Common adverse reactions reported in this study were haematological toxicities (leukopenia, neutropenia and decreased haemoglobin), HFS and stomatitis.

The median time to nadir for WBC, neutrophils and haemoglobin after the start of administration of PLD was 15–22 days, and the median time to recovery to baseline after reaching the nadir was 7–8 days. Repeated cycles did not lead to worsening the events. Most patients could receive PLD continually by concomitant use of G-CSF and dose modification, such as dose reduction and delay of next administration.

In the previous Phase III study (13), HFS and stomatitis occurred in 49% (Grade 3 or higher: 23%) and 40% (Grade 3 or higher: 8%) of patients, respectively. Although these toxicities were seen in 78.3 and 77.0% of patients in our study, only 16.2 and 8.1% of patients experienced Grade 3 or higher toxicities, respectively. Most patients could continually receive PLD treatment by dose modification of PLD and supportive care, and the patients discontinued due to toxicities were few.

Infusion-related reaction that is known as toxicity specific to PLD was seen in 14 patients (18.9%) during the first cycle, all of which were resolved on the day of the occurrence or the following day. The second cycle was administered in 11 of 14 patients with infusion-related reactions. No recurrence of infusion-related reactions was seen in all 11 patients. It is important to use PLD with close attention to the condition of patients at the first administration of PLD. Infusion-related reaction is related to the initial infusion rate of PLD. It has been reported that decreasing the infusion rate reduces the risk of the infusion-related reaction (21).

It has been reported that cardiac toxicity, which is a significant problem with the use of conventional doxorubicin, associated with PLD is mild (22). Also in this trial, all cardiac toxicities observed were Grade 1, and had no effect on continuation of the trial. Furthermore, no patients experienced Grade 2 or higher alopecia, and Grade 3 or higher gastrointestinal toxicities were rarely seen in our trial. These toxicities are frequently induced by treatment of conventional doxorubicin.

These results suggest that toxicity of PLD is manageable by dose modification of PLD and supportive care.

Most patients with ovarian carcinoma exhibited response to first-line chemotherapy, however, the incidence of recurrence is high and prognosis is poor. It might be important to recognize that the chemotherapy would be palliative treatment for treatment of recurrent ovarian carcinoma. PLD has a safety profile that is different from that of platinum and taxanes, which are used for the standard first-line chemotherapy. PLD has a low risk of enhancing cumulative toxicities (haematological toxicity or neurotoxicity) associated with first-line chemotherapy. PLD is expected to have a beneficial effect against disease progression as the proportion of patients with CR, PR or SD and time to progression were 60.3% and 166 days (median). Furthermore, PLD might make it easy to provide long-term outpatient chemotherapy since PLD would reduce a patient burden by dosing once every 4 weeks.

In conclusion, this trial demonstrated that PLD (50 mg/m^2 every 4 weeks) was expected to have antitumour effect in Japanese patients with Müllerian carcinoma previously treated with platinum-based chemotherapy and that toxicities associated with PLD are manageable by dose modification and supportive care. In the USA and Europe, combination chemotherapy with PLD and platinum has recently been investigated in the platinum-sensitive group where PLD is considered to be more effective (23,24,25). It is desirable to investigate the optimal regimen of the combination therapy in Japan.

Acknowledgements

The authors extend special thanks to Dr N. Saijo (National Cancer Center Hospital East, Chiba), Dr S. Isonishi (Jikei University School of Medicine, Tokyo), Dr H. Katabuchi (Kumamoto University, Kumamoto), Dr T. Koyama (Kyoto University, Kyoto), Dr K. Miyagawa (National Cancer Center Hospital, Tokyo), Dr H. Watanabe (National Cancer Center Hospital, Tokyo), Dr K Hasegawa (Inamino Hospital, Hyogo), Dr Y. Matsumura (National Cancer Center Research Institute East, Chiba), Dr T. Tamura (National Cancer Center Hospital, Tokyo) and Dr Y. Ohashi (University of Tokyo, Tokyo) for careful review of the protocol and the clinical data in this study.

Funding

Funding to pay the Open Access publication charges for this article was provided by Janssen Pharmaceutical K.K.

Conflict of interest statement

None declared.

References

1. Udagawa Y, Yaegashi Y. Ovarian Cancer Treatment Guideline. *Japan Society of Gynecologic Oncology*. 2nd edn. Tokyo: Kanehara & Co., Ltd 2007.
2. Markman M, Zaino RJ, Fleming PA, Gemignani ML. Carcinoma of the Fallopian Tube. In: Hoskins WJ, Perez CA, Young RC, Barakat R, Markman M, Randall M editors. *Principles and Practice of Gynecologic Oncology*. 4th edn. Philadelphia: Lippincott Williams & Wilkins 2004;1035–53.
3. Karlan BY, Markman MA, Eifel PJ. Ovarian Cancer, Peritoneal Carcinoma, and Fallopian Tube Carcinoma. In: Devita VT Jr, Hellman S, Rosenberg SA editors. *Cancer Principles & Practice of Oncology*. 7th edn. Philadelphia: Lippincott Williams & Wilkins 2005;1364–97.
4. Allen TM, Hansen C, Martin F, Redemann C, Yau-Young A. Liposomes containing synthetic lipid derivatives of poly (ethylene glycol) show prolonged circulation half-lives in vivo. *Biochim Biophys Acta* 1991;1066:29–36.
5. Jain RK. Vascular and interstitial barriers to delivery of therapeutic agents in tumors. *Cancer Metastasis Rev* 1990;9:253–66.

