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.

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

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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-

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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.

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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): []

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Postoperative whole abdominal radiotherapy in clear cell adenocarcinoma of the ovary

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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-

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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.

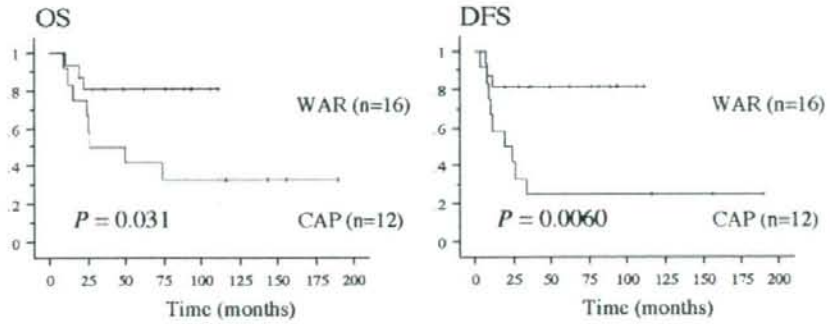

Fig. 1. Kaplan–Meier survival curve of the WAR and CAP groups. OS and DFS in the WAR group were superior to those in the CAP group ($p=0.031$ and $p=0.0060$, respectively).

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.

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CASE REPORT

Polypoid endocervical adenomyoma of the uterus: A case report with MR imaging and pathological analyses

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KEYWORDS
Polypoid endocervical adenomyoma;
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Abstract A case of polypoid endocervical adenomyoma in the uterine cervix was encountered in a 56-year-old woman. A well-circumscribed polypoid tumour was observed protruding from the uterine cervix. Based on the findings of MR imaging, the patient was assumed to have an adenoma malignum in the uterine cervix. The tumour was composed of a mixture of endocervical type proliferating glands and fascicles of smooth muscle. No distinct nuclear anaplasia, architectural abnormality, or evidence of destructive stromal invasion was observed. In our case, the tumour was a well-circumscribed polypoid lesion, with no cytologic abnormality, thus suggesting polypoid endocervical adenomyoma. The result of ancillary diagnostic modalities should be interpreted with caution and combined with gross and light microscopic findings.

Introduction

To date, there have been a few reports on adenomyomatous polyps in the cervix, containing endocervical type glands. Gilks et al. reported on endocervical adenomyomas including polypoid type.[1] The designation of endocervical adenomyoma has been used for biphasic tumours composed of an irregularly shaped endocervical gland with bundles of smooth muscle cells.[1,2] Endocervical adenomyoma usually appears as a polypoid feature, and may grow within the uterine cervix, therefore making it difficult to identify during vaginal inspections. Magnetic resonance (MR) imaging shows florid glandular proliferation with a cystic appearance. The appearance of polypoid endocervical adenomyoma may be similar to that of disease located in the uterine cervix. In particular, it can be easily confused with adenoma malignum of the uterine cervix in MR imaging and histological findings. Adenoma malignum of the uterine cervix can be a histological diagnostic problem, although

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there are clinical manifestations of mucoid vaginal discharge and existence of florid glandular proliferations extending deep into the cervical stroma. The histological findings of adenoma malignum are characterized by glands with a deceptively benign histological appearance. It may also grow within the cervix and not be obvious at clinical vaginal inspection. In this report, we describe an extremely rare case of polypoid endocervical adenomyoma.

