (3) no macroscopic residual disease in the upper abdomen; (4) maximal residual disease at the pelvic cavity ≤2 cm. WAR had been performed as the postoperative treatment in 16 patients (WAR group) until September 2004. As our historical control, we selected 12 patients with the same background who were treated with platinum-based chemotherapy, comprising cyclophosphamide, adriamycin, and cisplatin (CAP) between 1985 and 1996. We evaluated retrospectively these two groups of patients with regard to the efficacy of postoperative treatment, and assessed the early and late adverse events in WAR group. All patients gave their written informed consent for postoperative WAR.

Initial debulking surgery

All 28 patients in this series underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Pelvic and para-aortic lymphadenectomy were performed in 9 of 16 WAR-group patients (56%) and in 8 of 12 CAP-group patients (67%). Six patients in the WAR group and four patients in the CAP group underwent pelvic lymphadenectomy or para-aortic lymph node sampling. Two patients in the WAR group did not undergo lymph node dissection.

Postoperateive chemotherapy

The patients received CAP comprising CDDP 80 mg/m^2, adriamycin 50 mg/m^2, and cyclophosphamide 500 mg/m^2 on day 1. The chemotherapy was administered at 2–3 weeks after the initial debulking surgery and then every 3 weeks for six courses. Eligibility requirements included white blood cell count ≥3000/μL, granulocyte count ≥1500/μL, platelet count ≥100,000/μL, serum creatinine concentrations of ≤1.5 mg/dL, aspartate aminotransferase, and alkaline phosphatase ≤two times the upper limits of institutional norms, bilirubin level ≤1.5 mg/dL, and Gynecologic Oncology Group (GOG) performance status 0–2.

Postoperative WAR and PR

Sixteen patients underwent WAR+PR as postoperative irradiation for OCCA with intent to cure. Planning for WAR and PR was carried out with conventional fluoroscopic simulation. We started WAR at 4–5 weeks after the initial debulking surgery. WAR was performed by an open-field technique using an 18-MeV linear accelerator through anteroposterior-opposed portals. Following WAR, PR was started. The total doses to the upper abdomen and the whole pelvic region were ranged 22.0 or 24.0 Gy and 45.4 or 45.6 Gy, respectively. The daily fractions of WAR and PR were 1.0 Gy and 1.8 Gy, respectively. The external beam irradiation was performed five times (each weekday) in a week. On the irradiation field, the first important point is that the treatment portal should include the entire peritoneal cavity; thus the upper border was set 1–1.5 cm above the domes of the diaphragm on expiration, the lower border was set just below the obturator foramen, and the lateral border was well beyond the anterior iliac spine. The second point is that partial kidney shielding was performed to 75% of the total abdominal dose and no liver shielding was performed. Our WAR method is based on a similar report from the Princess Margaret Hospital, Toronto, Canada [12]. It is our practice to interrupt treatment for platelet counts ≤50,000/mm^3, and/or white blood cell counts ≤1500/mm^3.

Evaluation of acute and late toxicities

Acute and late toxicities were graded by the Common Terminology Criteria for Adverse Events (CTCAE) ver. 3.0 and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria, respectively.

Statistics

All data, which were collected retrospectively from clinical charts, pathological reports, and radiation charts, were analyzed using StatView® J-4.5 statistical software (Abacus Concepts, Inc., Berkeley, CA, 1995). The clinical characteristics of the WAR and CAP groups were evaluated by the χ^2 test or Fisher's exact test. OS and DFS curves were calculated according to the Kaplan–Meier method by using the date of initiation of WAR or CAP as the starting point, and the differences between patient groups were tested by the log-rank test. $p<0.05$ was considered significant for all statistical analysis.

Results

Patient characteristics

The patient characteristics of the WAR group and CAP groups are shown in Table 1. The mean age was 51.8±6.3 years (range, 35–61 years) in the WAR group. The FIGO stage distribution was as follows: stage Ic, 11 patients; stage II, 3; and stage III, 2. All 16

Table 1
Patient's characteristics according to postoperative treatment

		WAR group (n=16)	CAP group (n=12)	p value
Age: mean±SD (range)		51.8±6.3 (35–61)	48.1±9.2 (34–66)	0.23
FIGO stage	IC	11	8	0.38
	II	3	1	
	III	2	3	
Maximum size of macroscopic residual tumor	None	16	11	0.43
	≤2 cm	0	1	
Cytology of pelvic washing and/or ascites ust laparotomy	Negative	5	1	0.16
	Positive	11	11	
Rupture of the tumor	Before surgery	13	12	0.17
	During surgery	3	0	

The median follow-up for the WAR group and CAP group was 55.5 months (range, 11–111) and 38.5 months (range, 9–180), respectively.