6. Woodle MC. Surface-modified liposomes: assessment and characterization for increased stability and prolonged blood circulation. *Chem Phys Lipids* 1993;64:249–62.
7. Needham D, McIntosh TJ, Lasic DD. Repulsive interactions and mechanical stability of polymer-grafted lipid membranes. *Biochim Biophys Acta* 1992;1108:40–8.
8. Huang SK, Martin FJ, Jay G, Vogel J, Papahadjopoulos D, Friend DS. Extravasation and transcytosis of liposomes in Kaposi's sarcoma-like dermal lesions of transgenic mice bearing the HIV tat gene. *Am J Pathol* 1993;143:10–4.
9. Huang SK, Lee KD, Hong K, Friend DS, Papahadjopoulos D. Microscopic localization of sterically stabilized liposomes in colon carcinoma-bearing mice. *Cancer Res* 1992;52:5135–43.
10. Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, et al. Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997;15:987–93.
11. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, et al. Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. *J Clin Oncol* 2000;18:3093–100.
12. Johnston SRD, Gore ME. Caelyx: phase II studies ovarian cancer. *Eur J Cancer* 2001;37(Suppl. 9):S8–14.
13. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;19:3312–22.
14. Gordon AN, Tonda M, Sun S, Rackoff W. Long-term survival advantage for women treated with pegylated loposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. *Gynecol Oncol* 2004;95:1–8.
15. O'Byrne KJ, Bliss P, Graham JD, Gerber J, Vasey PA, Khanna S, et al. A phase III study of Doxil/Caelyx versus paclitaxel in platinum-treated, taxane-naive relapsed ovarian cancer. *Proc Am Soc Clin Oncol* 2002;21:203a [Abstract 808].
16. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer V.1.2008. Available from: http://www.nccn.org/professionals/physician_gls/PDF/ovarian.pdf.
17. National Cancer Institute. Ovarian Epithelial Cancer Treatment (PDQ®) Health Professional Version Recurrent or Persistent Ovarian Epithelial Cancer. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfessional/page7.
18. National Institute for Health and Clinical Excellence. Ovarian cancer (advanced) - paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. Available from: http://guidance.nice.org.uk/TA91.
19. Fujisaka Y, Horiike A, Shimizu T, Yamamoto N, Yamada Y'Tamura T. Phase 1 Clinical Study of Pegylated Liposomal Doxorubicin (JNS002) in Japanese Patients with Solid Tumors. *Jpn J Clin Oncol* 2006;36:768–74.
20. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized Phase III Trial of Gemcitabine Compared With Pegylated Liposomal Doxorubicin in Patients With Platinum-Resistant Ovarian Cancer. *J Clin Oncol* 2007;25:2811–8.
21. Chanan-Khan A, Szebeni J, Savay S, Liebes L, Rafique NM, Alving CR, et al. Complement activation following first exposure to pegylated liposomal doxorubicin (Doxil®): possible role in hypersensitivity reactions. *Ann Oncol* 2003;14:1430–7.
22. O'Brien MER, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, et al. Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYXTM/Doxil®) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Ann Oncol* 2004;15:440–9.
23. Ferrero JM, Weber B, Geay JF, Lepille D, Orfeuvre H, Combe M, et al. Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. *Ann Oncol* 2007;18:263–8.
24. du Bois A, Pfisterer J, Burchardi N, Loibl S, Huober J, Wimberger P, et al. Combination therapy with pegylated liposomal doxorubicin and carboplatin in gynecologic malignancies: A prospective phase II study of the Arbeitsgemeinschaft Gynäekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and Kommission Uterus (AGO-K-Ut). *Gynecol Oncol* 2007;107:518–25.
25. Alberts DS, Liu PY, Wilczynski SP, Clouser MC, Lopez AM, Michelin DP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). *Gynecol Oncol* 2008;108:90–4.

Analysis of the clinicopathological prognosis of stage IVb cervical carcinoma

SHIN NISHIO[1,3], NORIYUKI KATSUMATA[1], KOJI MATSUMOTO[1], HIROSHI TANABE[1], KAN YONEMORI[1], TSUTOMU KOHNO[1], CHIKAKO SHIMIZU[1], MASASHI ANDO[1], TAKAHIRO KASAMATSU[2] and YASUHIRO FUJIWARA[1]

Departments of [1]Medical Oncology and [2]Gynecologic Oncology, National Cancer Center Hospital, Tokyo 104-0045, Japan

Received July 23, 2007; Accepted October 22, 2007

Abstract. The aim of this study was to evaluate the clinicopathological prognostic factors in patients with stage IVb cervical carcinoma (CC). All patients with stage IVb CC included in the study were diagnosed from 1997 to 2006 at the National Cancer Center Hospital. We retrospectively examined clinicopathological parameters in these patients, including the efficacy of chemotherapy. Survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using a Cox's proportional hazard model. Thirty-six patients (median age 54 years) were diagnosed with stage IVb CC. The median progression-free survival and overall survival were 3.8 and 11.1 months, respectively. As initial treatment, 4 patients underwent hysterectomy, 13 received chemotherapy, 17 received radiotherapy, and the remaining 2 patients refused treatment. A total of 21 patients received chemotherapy, of which 13 were initial cases, 7 were persistent/recurrence cases, and 1 was a postoperative adjuvant case; 15 patients were never treated with chemotherapy. On univariate analysis, poor performance status (PS) and non-chemotherapy groups were considered poor prognostic factors, respectively. On multivariate analysis, poor PS (p=0.007; hazard ratio, 2.64) and non-chemotherapy (p=0.016; hazard ratio, 6.03) were independent prognostic factors of survival, respectively. Poor PS and non-chemotherapy groups were found to have poor prognosis in patients with stage IVb CC. Chemotherapy may improve the survival for stage IVb CC.

Correspondence to: Dr Shin Nishio, [3]*Present address*: Department of Obstetrics and Gynecology, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan
E-mail: nishio_shin@hotmail.com

Key words: stage IVb cervical carcinoma, prognostic factor, chemotherapy, performance status

Introduction

Cervical carcinoma is the main cause of death in females throughout the world, despite the fact that a useful screening method has been established (1). In stage I/II patients, conventional treatments such as surgery and radiotherapy have achieved good results. In stage III/IV patients, various treatments such as the combination of surgery and radiotherapy, radiotherapy, and chemoradiation therapy are being examined, though their long-term results are still poor (2,3). The 5-year survival of stage IVb patients ranges from 0 to 44%, and approximately 50% of these patients show a fatal outcome within 1 year (4-6). No standard therapy has been established, and palliative surgery, radiotherapy, and best supportive care (BSC) have been performed as initial treatment. However, since stage IVb cervical carcinoma is a systemic disease, surgery and radiotherapy are useful for local control, but are insufficient. In addition, BSC is not effective for the severe local pain characteristic of this disorder (7). Since 1990, chemotherapy has been employed as a type of BSC in patients with good general condition and organ function (8). However, as this therapy targets the relief of symptoms and improvements in quality of life (QOL), regimens with less toxic low-dose agents were initially administered (9). No randomized comparative study has examined whether chemotherapy for stage IVb cervical carcinoma prolongs survival compared to BSC.

Several studies have investigated single-agent chemotherapy for cervical carcinoma, and reported that the response rates to cisplatin, ifosfamide, paclitaxel, vinorelbine and topotecan of 20-30% (5,8,10-12), 14-40% (13-15), 17% (16), 15% (17,18) and 12-19% (19,20), respectively. Cisplatin has been the most frequently used agent, and has achieved the highest response rate. Therefore, cisplatin has been employed as a key drug for more than 20 years. However, the response to single-agent cisplatin has been limited, and combination chemotherapy with other agents has been administered to achieve improvement in prognosis, exceeding the enhancement of its toxicity. Result of recent phase III studies have indicated that combination regimens with cisplatin/paclitaxel (21) or cisplatin/topotecan (22) are more effective than single-agent cisplatin.

A few studies have reported that factors affecting the prognosis of stage IVb cervical carcinoma include main organ

metastases, multiple lymph node metastases, poor performance status (PS), and non-squamous cell carcinoma (23-29). According to some studies, the results of surgery combined with radiotherapy or radiotherapy alone are relatively good in stage IVb cervical carcinoma patients with para-aortic lymph node metastases alone (30-33). However, chemotherapy for stage IVb patients with cervical/mediastinal lymph node or main organ metastases, without surgery and radiotherapy, has been reported to have only slight effect.

In this study, we retrospectively investigated the clinicopathological features of stage IVb cervical carcinoma, and evaluated the efficacy of chemotherapy for this stage of cancer.

Patients and methods

Patients with stage IVb cervical carcinoma were diagnosed and treated in the National Cancer Center Hospital between April 1997 and March 2006. Stage was evaluated according to the FIGO staging. We rectrospectively reviewed the medical chart of these patients.