Case report

A 56-year-old Japanese nulligravia woman who had been in good health without any notable family history, was referred to our hospital because of an increasingly watery vaginal discharge and an enlarging cervical mass, which her previous physician had suspected to be adenoma malignum. A vaginal examination revealed a firm tumour, 5 cm in diameter, in the uterine cervix. A colposcopic examination revealed that the entire cervical canal seemed to be occupied by the swollen tumour, but it was unclear whether the tumour had been growing in the cervical wall or into the cervical stroma, because of massive amounts of watery discharge from the external os. The cytological diagnosis of the uterine cervix suspected glandular abnormality. Histopathological examination of a biopsy specimen showed an increased number of irregular shaped glands consisting of a monolayered columnar epithelium surrounded by proliferating spindle shaped cells. The serum tumour markers (including CA125, CEA, SCC, CA19-9) were all within the normal limits. Pelvic magnetic resonance imaging (MRI) showed multiple cysts, mostly with low T1 and high T2. The T2-weighted images parallel to the uterine long axis disclosed multiple irregular cystic lesions with high signal intensity, varying in size from several millimeters to several centimeters. (Fig. 1) The walls of the cysts were smooth and thin. The solid parts were visualized as lesions surrounding or adjacent to the cyst. These areas were slightly hyperintense to the uterus on T2-weighted images and were more clearly visualized as enhanced lesions on gadolinium-enhanced T1-weighted images. (Fig. 2) Taking all findings into consideration, adenoma malignum was considered the most likely diagnosis, but other cervical glandular tumours could not be ruled out with confidence. Therefore, the patient underwent a radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The operative findings revealed a normal uterine corpus and enlarged cervix, however there were no signs of metastasis to the lymph nodes or no other lesions were observed. The patient was followed up for 50 months after surgery with no evidence of recurrence.

Pathological findings

Grossly, a longitudinal cut surface of the anterior cervical wall showed a polypoid tumour protruding from the posterior cervical wall. (Fig. 3) The polypoid tumour was well-circumscribed and measured 5 × 5 × 5 cm in size. The cut surface was solid, whitish to yellowish in color, and contained some cystic spaces, filled with clear mucus. (Fig. 4) Microscopically, the mass was composed of a mixture of proliferating cervical glands and haphazardly arranged smooth muscle cells. All glands were lined by mucus secreting columnar epithelium of cervical type, with bland nuclei. (Fig. 5) No distinct architectural abnormalities or desmoplastic reaction, suggesting destructive stromal invasion were observed. Smooth muscle cells did not show nuclear atypia including mitosis. The tumour glands and the smooth muscle were limited to within the polypoid tumour without any invasion to the cervical wall. Immunohistochemically, intracytoplasmic mucin of the glands was positive for Alcian-blue and Periodic acid–Schiff base (PAS) staining. The mucin in the glands was focally positive for CEA or HIK-1083 (mammalian gastric gland mucus cells-1, Kanto Kagaku, Tokyo,

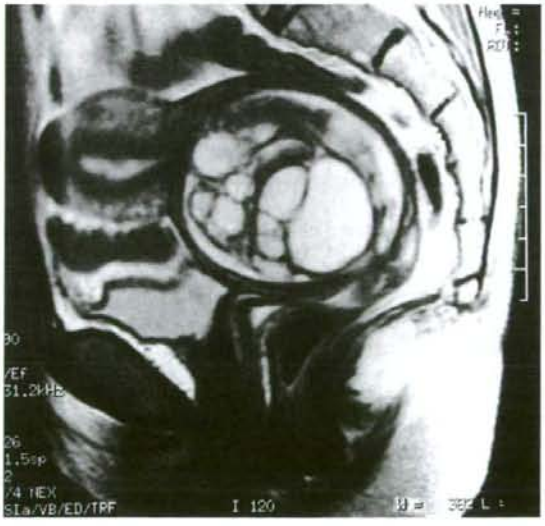

Figure 1 Sagittal T2-weighted image shows multiple irregular cystic lesions in the uterine cervix.

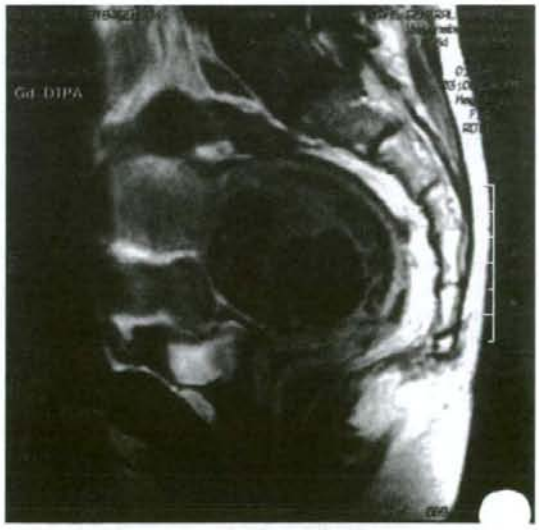

Figure 2 Sagittal gadolinium-enhanced T1-weighted images.