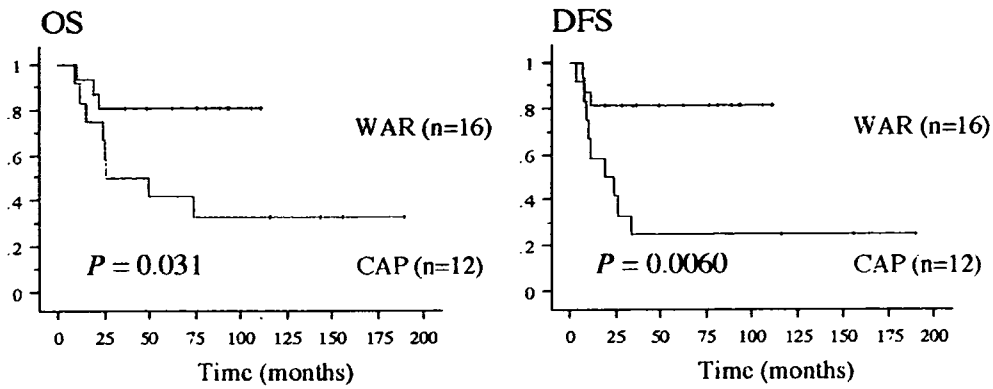

Fig. 1. Kaplan–Meier survival curve of the WAR and CAP groups. OS and DFS in the WAR group were superior to those in the CAP group ($p=0.031$ and $p=0.0060$, respectively).

patients had no macroscopic residual tumor in the pelvic or upper abdominal cavity at the initial debulking surgery. Five patients were negative and 11 patients were positive for peritoneal cytology. Preoperative and intraoperative ruptured tumor were observed in 13 and in 3 patients, respectively. The median duration of WAR+PR was 50 days (range, 48–87 days). In the CAP group, the mean age was 48.1±9.2 years (range, 34–66 years). All 12 patients completed six courses of CAP for postoperative chemotherapy. The FIGO stage distribution in patients was as follows: stage Ic, 8; stage II, 1; and stage III, 3. Eleven of the 12 patients had no macroscopic residuals and one had a residuum of less than 5 mm in the pelvic cavity. One patient was negative and 11 were positive for peritoneal cytology. In all 12 patients, the surface of the tumor was seen to be ruptured at the laparotomy. No variables showed statistically significant difference between the groups.

OS and DFS in WAR group and CAP group

The median follow-up for the entire group, WAR group and CAP group was 49.5 months (range, 9–180 months), 55.5 months (range, 10–111 months), and 38.5 months (range, 9–180 months), respectively. The 5-year OS and DFS rates in the WAR group were 81.8% and 81.2%, respectively. In contrast, the 5-year OS and DFS rates in the CAP group were 33.3% and 25.0%, respectively. OS and DFS in the WAR group were superior to those in the CAP group ($p=0.031$ and $p=0.0060$, respectively) (Fig. 1).

Initial recurrence site and time to recurrence

Table 2 shows the recurrence sites in each group. Three of 16 patients (18.8%) in the WAR group and 7 of 12 patients (58.3%) in the CAP group had a recurrence ($p=0.039$). The median times to recurrence in the WAR and CAP groups were 8 months (range, 7–11 months), and 10 months (range, 3–34 months), respectively. Three patients had a recurrence in WAR group. Only one patient developed an isolated locoregional failure in the abdomen. Regarding the remaining two patients, one had abdominal relapse and lung metastasis, and the other had lung and liver metastases. No distant organ metastasis was observed in the CAP group, but five of the seven patients (71.4%) had an abdominal relapse. Regional lymph node relapse was observed in two patients in the CAP group, both of whom underwent regional lymphadenectomy at the initial surgery.