Treatment. Therapeutic strategies were selected for individual patients. For surgery, total hysterectomy (radical hysterectomy in some patients) and bilateral salpingo-oophorectomy were performed. Pelvic and/or para-aortic lymphadenctomy were performed in some patients. For radiotherapy, the area of external irradiation was established as the entire pelvic region from the closed pore to the L4/5 lumbar vertebrae, with a radiation dose of 2 Gy per treatment (total dose, 50-60 Gy). When the cumulative dose reached 20-30 Gy, external irradiation was combined with high-dose intra-cavity irradiation, with a central shield, at a radiation dose of 5 Gy (total dose, 20-25 Gy). When imaging findings suggested para-aortic lymph node metastases, biopsy was performed. After a definitive diagnosis of metastases was made, the irradiation field was extended to include the para-aortic node. For chemotherapy, eligible patients participated in a phase II clinical study with an in-house protocol that we previously reported, including paclitaxel (PTX)/carboplatin (CBDCA) therapy (Kitagawa R, *et al*, Proc ASCO 22: abs. 5048, 2004) (PTX, 175 mg/m^2, CBDCA AUC5, day 1, every 3 weeks for 6 cycles), and carboplatin (CBDCA)/irinotecan (CPT) therapy (Hori S, *et al*, Proc ASCO 21: abs. 835, 2002) (CBDCA AUC5, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles). For patients with PS of 3, weekly PTX/CBDCA therapy (PTX 80 mg/m^2, CBDCA AUC2, continuous administration for 20 weeks) was administered. In 1 patient with small cell carcinoma, cisplatin (CDDP)/CPT therapy (CDDP, 60 mg/m^2, day 1, CPT 60 mg/m^2, days 1, 8 and 15, every 4 weeks for 6 cycles) was administered as postoperative adjuvant therapy.

Best supportive care (BSC) was defined as treatment targeting the relief of symptoms without surgery, radiotherapy or chemotherapy, as described above.

Evaluation. Pretreatment clinical evaluation was repeated before each treatment cycle with the exception of radiography or CT/MRI imaging, which was repeated at least every other treatment cycle. Treatment was continued until disease progression or adverse effects precluded further administration. The response to treatment, in terms of the best response achieved in a given patient, was assessed using standard clinical criteria. A complete response (CR) was defined as the disappearance of all gross evidence of disease for at least 4 weeks. A partial response (PR) was defined as a >50% reduction in the product of perpendicular diameters obtained from the measurement of each lesion, sustained for at least 4 weeks. Progressive disease (PD) was defined as a >50% increase in the product of perpendicular diameters of any lesion documented within 2 months of study entry or the appearance of any new lesion within 8 weeks of study entry. Stable disease (SD) was any condition not meeting any of the above three criteria. Overall survival was measured as the observed length of life from protocol entry to death or (for living patients) date of last contact. Progression-free survival was measured from the date of initiation of protocol to the first progression or death, or to the date of last contact for patients who were alive and progression-free.

Persistent disease was defined as carcinoma at a pelvic site known to be previously involved within 6 months of staging. Recurrent disease was classified as a new tumor in the extrapelvic area or pelvic disease >6 months after staging in a location previously tumor-free. Persistent or recurrent disease was documented by surgical exploration, biopsy or progression on imaging studies. The time of recurrence or death was calculated from the date of original staging. The end of the follow-up period was March 2006.

Statistical analysis. Statistical analysis was performed using SPSS. The impact of clinical and pathologic risk factors on survival was evaluated using Kaplan-Meier curve analysis and log-rank test. The independent prognostic factors found to be predictive of survival in univariate and multivariate analysis were evaluated using Cox's proportional hazard model. P-values <0.05 were considered significant.

Results

Thirty-six patients were treated between April 1997 and March 2006. Table I shows the patient characteristics. The median age was 54 years. In 34 patients, PS was almost 0, 1 or 2. In the remaining 2 patients, PS was 3. As initial treatment, surgery was performed in 4 patients, radiotherapy in 17, and chemotherapy in 13. BSC was performed in two patients who did not wish to receive aggressive treatment. Histopathologically, 18 patients had squamous cell carcinomas, 16 had adenocarcinomas and 2 had small cell carcinomas. The median primary tumor diameter was 4.1 cm, with a maximum of 7.7 cm. In addition, a bulky mass was detected in 28 patients. In 13 patients, hydronephrosis was noted, with 8 of these having bilateral hydronephrosis. The number of distant metastases was 1 in most patients, but 3 or 4 in some patients. The metastatic lesion sites included the para-aortic node in 7 patients and the main organs in 8 patients. Table II shows the sites of distant metastases (including duplicating patients). In the abdominal cavity, para-aortic lymph node metastases were detected in 18 patients (50%), comprising the highest percentage. In the extraperitoneal region, supraclavian lymph node metastases were detected in 13 patients (36%). Among main organ metastases, liver metastases were detected in 7

Table I. Patient characteristics.

Age (year), median (range)	54 (28-77)
PS 0/1/2/3	5/18/11/2
No. of patients	36
Initial treatment	
Surgery	4
Radiotherapy	17
Chemotherapy	13
Best supportive care	2
Pathology	
Squamous cell carcinoma	18
Adenocarcinoma	16
Small cell carcinoma	2
Primary tumor size (cm), median (range)	4.1 (2.1-7.7)
Bulky mass >4 cm	
Negative	8
Positive	28
Hydronephrosis	
Negative	23
Unilateral	5
Bilateral	8
No. of distant metastases	
1	20
2	13
3	2
4	1
Site of distant metastases	
Para-aortic lymph node only	7
Distant lymph node only	7
Organ metastases only	1
Para-aortic lymph node + Distant lymph node	10
Para-aortic lymph node + Organ metastases	1

Table II. Distant metastases in patients.

Metastatic sites	n (%)
Intra-abdominal metastases	
Para-aortic lymph node	18 (50)
Liver	7 (19)
Spleen	2 (5.5)
Small intestine	1 (2.7)
Extra-abdominal metastases	
Lung	4 (11)
Bone	2 (5.5)
Supraclavicular lymph node	13 (36)
Mediastinal lymph node	2 (5.5)
Inguinal lymph node	2 (5.5)

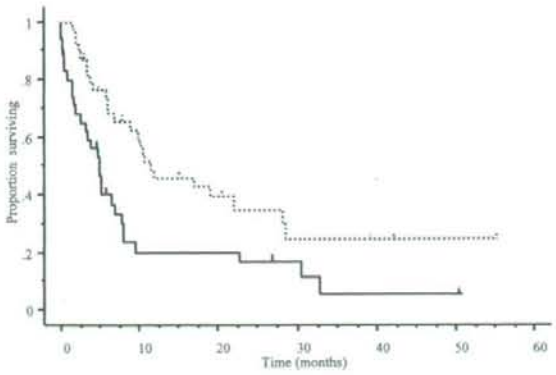

Figure 1. Kaplan-Meier analysis of progression-free survival (solid line) and overall survival (dotted line). Vertical bars indicate censored cases.

Table III. Characteristics of 21 patients with chemotherapy.

	n=21
Indication for therapy	
Initial case	13
Persistent/recurrence case	7
Postoperative case	1
Regimens	
Paclitaxel/carboplatin	9
Irinotecan/carboplatin	9
Weekly paclitaxel/carboplatin	2
Irinotecan/cisplatin	1

patients, comprising the highest percentage, followed by lung metastases in 4 patients. The median progression-free survival and overall survival were 3.8 months and 11.1 months, respectively (Fig. 1).