Figure 3 Resected uterus with a polypoid mass protruding from the uterine cervical wall.

Japan; dilution 1:20). On the other hand, normal endocervical glands showed no immunoreactivity for CEA and HIK-1083. (Fig. 6) The smooth muscle cells were positive for alpha smooth muscle actin (Immunon, Pittsburgh, PA, USA; dilution 1:50). Therefore, these findings were considered to correspond more to polypoid endocervical adenomyoma than adenoma malignum.

Discussion

Polypoid endocervical adenomyoma is a rare tumour of the uterine cervix.[1,3,4] Gilks et al. reported eight cases of polypoid endocervical adenomyoma, in which the tumours protruded from the cervical canal.[1] The tumours were well demarcated in five cases and showed clear borders with adjacent normal cervical tissue.[1] Microscopically, endocervical adenomyoma is characterized by glands and cysts lined by a single layer of an endocervical type mucus epithelium with intermittent smooth muscle.[5] At MR imaging, polypoid endocervical adenomyoma is characterized by multicystic lesions with solid components that extend from

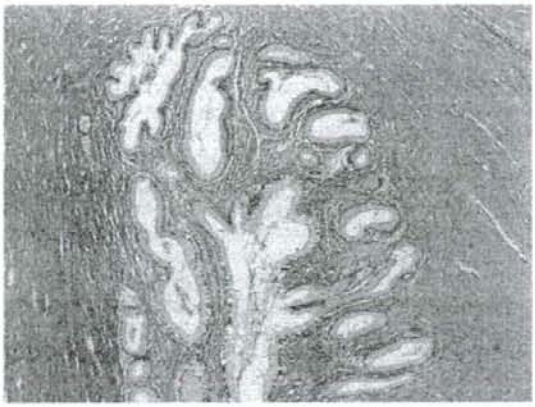

Figure 5 Glands lined by mucinous epithelium surrounded by smooth muscle stroma, without evidence of desmoplastic reaction (×20).

the endocervical glands on T1-weighted images, and as an area of hyperintensity on T2-weighted images. The differential diagnosis includes a deep nabothian cyst, florid endocervical hyperplasia and adenoma malignum. The appearance of polypoid endocervical adenomyoma may be similar to that of the diseases which may be located in the superficial epithelium of the uterine cervix. Therefore, the possibility of differentiating these lesions from polypoid endocervical adenomyoma with MR imaging is controversial. Polypoid endocervical adenomyoma can be distinguished from adenoma malignum, because it is macroscopically gross, i.e. polypoid adenomyomas are grossly circumscribed, whereas adenoma malignum is typically an ill-defined mass expanding into the cervical stroma. In our case, it was difficult to distinguish from adenoma malignum, because the swollen polypoid tumour completely obstructed the cervical canal during vaginal inspection and in MR imaging. Regarding the light microscopic features of endocervical adenomyoma, these glands are typically less numerous and more evenly spaced

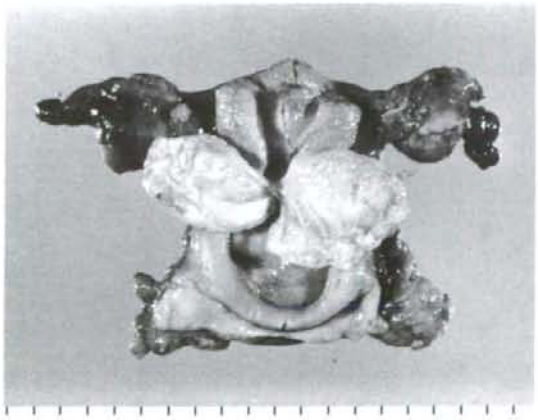

Figure 4 Longitudinal cut surface of a polypoid mass. Numerous cysts of various sizes are seen in the polypoid mass.