Acute toxicity of WAR

Fifteen of the 16 patients (94%) completed their scheduled WAR. In one patient, WAR was not completed due to elevation of liver enzymes (Table 3). Her total upper abdominal dose was 18.0 Gy, but she received the full scheduled total pelvic dose of 45.4 Gy. Treatment was interrupted for over 1 day in 7 patients (43.7%), due to myelosuppression in three patients, mild abdominal pain in one, and elevation of the liver enzyme in one. One-day interruption due to myelosuppression occurred in two patients. The median duration of interruption in the seven patients was 4 days (range, 1–24 days). WAR was not interrupted due to severe diarrhea or sub-ileus.

Late toxicity of WAR

No Grade 4 adverse effect was observed during the follow-up period. Two of the 16 patients (12.5%) suffered a Grade 3 late intestinal toxicity on RTOG/EORTC Scoring (Table 3). No patients with abdominal relapse suffered small bowel obstruction during the entire follow-up period in WAR group. These two patients with radiation enterocolitis required intestinal surgery. Two of the 16 patients (12.5%) suffered a Grade 2 late intestinal

Table 2
Recurrence according to postoperative treatment

	WAR ($n=16$)	CAP ($n=12$)
No evidence of disease	13 (81.2%)	5 (41.7%)
Recurrence	3 (18.8%)	7 (58.3%)
First recurrent site		
Abdomen	2	5
Regional lymph node	0	2
Lung	2	0
Liver	1	0

In WAR group, one patient had abdominal relapse alone, one patient had lung and liver metastases, and one patient had abdominal relapse and lung metastases.

Table 3
Acute and late toxicity of WAR

Toxicites	Grade				
	0	1	2	3	4
Acute					
Blood/Bone marrow					
Leukocytes	1	4	10	1	0
Platelets	10	3	2	1	0
Gastrointestinal					
Nausea/Vomiting	2	10	4	0	0
Diarrhea	3	9	4	0	0
Pain	15	1	0	0	0
Metabolic/Laboratory					
ALT/AST	14	1	0	1	0
Bilirubin	16	0	0	0	0
ALP	14	2	0	0	0
Creatinine	16	0	0	0	0
Hemorrhage					
Bladder	16	0	0	0	0
Gastrointestine	16	0	0	0	0
Late					
Bladder	16	0	0	0	0
Kidney	16	0	0	0	0
Liver	16	0	0	0	0
Small/Large intestine	12	0	2	2	0

toxicity. These two patients developed a colic bowel movement and vomiting requiring IV fluid administration within a day. No radiation-induced hepatitis or pneumonitis was observed, and serum levels of liver enzymes, and creatinine were within the normal range during the follow-up period in all cases.

A comparison of acute, late toxicity, and treatment-related death between WAR group and CAP group

Regarding acute toxicity in CAP group, six of 12 patients (50.0%) suffered a ≥Grade 3 leukocytopenia/neutropenia, one had a Grade 4 leukocytopenia/neutropenia, and no patients suffered a ≥Grade 3 thrombocytopenia and 7 of 12 (58.3%) suffered a ≥Grade 2 nausea/vomiting. There was no statistical significance in a comparison with the above-mentioned acute toxicities between the WAR group and CAP group.

We have not experienced late toxicity in he CAP group; furthermore, we have not experienced treatment-related death in each group during entire the follow-up period.

Discussion

Chemotherapy is the standard postoperative treatment for ovarian cancer. Unfortunately, cisplatin-based chemotherapy has been reported to be ineffective to OCCA. Use of paclitaxel-based chemotherapy and irinotecan hydrochloride (CPT-11)-containing chemotherapy was recently reported. An advantage of paclitaxel and carboplatin regimen in OCCA has been reported [8]; however, other data showed that the clinical response rate of OCCA to paclitaxel and carboplatin was only 18.0% [9]. There have been two retrospective studies of CPT-11 containing regimen for OCCA. The first study found that CPT-11+ mitomycin C was superior to CAP as an adjuvant and the second found that CPT-11+cisplatin had a therapeutic benefit in advanced OCCA [10,11]. However, the efficacy of paclitaxel and CPT-11 chemotherapy for OCCA needs to be further investigated.