We examined the effects of chemotherapy on stage IVb cancer (Table III). Chemotherapy was administered to 21 patients, 13 of whom were undergoing initial treatment, 7 of whom had persistent/recurrence, and 1 of whom was undergoing postoperative therapy. The regimens consisted of paclitaxel/carboplatin in 9 patients, irinotecan/carboplatin in 9, weekly paclitaxel/carboplatin in 2, and cisplatin/irinotecan in 1. In 2 patients, including 1 undergoing postoperative adjuvant therapy, chemotherapy was discontinued due to adverse effects. For lesions that could be measured, the response rate was 61.9% (95% CI, 41.1-82.6) including 4 patients with CR and 9 patients with PR (Table IV).

We compared survival in the chemotherapy and non-chemotherapy groups. The median survivals of the chemotherapy and non-chemotherapy groups were 11.1 and 5.1 months, respectively, with a significant difference (p=0.0055) (Fig. 2).

We also compared survival between initial chemotherapy and initial other treatment groups. The median survivals in the initial chemotherapy and initial other treatment groups

Table IV. Response rate of chemotherapy (n=21).

Response (%)					
CR	PR	SD	PD	NE	RR
4	9	4	1	3	61.9%
					(95% CI, 41.1-82.6%)

CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; NE, not evaluable; RR, response rate.

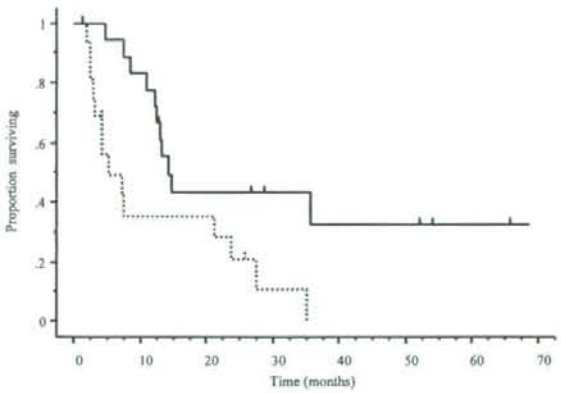

Figure 2. Kaplan-Meier analysis of overall survival according to with/without chemotherapy in stage IVb cervical carcinoma. Chemotherapy group (solid line) is significantly better prognosis (p=0.0055) than non-chemotherapy group (dotted line). Vertical bars indicate censored cases.

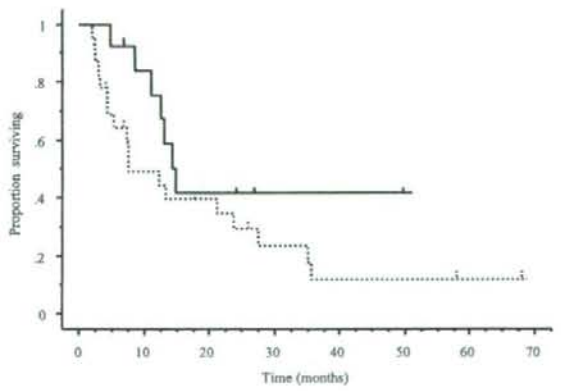

Figure 3. Kaplan-Meier analysis of overall survival according to with/without initial chemotherapy in stage IVb cervical carcinoma. There are no statistical differences (p=0.09) between initial chemotherapy group (solid line) and other initial treatment group (dotted line). Vertical bars indicate censored cases.

were 13.2 and 7.5 months, respectively, but it did not reach statistical significant (p=0.09) (Fig. 3). Two patients treated by chemotherapy alone as an initial treatment have survived

Table V. Prognostic factors of overall survival.

	Univariate	Multivariate		
Factor	P-value	P-value	HR	95% CI
Age ≥50	0.171	0.506	1.36	0.54-3.43
PS (0 and 1 vs. 2 and 3)	0.005	0.007	2.64	1.42-4.91
Pathology (SCC vs. non-SCC)	0.638	-	-	-
Organ metastases (0 vs. ≥1)	0.792	-	-	-
No. of distant metastases (1 vs. ≥2)	0.109	0.546	1.22	0.63-2.35
Bulky mass	0.478	-	-	-
Chemotherapy	0.011	0.016	6.03	1.97-18.37

disease-free for 51.8 and 68.6 months, respectively. One patient had stage IVb CC with para-aortic lymph node metastases while the other had stage IVb CC with subclavian lymph node metastases and mediastinal lymph node metastases. Both patients were administered paclitaxel/carboplatin for 6 cycles. After 6 cycles, the primary lesion and metastatic site exhibited complete response.

We analyzed chemotherapy, age, PS, histological type, main organ metastases, number of distant metastases, and bulky masses as prognostic factors. On univariate analysis, poor PS and non-chemotherapy groups were prognostic factors. On multivariate analysis, a poor PS (p=0.007; hazard ratio, 2.64; 95% CI, 1.42-4.91) and non-chemotherapy groups (p=0.016; hazard ratio, 6.03; 95% CI, 1.94-18.37) also affected overall survival (Table V).

Discussion

The prognosis of stage IVb cervical carcinoma is poor in patients with systemic metastases. No treatment has been established. In the NCI-PDQ, it is described that therapeutic strategies for this stage of cancer include palliative radiotherapy, chemotherapy as a regimen designed by a clinical study, and chemotherapy with cisplatin, which has previously been reported (34).

In stage IVb patients with para-aortic lymph node metastasis alone, surgery with postoperative radiotherapy and extended radiotherapy achieved a 5-year survival rate of 50% (30-33), and radical surgery may also be an option. However, since most metastases involve the main organs, it is difficult to control them by local treatment, and chemotherapy is indicated for most patients (4).

Various regimens of chemotherapy for this stage of cancer, including single-agent, have been investigated. In particular, cisplatin has most frequently been employed, and yields the highest response rate as a single-agent. It has therefore been

used as a key drug for more than 20 years (5,8,10-12). However, since the efficacy of cisplatin as a single-agent persists for only 6 months, combination regimens have been administered to improve in the prognosis to an extent exceeding the enhancement of its toxicity. In the 1990s, many phase II clinical studies investigated combination regimens with 2-4 agents including cisplatin. Cisplatin with ifosfamide (IFM) yielded the second highest response rate, and bleomycin (BLM), which has commonly been employed to treat other cancers due to its similar high response rate and low toxicity. The usefulness of IP (IFM + CDDP) (35) and BIP (BLM + IFM + CDDP) (36) regimens has also been examined. Some regimens have achieved a response rate of 60% or higher; however, these regimens for the non-advanced and locally advanced stages are quite toxic and shorten the survival of some patients. In addition, no comparative study has been conducted, and the evaluation of each regimen has been insufficient. In the latter half of the 1990s, combination regimens with new agents were designed, and the need for a standard therapy was emphasized.

Recently, carboplatin (37-39), topotecan (19,20) and paclitaxel (40-42) have also been reported to be tolerable and efficacious. Complete responses have also been observed with topotecan and paclitaxel. However, topotecan has greater toxicity than carboplatin or paclitaxel. Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel or topotecan is a reasonable approach in patients with recurrent disease. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S).

Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel (21) and cisplatin/topotecan (22) have been extensively investigated in clinical studies. A randomized phase III study comparing paclitaxel and cisplatin versus cisplatin alone showed that the two-drug combination yielded a higher response rate (36 versus 19%) and improved progression-free survival (4.8 versus 2.8 months; $p<0.001$), although no improvement has been seen in median survival (21). Another randomized phase III GOG study investigated the combination of cisplatin and topotecan versus cisplatin alone for persistent/recurrent cervical cancer. In this study of 294 eligible patients, the topotecan combination regimen was superior to single-agent cisplatin with respect to overall response rate (27 versus 13%; $p=0.004$), progression-free survival (4.6 versus 2.9 months; $p=0.014$), and median survival (9.4 versus 6.5 months; $p=0.017$) (22). A phase II study assessed cisplatin and gemcitabine in patients with advanced, persistent/recurrent cervical cancer; 17 patients were evaluated (43). The response rate was 57% in patients who had not previously received radiotherapy, and there was 1 complete response of 14 months. Paclitaxel and carboplatin have recently been assessed for recurrent or persistent cancer of the cervix; 4 of 15 patients had a complete response and 5 showed a partial response for an overall response rate of 60% (39). The median survival of all 15 patients treated was 17 months (range, 4-39 months). The combination of vinorelbine and cisplatin has also been assessed in 42 patients with recurrent or metastatic cervical cancer; the overall response rate was 48% (44). The GOG is currently conducting a phase III trial (GOG204) to assess 4 cisplatin-doublet regimens in patients with advanced metastatic or recurrent cancer (cisplatin/paclitaxel, cisplatin/topotecan, cisplatin/gemcitabine, versus cisiplatin/vinorelbine).

In our hospital, we conducted an in-house clinical study. For eligible patients, paclitaxel/carboplatin or irinitecan/carboplatin therapy was administered. Adverse effects were within the permissible ranges, and there were no treatment-related deaths, as reported in other studies. Response rate as an end-point was also similar to or exceeded that previously reported, suggesting the usefulness of these treatment options in chemotherapy for cervical carcinoma. In patients with poor PS, weekly paclitaxel/carboplatin therapy was safe. Several reports have indicated that the hematological toxicity of this therapy is lower than that of tri-weekly therapy, and that the therapeutic effects of these two regimens are similar (45,46). Weekly paclitaxel/carboplatin therapy may be useful for treating stage IVb cancer patients with poor PS.

In patient with this stage of cancer, nephropathy is frequent, making cisplatin administration difficult in many cases. Carboplatin can be administered to patients with nephropathy, without hydration. Considering the adverse effects, less toxic agents should be reviewed.

In this study, two patients treated by chemotherapy alone as an initial treatment have survived disease-free for 51.8 and 68.6 months, respectively. For patients with recurrence who desired sequential treatment, chemotherapy was administered when we considered them eligible. Considering that the prognosis was significantly better than that in the non-chemotherapy group, chemotherapeutic intervention may be useful in stage IVb patients who have undergone initial treatment and in those with persistent/recurrent metastases.

Eligible, consenting patients should be enrolled in clinical trials employing new drugs and/or strategies. Since there is as yet no evidence for the curative potential of chemotherapy in cervical cancer and no established survival benefit, and uncertainty exists as to how often response translates into symptom relief ('palliation'), non-protocol therapy should not be encouraged. Nevertheless, for a patient who is ineligible or unwilling to participate in a study but who wants treatment, there may still be an indication for chemotherapy giving 'psychological support' or hope. When such a patient insists on treatment and seeks untested remedies rather than a hospice if orthodox chemotherapy is not offered, single-agent cisplatin or carboplatin may be justified, with due attention being paid to contraindications and the toxic side effects. An interval response assessment and finite period of treatment are indicated. Objective benefit is possible, but not likely.

Prognostic factors for stage IVb cervical carcinoma include PS, age, histological type, main organ metastases, and distant metastases (23-29). In this study, univariate and multivariate analysis revealed that non-chemotherapy and poor PS influenced prognosis. In patients with poor PS, it is difficult to continue treatment, and chemotherapy may exceed cancer control due to systemic disease. However, we can not conclude the efficacy of chemotherapeutic intervention, as this study was a retrospective study and involved only a small number of patients. Previously, surgery and radiotherapy have been selected for this stage of cancer. The results of chemotherapy for initial treatment were similar to those for conventional treatment, suggesting the efficacy of chemotherapy as initial

treatment. However, a randomized comparative study should be conducted to demonstrate its efficacy.

In conclusion, the prognosis of stage IVb cervical carcinoma remains poor. Chemotherapy may improve the survival of patients with stage IVb CC.

Acknowledgments

This work was supported by The Supporting Fund of Obstetrics and Gynecology Kurume University.