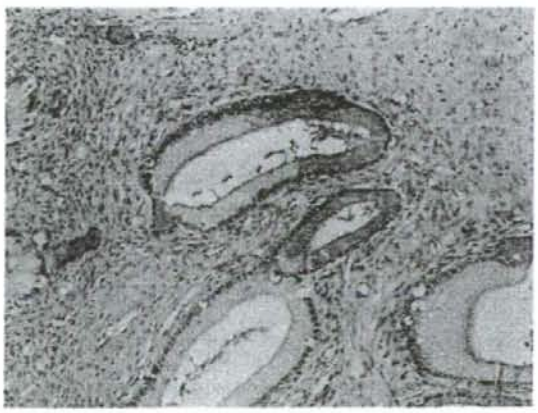

Figure 6 Immunohistochemistry using HIK-1083 (×40). Glands show focal cytoplasmic staining.

than in adenoma malignum. The glands in adenoma malignum often have a lobular appearance with large central glands surrounded by smaller glands. Cervical adenomyoma also lacks stromal desmoplastic reaction, foci of cytologic atypia, vascular space invasion, and perineural invasion, which are all commonly seen in adenoma malignum.[5–7] In our case, there were no features indicating a stromal desmoplastic reaction. The result of histochemical analyses and immunoreactivity should therefore be combined with macro- and microscopic findings, in order to avoid confusing this rare tumour with adenoma malignum. Familiarity with the characteristic features of endocervical adenomyoma in MR imaging and histochemical findings should facilitate accurate diagnosis and distinction from adenoma malignum.

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Cap43/NDRG1/Drg-1 is a molecular target for angiogenesis and a prognostic indicator in cervical adenocarcinoma

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Abstract

Cap43 is a nickel- and calcium-inducible gene that plays important roles in the primary growth of malignant tumors, as well as in invasion and metastasis, most likely through its ability to induce cellular differentiation. This study investigated associations of Cap43 expression with angiogenesis and other clinicopathological factors in cervical adenocarcinoma. The clinical records of 100 women who underwent surgery for cervical adenocarcinoma were reviewed retrospectively. Microvessel density and the expression of Cap43 and VEGF in the surgical specimens were evaluated immunohistochemically. The Cap43 expression level was significantly associated with angiogenesis, tumor diameter, stromal invasion, lymphovascular space invasion, lymph node metastasis, and histopathological differentiation. Kaplan–Meier analysis showed a significant association between the Cap43 expression level and survival: high Cap43 expression was related to poor survival. Our results suggest that increased expression of Cap43 is associated with angiogenesis and may be a poor prognostic indicator in women with cervical adenocarcinoma.

Keywords: Cap43; Cervical adenocarcinoma; Angiogenesis; Prognosis

1. Introduction

The Cap43 gene is a nickel- and calcium-inducible gene [1], identical to the previously described N-myc downstream-regulated gene 1 (NDRG1). It

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is one of the four closely related genes (NDRG1-4) whose expression is down-regulated by c-myc or the N-myc/Max complex [2–5]. Cap43 is also identical to the homocysteine-inducible gene, whose expression is reduced in tumor cells (RTP/rit42) [6], and to the differentiation-related gene-1 (Drg-1) [7]. The protein encoded by Cap43 has a molecular weight of 43 kDa. It has three unique 10-amino acid tandem-repeat sequences at its carboxyl terminal and is phosphorylated by protein kinase A [8].

The functions of Cap43 remain poorly understood. Expression of the Cap43 gene has been strongly associated with nickel, cobalt, oxidative stress, hypoxia, phorbol esters, vitamins A and D, steroids, histone deacetylase-targeting drugs, homocysteine, β-mercaptoethanol, tunicamycin, and lysophosphatidylcholine, as well as with oncogenes (N-myc and c-myc) and the products of tumor-suppressor genes (p53 and VHL) [1,2,6,9,10]. Cap43 is expressed in most organs, most prominently in the prostate, ovary, colon, and kidney. Its expression in the kidney, brain, liver, and gut is actively modulated during postnatal development [2,3,11,12], suggesting that Cap43 plays a key role in organ maturation.