Dembo and colleagues demonstrated the efficacy of WAR and established appropriate indications and radiation dose following initial debulking surgery for ovarian cancer. A randomized study was conducted in patients with stages Ib to III ovarian cancer comparing WAR+PR with chlorambucil+PR, and showed a significant survival improvement (27%) in the WAR+PR group [1]. Another randomized study comparing WAR+PR with melphalan showed that the 5-year DFS and OS were not statistically significant [2]. The field of WAR used in this study was completely different from Dembo's. It is important that the "moving strip technique" that was used in MDACC WAR trial from the 1960s to 70s, resulted in uncertain dosimetry, and potentially greater hot and cold spots through the abdomen, that may have influenced the outcome including both toxicity and survivals. Furthermore, Smith and colleagues of MDACC used liver shielding, and the total dose to both the diaphragm and the liver was lower than that in Dembo's study. Our WAR procedure was almost the same as that performed at the Princess Margaret Hospital using the "open field technique" and no liver shielding [12].

Because of the poor survival benefit of CAP chemotherapy in our historical control group, we changed postoperative treatment for OCCA from CAP to WAR in October 1996, and evaluated retrospectively postoperative WAR in OCCA compared with cisplatin-based chemotherapy (CAP). This study is the first report of patients with OCCA treated with postoperative WAR. In our series, 5-year OS and DFS in the WAR group were superior to those in the CAP group. Recurrence occurred in 3 of 16 patients in the WAR group and 7 of 12 patients in the CAP group. Two patients had distant metastasis in the WAR group whereas there was no such occurrence in the CAP group. Distant metastasis in the WAR group was detected within 1 year after the initial surgery. Abdominal relapse was observed in 1 patient (6.3%) concurrent with distant metastasis in the WAR group and 7 of 12 patients in the CAP group. These results indicate that WAR is appropriate for abdominal control, but not for systemic disease.

Acute toxicity of WAR was recorded in 75% of our patients; however, it was tolerated in most cases. Only one patient (6.3%) did not complete the scheduled WAR due to elevation of liver enzymes. Nausea and vomiting were observed in 87.5% and diarrhea in 81% of our series. In no patient, however, was treatment interrupted for these. These observations were similar to those in Dembo's review of 1098 patients, in which nausea and vomiting were recorded in 95% and diarrhea in 60% [13]. Late toxicity (Grade ≥3) of our series was observed in two patients (12.5%). No treatment-related death was observed, but these two patients had late intestinal toxicity requiring bowel surgery. This percentage was somewhat higher than in previous reports, in which 2.7–7% of patients developed late toxicity requiring bowel surgery [13–16]. With a total dose of 22.5 Gy in 22 fractions to the upper part of the abdomen, the risk of serious late bowel toxicity was less than 5% and no difference in survival or tumor control was observed compared with a total dose of 27.5Gy in 27 fractions [17,18]. During the earlier period

in this series (1996–2000), we prescribed a total dose of 24.0 Gy in 24 fractions as WAR followed by a pelvic boost of 21.6 Gy in 12 fractions. To reduce late bowel toxicity, we reduced the dose of WAR from 24.0 Gy to 22.0 Gy in 2001, with reference to the report from the Princess Margaret Hospital [17]. Following this, none of the six patients treated with a total dose of 22.0 Gy to the upper abdomen had serious late bowel toxicity over a median follow-up period of 43 months.

Recently, two randomized trials from Austria and Sweden in stage III ovarian cancer using chemotherapy followed by WAR for consolidation treatment showed a survival advantage in patients with clinical remission or negative second look laparotomy after platinum-based chemotherapy [19,20]. Because consolidation WAR following chemotherapy did not show high acute and late toxicity, the treatment was considered to be a promising adjuvant regimen. In our study, 7 of the 12 patients (58.3%) in CAP group had a locoregional failure, but no distant failure was observed as the first recurrent site. Furthermore, only one patient had locoregional failure in WAR group. Our data indicate that consolidation chemotherapy followed by WAR may have produced a more optimal response for both locoregional and distant control in patients with OCCA.

Postoperative WAR should be performed in certified institutes owing to lack of experience and to avoid adverse events. Our retrospective study suggests that postoperative WAR may be a useful treatment for the selected patients with OCCA. A prospective randomized control trial comparing WAR with promising chemotherapy for OCCA should be considered.