References

1. Sasieni PD, Cuzick J and Lynch-Farmery E: Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Coordinating Network for Cervical Screening Working Group. Br J Cancer 73: 1001-1005, 1996.
2. Wong LC, Ngan HY, Cheung AN, Cheng DK, Ng TY and Choy DT: Chemoradiation and adjuvant chemotherapy in cervical cancer. J Clin Oncol 17: 2055-2060, 1999.
3. NCI Clinical Alert Urges New Standard of Care for Invasive Cervical Cancer, URL:http://www.nci.nih.gov/clinicaltrials/developments/cervical-cancer-alert0600.
4. Omura GA: Current status of chemotherapy for cancer of the cervix. Oncology 6: 27-32, 1992.
5. Omura GA: Chemotherapy for stage IVb or recurrent cancer of the uterine cervix. J Natl Cancer Inst Monogr 21: 123-126, 1996.
6. Lea JS, Sheets EE, Wenham RM, Duska LR, Coleman RL, Miller DS and Schorge JO: Stage IIB-IVB cervical adenocarcinoma: prognostic factors and survival. Gynecol Oncol 84: 115-119, 2002.
7. Cleeland CS: Pain assessment in cancer. In: Effect of Cancer on Quality of Life. Osoba D (ed). CRC Press, Boston, MA, pp293-306, 1991.
8. Thigpen T: The role of chemotherapy in the management of carcinoma of the cervix. Cancer J 9: 425-432, 2003.
9. Thigpen JT, Vance R, Puneky L and Khansur T: Chemotherapy as a palliative treatment in carcinoma of the uterine cervix. Semin Oncol 22: 16-24, 1995.
10. Thigpen T, Shingleton H, Homesley H, Lagasse L and Blessing J: Cis-platinum in treatment of advanced or recurrent squamous cell carcinoma of the cervix: a phase II trial of the Gynecologic Oncology Group. Cancer 48: 899-903, 1981.
11. Bonomi P, Blessing J, Stehman FB, DiSaia PJ, Walton L and Major FJ: Randomized trial of three cisplatin dose schedules in squamous-cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 3: 1079-1085, 1985.
12. Thigpen JT, Blessing JA, DiSaia PJ, Fowler WC Jr and Hatch KD: A randomized comparison of rapid versus prolonged (24 h) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. Gynecol Oncol 32: 198-202, 1989.
13. Coleman RE, Harper PG, Gallagher C, *et al*: A phase II study of ifosfamide in advanced and relapsed carcinoma of the cervix. Cancer Chemother Pharmacol 18: 280-283, 1986.
14. Meanwell CA, Mould JJ, Blackledge G, Lawton FG, Stuart NS, Kavanagh JJ, Latief TN, Spooner D and Chetiyawardana AD: Phase II study of ifosfamide in cervical cancer. Cancer Treat Rep 70: 727-730, 1986.
15. Sutton GP, Blessing JA, McGuire WP, Patton T and Look KY: Phase II trial of ifosfamide and mesna in patients with advanced or recurrent squamous carcinoma of the cervix who had never received chemotherapy: a Gynecologic Oncology Group study. Am J Obstet Gynecol 168: 805-807, 1993.
16. McGuire WP, Blessing JA, Moore DH, Lentz SS and Photopulos G: Paclitaxel has moderate activity in squamous cervix cancer: a Gynecologic Oncology Group study. J Clin Oncol 14: 792-795, 1996.
17. Morris M, Brader KR, Levenback C, Burke TW, Atkinson EN, Scott WR and Gershenson DM: Phase II study of vinorelbine in advanced and recurrent squamous cell carcinoma of the cervix. J Clin Oncol 16: 1094-1098, 1998.
18. Muggia FM, Blessing JA, Method M, Miller DS, Johnson GA, Lee RB and Menzin A: Evaluation of vinorelbine in persistent or recurrent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 92: 639-643, 2004.
19. Bookman MA, Blessing JA, Hanjani P, Herzog TJ and Anderson WA: Topotecan in squamous cell carcinoma of the cervix: a phase II study of the Gynecologic Oncology Group. Gynecol Oncol 77: 446-449, 2000.
20. Muderspach LI, Blessing JA, Levenback C and Moore JL Jr: A phase II study of topotecan in patients with squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecol Oncol 81: 213-215, 2001.
21. Moore DH, Blessing JA, McQuellon RP, Thaler HT, Cella D, Benda J, Miller DS, Olt G, King S, Boggess JF and Rocereto TF: Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 22: 3113-3119, 2004.
22. Long HJ III, Bundy BN, Grendys EC Jr, Benda JA, McMeekin DS, Sorosky J, Miller DS, Eaton LA and Fiorica JV: Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 23: 4626-4633, 2005.
23. Leath CA III, Straughn M Jr, Kirby TO, Huggins A, Partridge EE and Parham GP: Predictors of outcomes for women with cervical carcinoma. Gynecol Oncol 99: 432-436, 2005.
24. Kastritis E, Bamias A, Efstathiou E, Gika D, Bozas G, Zorzou P, Sarris K, Papadimitrou C and Dimopoulos MA: The outcome of advanced or recurrent non-squamous carcinoma of the uterine cervix after platinum-based combination chemotherapy. Gynecol Oncol 99: 376-382, 2005.
25. Sommers GM, Grigsby PW, Perez CA, Camel HM, Kao MS, Galakatos AE and Lockett MA: Outcome of recurrent cervical carcinoma following definitive irradiation. Gynecol Oncol 35: 150-155, 1989.
26. Yamamoto K, Yoshikawa H, Shiromizu K, Saito T, Kuzuya K, Tsunematsu R and Kamura T: Pulmonary metastasectomy for uterine cervical: a multivariate analysis. Ann Thorac Surg 77: 1179-1182, 2004.
27. Brader KR, Morris M, Levenback C, Levy L, Lucas KR and Gershenson DM: Chemotherapy for cervical carcinoma: factors determining response and implications for clinical trial design. J Clin Oncol 16: 1879-1884, 1998.
28. Potter ME, Hatch KD, Potter NY, Shingleton HM and Baker VV: Factors affecting the response of recurrent squamous cell carcinoma of the cervix to cisplatin. Cancer 63: 1283-1286, 1989.
29. Seki M, Nakagawa K, Tsuchiya S, Matsubara T, Kinoshita I, Weng SY and Tsuchiya E: Surgical treatment of pulmonary metastases from uterine cervical cancer. Operation method by lung tumor size. J Thorac Cardiovasc Surg 104: 876-881, 1992.
30. Lovecchio JL, Averette HE, Donato D and Bell J: Five-year survival of patients with periaortic nodal metastases in clinical stage IB and IIA cervical carcinoma. Gynecol Oncol 34: 43-45, 1989.
31. Varia MA, Bundy BN, Deppe G, Mannel R, Averette HE, Rose PG and Connelly P: Cervical carcinoma metastatic to para-aortic nodes: extended field radiation therapy with concomitant 5-fluorouracil and cisplatin chemotherapy: a Gynecologic Oncology Group Study. Int J Radiat Oncol Biol Phys 42: 1015-1023, 1998.
32. Grigsby PW, Lu JD, Mutch DG, Kim RY and Eifel PJ: Twice-daily fractionation of external irradiation with brachytherapy and chemotherapy in carcinoma of the cervix with positive para-aortic lymph nodes: phase II study of the RTOG 92-10. Int J Radiat Oncol Biol Phys 41: 817-822, 1998.
33. Grigsby PW, Heydon K, Mutch DG, Kim RY and Eifel P: Long-term follow-up RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. Int J Radiat Oncol Biol Phys 51: 982-987, 2001.
34. NCI Cancer Topics Cervical Cancer (PDQ®): Treatment URL: http://www.nci.nih.gov/cancertopics/pdq/treatment/health-professional/.
35. Omura GA, Blessing JA, Vaccarello L, Beman ML, Clarke-Pearson DL, Mutch DG and Anderson B: Randomized trial of cisplatin versus cisplatin plus mitolactol versus cisplatin plus ifosfamide in advanced squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 15: 165-171, 1997.
36. Bloss JD, Blessing JA, Behrens BC, Mannel RS, Rader JS, Sood AK, Markman M and Benda J: Randomized trial of cisplatin and ifosfamide with or without bleomycin in squamous carcinoma of the cervix: a Gynecologic Oncology Group Study. J Clin Oncol 20: 1832-1837, 2002.