Transfection studies by Kurdistani and colleagues demonstrated that Cap43 inhibits the primary growth of human breast, prostate, and bladder cancer cell lines and suppresses the anchorage-independent growth of these cell lines in soft agar [6]. Moreover, the overexpression of Cap43 markedly promotes the growth of human pancreatic cancer xenografts in mice, but not of pancreatic cancer cells in culture [13]. The survival rate of patients with pancreatic cancer whose tumors expressed high levels of Cap43 was found to be significantly higher than that of patients whose tumors expressed low levels of Cap43 [13]. In another study, low tumor Cap43 expression was strongly associated with poor outcomes in women with breast cancer [14]. Chua and colleagues recently reported that Cap43 overexpression significantly correlates with tumor differentiation, vascular invasion, and overall survival in patients with hepatocellular carcinoma, suggesting that increased Cap43 expression may be a useful indicator of tumor aggressiveness and prognosis [15]. Taken together, the above findings suggest that Cap43 may have tissue-of-origin-specific functions in human malignancies [16].

The incidence of invasive cervical cancer has decreased in developed countries, presumably because of intensive national screening programs. This declining incidence is attributed primarily to a decrease in squamous cell carcinoma, whereas the incidence of adenocarcinoma has remained stable or risen slightly [17,18]. The prevalence of adenocarcinoma among women with cervical cancer has increased from 5% to 13% in the 1950s to 20% in the 1990s [19,20]. Recent studies attribute this rise to an increased incidence of cervical adenocarcinoma among young women [21,22]. Cervical adenocarcinoma is associated with unfavorable outcomes, attributed to late detection on Papanicolaou smears, a poorer response to radiotherapy than squamous cell carcinoma, or the inclusion of subtypes with particularly poor outcomes, such as clear cell carcinoma [23]. New tumor markers that can be used to predict outcomes predictors have been identified by numerous studies, including immunohistochemical analyses [24–26].

Angiogenesis is an important pathological aspect of tumor growth and chronic inflammatory diseases [27]. Of the various angiogenesis factors identified to date, vascular endothelial growth factor (VEGF)-A plays a key role in pathological angiogenesis, including that required for the rapid growth of solid tumors. Antiangiogenesis agents targeting VEGF-A and VEGF-receptor 2 have been developed and are currently used clinically [28,29]. In a previous study, we demonstrated that higher tumor Cap43 expression is associated with higher tumor microvessel density (MVD) than lower tumor Cap43 expression in patients with pancreatic cancer [13]. Angiogenesis in cervical carcinoma has been shown to be inversely related to survival [30,31]. Kaku and colleagues [32] demonstrated a significant correlation of MVD with both progression-free survival and overall survival in cervical adenocarcinoma.

In this study we immunohistochemically evaluated the intensity of Cap43 expression in patients with stage I or II cervical adenocarcinoma according to the staging system of the International Federation of Gynecology and Obstetrics (FIGO). We also examined correlations of Cap43 staining intensity with angiogenesis and other clinicopathological factors.

2. Materials and methods

2.1. Patients and treatment

Between 1990 and 2005, a total of 100 patients with stage I or II cervical adenocarcinoma underwent surgery at Kurume University Hospital and National Cancer

Center Hospital. The procedure was radical hysterectomy in 93 patients and simple abdominal hysterectomy in the other seven. Pelvic lymphadenectomy and para-aortic lymph node biopsy were performed in all patients. Patients with deep stromal invasion, lymph node metastasis, or both were considered candidates for postoperative adjuvant therapy. After surgery, 23 patients received postoperative adjuvant radiotherapy, and 5 received adjuvant platinum-containing chemotherapy. For external beam radiotherapy, a dose of 50.4 Gy was delivered to the entire pelvis. Intracavitary brachytherapy was performed if the surgical margin in the vaginal cuff was histologically positive or if the free margin was <1 cm.