References

[1] Dembo AJ, Bush RS, Beale FA, et al. Ovarian carcinoma: improved survival following abdominopelvic irradiation in patients with a completed pelvic operation. Am J Obstet Gynecol 1979;134:793–800.

[2] Smith JP, Rutledge FN, Delclos L. Postoperative treatment of early cancer of the ovary: a random trial between postoperative irradiation and chemotherapy. Natl Cancer Inst Monogr 1975;42:49–53.

[3] Tropé C, Karen J. Adjuvant treatment for early-stage epithelial ovarian cancer. In: Gershenson DM, McGuire WP, Gore M, Quinn MA, Thomas GM, editors. Gynecologic cancer: controversies in management. Philadelphia: Elsevier; 2004. p. 411–28.

[4] Young RC, Walton LA, Ellenberg SS, et al. Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. N Engl J Med 1990;322:1021–7.

[5] Schiller W. Mesonephroma ovarii. Am J Cancer 1939;35:1–21.

[6] Serov SF, Scully RE, Sobin LH. International Histological Classification of Tumors No.9: histological typing of ovarian tumors. Geneva: World Health Organization; 1973. p. 37–42.

[7] Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer 2000;88:2584–9.

[8] Ho CM, Chien TY, Shih BY, Huang SH. Evaluation of complete surgical staging with pelvic and para-aortic lymphadenectomy and paclitaxel plus carboplatin chemotherapy for improvement of survival in stage I ovarian clear cell carcinoma. Gynecol Oncol 2003;88:394–9.

[9] Enomoto T, Kuragaki C, Yamasaki M, et al. Is clear cell carcinoma and mucinous carcinoma of the ovary sensitive to combination chemotherapy with paclitaxel and carboplatin? Proc Am Soc Clin Oncol 2003;22:447. Abstract 1797.

[10] Nishino K, Aoki Y, Amikura T, et al. Irinotecan hydrochloride (CPT-11) and mitomycin C as the first line chemotherapy for ovarian clear cell adenocarcinoma. Gynecol Oncol 2005;97:893–7.

[11] Takano M, Kikuchi Y, Yaegashi N, et al. Adjuvant chemotherapy with irinotecan hydrochloride and cisplatin for clear cell carcinoma of the ovary. Oncol Rep 2006;16:1301–6.

[12] Dembo AJ. Abdominopelvic radiotherapy in ovarian cancer. A 10-year experience. Cancer 1985;55:2285–90.

[13] Dembo AJ. Epithelial ovarian cancer: the role of radiotherapy. Int J Radiat Oncol Biol Phys 1992;22:835–42.

[14] Sell A, Bertelsen K, Anderson JE, et al. Randomized study of whole-abdomen irradiation versus pelvic irradiation plus cyclophosphamide in treatment of early ovarian cancer. Gynecol Oncol 1990;37:367–73.

[15] Fyles AW, Dembo AJ, Bush RS, et al. Analysis of complications in patients treated with abdominopelvic radiation therapy for ovarian carcinoma. Int J Radiat Oncol Biol Phys 1992;22:847–51.

[16] Skirnisdottir I, Nordoqvit S, Sorbe B. Is adjuvant radiotherapy in early stages (FIGO I–II) of epithelial ovarian cancer a treatment of the past? Oncol Rep 2005;14:521–9.

[17] Fyles AW, Thomas GM, Pintile M, et al. A randomized study of two doses of abdominopelvic radiation therapy for patients with optimally debulked stage I, II, and III ovarian cancer. Int J Radiat Oncol Biol Phys 1998;41: 543–9.

[18] Morton GC, Thomas GM. Is there a place for whole abdominal radiotherapy in the management of ovarian cancer? Ann Acad Med 1996;25:429–36.

[19] Pickel H, Lahousen M, Petru E, et al. Consolidation radiotherapy after carboplatin-based chemotherapy in radically operated advanced ovarian cancer. Gynecol Oncol 1999;72:215–9.

[20] Sorbe B, on behalf of the Swedish-Norwegian ovarian cancer study group. Consolidation treatment of advanced (FIGO stage III) ovarian carcinoma in complete surgical remission after induction chemotherapy: a randomized, controlled, clinical trial comparing whole abdominal radiotherapy, chemotherapy, and no further treatment. Int J Gynecol Cancer 2003;13: 276–8.