37. McGuire WP, Arseneau J, Blessing JA, DiSaia PJ, Hatch KD, Given FT Jr, Teng NN and Creasman WT: A randomized comparative trial of carboplatin and iproplatin in advanced squamous carcinoma of the uterine cervix: a Gynecologic Oncology Group study. J Clin Oncol 7: 1462-1468, 1989.
38. Higgins RV, Naumann WR, Hall JB and Haake M: Concurrent carboplatin with pelvic radiation therapy in the primary treatment of the cervix cancer. Gynecol Oncol 89: 499-503, 2003.
39. Sit AS, Kelley JL, Gallion HH, Kunschner AJ and Edwards RP: Paclitaxel and carboplatin for recurrent or persistent cancer of the cervix. Cancer Invest 22: 368-373, 2004.
40. Papadimitriou CA, Sarris K, Moulopoulos LA, Fountzilas G, Anagnostpoulos A, Voulgaris Z, Gika D, Giannakoulis N, Diakomanolis E and Dimopoulos MA: Phase II trial of paclitaxel and cisplatin in metastatic and recurrent carcinoma of the uterine cervix. J Clin Oncol 17: 761-766, 1999.
41. Rose PG, Blessing JA, Gershenson DM and McGehee R: Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 17: 2676-2680, 1999.
42. Tinker AV, Bhagat K, Swenerton KD and Hoskins PJ: Carboplatin and paclitaxel for advanced and recurrent cervical carcinoma: The British Columbia Cancer Agency experience. Gynecol Oncol 98: 54-58, 2005.
43. Burnett AF, Roman LD, Garcia AA, Muderspach LI, Brader KR and Morrow CP: A phase II study of gemcitabine and cisplatin in patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix. Gynecol Oncol 76: 63-66, 2006.
44. Gebbia V, Caruso M, Testa A, Mauceri G, Borsellino N, Chiarenza M, Pizzardi N and Palmeri S: Vinorelbine and cisplatin for the treatment of recurrent and/or metastatic carcinoma of the uterine cervix. Oncology 63: 31-37, 2002.
45. Schuette W, Blankenburg T, Guschall W, Dittrich I, Schroeder M, Schweisfurth H, Chemaissani A, Schumann C, Dickgreber N, Appel T and Ukena D: Multicenter randomized trial for stage IIIb/IV non-small-cell lung cancer using every-3-weeks versus weekly paclitaxel/carboplatin. Clin Lung Cancer 7: 338-343, 2006.
46. Van der Burg ME, van der Gaast A, Vergote I, Burger CW, van Doorn HC, De Wit R, Stoter G and Verweij J. What is the role of dose-dense therapy? Int J Gynecol Cancer 15 (Suppl. 3): S233-S240, 2005.

Original Research

Carcinosarcoma of the Uterus: MR Findings

Yumiko O. Tanaka, MD,[1]* Hajime Tsunoda, MD,[2] Rie Minami, MD,[2] Hiroyuki Yoshikawa, MD,[2] and Manabu Minami, MD[1]

Purpose: To clarify the imaging characteristics of carcinosarcomas, which are the most common malignant mixed epithelial and mesenchymal tumors (MEMTs) of the uterus.

Materials and Methods: We retrospectively reviewed MR findings of 17 histopathologically confirmed cases with carcinosarcomas, including the size, growth pattern, signal intensity, contrast enhancement, and extrauterine spread in each case.

Results: The maximum tumor diameter was 11–165 mm (mean 88 mm). Nine cases (53%) showed exophytic with a stalk and eight cases (47%) showed broad-based exophytic growth. None of them showed invasive growth. Fourteen cases (82%) were isointense and three cases (18%) were hyperintense to myometrium on T1-weighted images (T1WI). An extremely high intensity area suggesting intratumoral hemorrhage was seen in only two cases. In 15 cases (88%), more than half of the tumor showed higher signal intensity than the outer myometrium on T2WI. Eight of the 16 cases (50%) had an unenhanced area, whereas 13 cases (81%) had a strongly enhanced area. Extrauterine extension was observed in only two cases (12%) at initial presentation.

Conclusion: Uterine carcinosarcomas reveal a spectrum of imaging findings with a high signal on T2WI, with a prolonged intense enhancement being the most common imaging feature.

Key Words: malignant mixed epithelial and mesenchymal tumor; carcinosarcoma; uterus; MR
J. Magn. Reson. Imaging 2008;28:434–439.

CARCINOSARCOMAS are the most common subtype of malignant mixed epithelial and mesenchymal tumors (MEMTs) of the uterine corpus (1). These tumors are still classified as "mixed" by convention, although there is increasing evidence that they are subsets of endometrial carcinoma (1). Various imaging characteristics of carcinosarcomas have been reported (2–7). Some investigators have reported them as a large endometrial mass deeply invading the myometrium (2,8), others have reported a clearly demarcated exophytic mass (6,7). The purpose of the present study was to clarify the imaging characteristics of carcinosarcomas. This is the largest series concerning the imaging characteristics of this tumor reported to date.

MATERIALS AND METHODS

From 1994 to 2005 we experienced 17 cases with pathologically proven carcinosarcomas. The patients were from 21 to 80 years old (mean age 63 years old).

Magnetic resonance (MR) examinations were performed with 1.5 T superconducting units (Signa, GE Medical Systems, Milwaukee, WI, and Gyroscan, Best, The Netherlands). Images were obtained with a phased array body coil in all but one case, in which a body coil was used. Butyl scopolamine (Buscopan, Boehringer Ingelheim, Ingelheim am Rhein, Germany) was given intramuscularly just before the examination to reduce bowel peristalsis in all cases. Sagittal T1- and T2-weighted images (T1WI, T2WI) and additional axial T2WI were obtained in all cases. Contrast enhancement was also performed with intravenous administration of 5 mmol of gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany) in all but one case. The field of view was 28 cm in all cases; however, other scan parameters varied because the study was conducted for more than 10 years. All T1WI were obtained with a spin echo sequence (TR/TE = 340–545/11–20 msec, 4–10 mm slice thickness with 0.4–2 mm intersection gap, 2–4 excitations). All but one T2WI was obtained with fast spin echo (TR/TE = 1800/100 msec, 16 echo train length, 4–10 mm slice thickness with 0.4–2 mm intersection gap, 2 excitations) and T2WI in one case was obtained with conventional spin echo (TR/TE = 2000/90 msec, 5 mm slice thickness with 2 mm intersection gap, 2 excitations). After administration of contrast materials, conventional T1WI were obtained in seven cases and fat-saturated T1WI (spectral presaturation inversion recovery, TR/TE = 425–650/10–12 msec, slice thickness and intersection gap were the same as T1WI before contrast administration in each case, with 2–3 excitations) in nine cases. MR examinations were retrospectively reviewed by two of the au-

[1]Department of Radiology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan.
[2]Department of Obstetrics and Gynecology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Japan.
*Address reprint requests to: Y.O.T., Department of Radiology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.
E mail: ytanaka@md.tsukuba.ac.jp
Received May 13, 2007; Accepted May 9, 2008.
DOI 10.1002/jmri.21469
Published online in Wiley InterScience (www.interscience.wiley.com).

thors with consensus. We studied the size, growth pattern, signal intensity on T1WI, T2WI, contrast enhancement, and extrauterine extension in each case. The tumor size was calculated as the maximum diameter of the tumors. The tumor growth pattern was classified into three types: exophytic with a stalk, broad-based exophytic, and invasive. The tumor was classified as exophytic with a stalk when it grew into the endometrial cavity with sessile pedicle and as broad-based exophytic when it grew filling the endometrial cavity with a broad base to the uterine inner wall. Masses with deep myometrial invasion replacing the uterine architecture were classified as invasive. Signal intensities on T1- and T2WI were classified into high, intermediate, and low intensity compared with the signal intensity to those of the outer myometrium. The existence of an extremely high signal intensity area on T1WI, which indicates intratumoral hemorrhage, was also evaluated in each case. As the signal intensity on T2WI was heterogeneous in most cases, we classified it into five groups by the percentage of the hyperintense area: none, less than 25%, 25%–50%, 50%–75%, and more than 75%. Contrast enhancement was seen in parts of all tumors. We evaluated the existence of unenhanced areas, which could indicate necrosis. We also evaluated the existence of the strongly enhanced areas, which showed hyperintensity compared to the outer myometrium on the contrast-enhanced T1WI obtained at the equilibrium phase. Lymph node metastases were considered positive when there were lymph nodes more than 10 mm in maximum diameter. We considered adnexal masses and any signs of intraperitoneal dissemination such as massive ascites or intraperitoneal masses as extrauterine extension.