2.2. Immunohistochemical staining

All specimens were fixed in 10% formalin and embedded in paraffin wax. Tissue sections 4 μm thick were mounted on slides, deparaffinized, rehydrated, and heated in a microwave oven for 60 min in CCI buffer. Immunohistochemical staining was performed using a Ventana NX automated immunohistochemistry system (Ventana Medical Systems, Tucson, AZ, USA) and polyclonal primary antibodies to Cap43 (produced in our laboratory), [10,33] VEGF (upstate, Cosmo Bio Co. Ltd., Lake Placid, NY, USA; dilution 1:50), and CD34 (Nichirei, Tokyo, Japan; dilution 1:1). A preliminary study of Cap43 immunohistochemical staining of cervical adenocarcinoma revealed that only the membrane of tumor cells stained positively; normal glands and the nuclei and cytoplasm of tumor cells stained negatively. Since the staining intensity varied, we considered the staining intensity of the tumor cell membranes to represent the expression intensity of Cap43 in the cervical adenocarcinoma specimens. The intensity of membrane staining was scored as follows: no staining, 0; dotted pattern staining, 1+; weak or moderate circumferential staining in >10% of the tumor cells, 2+; strong circumferential staining in >10% of the tumor cells, 3+ (see Fig. 1A–D). To statistically analyze the patients' survival curves (data not shown), we classified Cap43 expression scores of 0, 1+, and 2+ as low Cap43 expression, and scores of 3+ as high Cap43 expression. VEGF expression in the tumor cells was evaluated according to the following semiquantitative scoring system: no staining at all or staining in <10% of the tumor cells, 0; light staining in >10% of the tumor cells, 1+; moderate staining in >10% of the tumor cells, +2; and dark staining in >10% of the tumor cells, +3. Staining of the tumor stroma was ignored in this assessment (see Fig. 1E–H). All procedures were performed by one gynecological oncologist and two pathologists who were blinded to clinical outcomes in this series of patients. Discordant results among the investigators were re-evaluated. MVD was calculated on the basis of the immunohistochemical expression of CD34. For each sample, the mean number of microvessels was calculated for five vascular hotspots to assess the MVD for each case. Only CD34 staining in tumor areas was reviewed, and endothelial cell clusters of two or more cells were considered a single, countable microvessel (see Fig. 1I and J). All counts were made by three independent observers who had no knowledge of the corresponding clinicopathological data.

2.3. Statistical analysis

Statistical calculations were performed with the SAS version 9.1.3 (SAS Institute, Cary, NC, USA) software package. The Kaplan–Meier method was used to calculate the progression-free survival rate and overall survival rate; prognostic significance was evaluated by the log-rank test. The Mann–Whitney *U*-test was used to compare continuous variables. *P* values for correlations of Cap43 expression with VEGF expression and other clinicopathological factors were calculated with Fisher's exact test. Differences were considered significant at $P < 0.05$.

3. Results

3.1. Patient characteristics

The patients' characteristics are shown in Table 1. The median follow-up time was 51.3 months. At the time of the analysis, tumor recurrence had been diagnosed in 30 patients, and 25 patients had died. Table 2 shows the Cap43 expression, VEGF expression, and microvessel density.

3.2. Correlation between Cap43 expression and angiogenesis

High Cap43 expression correlated with high VEGF expression (Table 3). Immunohistochemical staining analysis showed that median MVD was 39.4 in the specimens with high Cap43 expression and 26.1 in the specimens with low Cap43 expression. MVD correlated with the intensity of Cap43 expression ($P < 0.0001$, Fig. 2). These results suggested that high Cap43 expression was closely associated with high angiogenic activity in cervical adenocarcinoma.

3.3. Correlation between Cap43 expression and clinicopathological factors

High Cap43 expression significantly correlated with tumor diameter, stromal invasion, lymphovascular space invasion, lymph node metastasis, and histopathological differentiation, but not with FIGO stage (Table 4).

3.4. Correlation between Cap43 expression and survival time

The median progression-free survival time was 52.4 months in patients with tumors showing low Cap43