RESULTS

Clinical and Histopathological Features of the Cases

The histopathological diagnosis, which was confirmed by hysterectomy specimen, was homologous subtype in four, heterologous subtype in ten, and three were not classified. Patients presented vaginal bleeding in 16 cases, lower abdominal pain in three cases, anemia in two cases, and asymptomatic (incidentally found at routine check up for cholecystolithiasis on transabdominal ultrasound) in one case. Postoperative staging along with the classification established by the International Federation of Gynecology and Obstetrics (FIGO) (9) was Ia in two cases, Ib in six cases, Ic in six cases, IIIa in one case, and IVb in two cases. Two of the seventeen cases had no myometrial invasion, six showed superficial, and nine showed deep myometrial invasion. The clinical outcome reviewed by medical record was disease-free survival in nine cases, alive with recurrence in one case, death in three cases, and four cases were lost to the study. The clinical background of the cases is summarized in Table 1.

MR Findings of the Cases

The MR findings of each case are summarized in Tables 1 and 2. The maximum tumor diameter was 11–165 mm (mean 83 mm). Nine cases (53%) showed exophytic with a stalk (Fig. 1) and eight cases (47%) showed broad-based exophytic growth (Fig. 2). None of the cases showed invasive growth. Three tumors showed higher signal intensity and isointensity to the myometrium in 14 cases on T1WI. An extremely high intensity area suggesting intratumoral hemorrhage was seen in only two cases. In most cases the signal intensity of the T2WI was predominantly high; the whole tumor showed high intensity in five cases, more than 75% in 10 cases, 50%–75% in no cases, 25%–50% in 2 cases, less than 25% in no cases. Therefore, more than half of the tumors showed higher signal intensity than the outer myometrium on T2WI in 15 of the 17 cases (88%). Eight of the 16 cases with contrast enhancement (50%) had an unenhanced area and 13 of the 16 cases had a strongly enhanced area (81%). Extrauterine extension was observed in only two cases (12%) at presentation: ovarian metastasis in one case and peritoneal dissemination in two cases. In one case with both adnexal and intraperitoneal extension, multiple lung metastases were depicted by plain chest radiography.

DISCUSSION

Uterine sarcomas include endometrial stromal sarcoma, leiomyosarcoma, and malignant MEMTs. The former two are composed of purely nonepithelial components and the latter are composed of an epithelial and a mesenchymal component. MEMTs are classified as follows: adenofibromas and adenomyomas as the benign group, and adenosarcomas, carcinosarcomas, and carcinofibromas as the malignant group (1,10,11). They are also classified as homologous or heterologous depending on the mesenchymal element present. Homologous tumors only contain mesenchymal elements, which are normally seen in the uterus, whereas heterologous tumors include some mesenchymal tissues that are not usually seen in the uterus (11). Carcinosarcomas are the most common malignant MEMTs and they were formerly called malignant Muellerian mixed tumor or malignant mesodermal mixed tumor. However, recent immunohistochemical, ultrastructural, and molecular studies have all suggested that carcinosarcomas are really metaplastic carcinomas in which the mesenchymal component retains at least some epithelial features in the vast majority of cases. Therefore, some researchers maintain that carcinosarcomas are better classified as a special type of endometrial carcinoma (1). In the current classification, carcinosarcomas are the most common sarcoma affecting the uterine corpus, which affects 1.8 white and 4.3 black women per 100,000 in the US population older than 35 years of age (12). Their incidence increases with age (1,11). It represents less than 2% of all uterine tumors (11). Their most common presentation is vaginal bleeding followed by abdominal mass or lower abdominal pain (1). Tumors after pelvic irradiation or long-term tamoxifen therapy have also been reported (1). The clinical course of uterine carcinosarcomas is aggressive, with poor overall prognosis (13). In our series, only two of the 17 cases showed extrauterine spread at initial

Table 1
Clinical Manifestation and Imaging Findings of the Cases

Case no.	Clinical manifestation					Imaging findings								
	Age	Histological subtype	Depth of the myometrial invasion	FIGO staging	Presentation	Outcome	Tumor size (mm)	Growth pattern	Signal intensity on T1WI	Extremely high intensity area on T1WI	% high signal intensity on T2WI	Unenhanced area	Strongly enhanced area	Extrauterine extension
1	21	Not specified	None	Ia	Vaginal bleeding	Alive without disease	11	Exophytic with a stalk	Low	−	100	−	—	−
2	58	Homologous	None	Ia	Vaginal bleeding	Alive without disease	48	Exophytic with a stalk	Low	−	25–50	NA	NA	−
3	54	Heterologous	Superficial	Ib	Lower abdominal pain Vaginal bleeding	Alive without disease	25	Broad-based exophytic	Low	−	100	−	+	−
4	61	Homologous	Superficial	Ib	Vaginal bleeding	Alive without disease	120	Exophytic with a stalk	Low	−	25–50	−	+	−
5	63	Not specified	Superficial	Ib	Vaginal bleeding	Lost	75	Exophytic with a stalk	Low	−	100	−	+	−
6	73	Heterologous	Superficial	Ib	Vaginal bleeding	Alive without disease	51	Exophytic with a stalk	Low	−	75–100	−	+	−
7	80	Heterologous	Superficial	Ib	Vaginal bleeding	Lost	80	Broad-based exophytic	Low	−	75–100	+	+	−
8	80	Not specified	Superficial	Ib	Vaginal bleeding	Tumor death	60	Exophytic with a stalk	Low	−	100	−	+	−
9	59	Homologous	Deep	Ic	Vaginal bleeding Anemia	Alive without disease	90	Broad-based exophytic	Low	−	75–100	+	+	−
10	62	Heterologous	Deep	Ic	Vaginal bleeding	Alive without disease	165	Exophytic with a stalk	Low	−	75–100	+	—	−
11	71	Heterologous	Deep	Ic	Asymptomatic	Alive without disease	160	Broad-based exophytic	High	−	75–100	+	+	−
12	72	Heterologous	Deep	Ic	Vaginal bleeding	Lost	60	Broad-based exophytic	High	−	75–100	+	+	−
13	73	Heterologous	Deep	Ic	Vaginal bleeding	Tumor death	105	Exophytic with a stalk	Low	−	75–100	+	+	−
14	75	Homologous	Deep	Ic	Vaginal bleeding	Lost	50	Broad-based exophytic	Low	−	75–100	−	+	−
15	60	Heterologous	Full thickness	IIIa	Lower abdominal pain Vaginal bleeding	Alive with disease	140	Broad-based exophytic	Low	+	75–100	+	—	−
16	50	Heterologous	Deep	IVb	Vaginal bleeding	Alive without disease	150	Exophytic with a stalk	High	+	75–100	+	+	IPD
17	52	Heterologous	Full thickness	IVb	Vaginal bleeding Anemia	Tumor death	110	Broad-based exophytic	Low	−	100	−	+	IPD Adnexa, lung

NA, not available; T1/2WI, T1/2-weighted imaging; IPD, intraperitoneal dissemination.

Table 2
Summary of the Imaging Findings of the Cases

Mean tumor diameter		88mm	
Growth pattern	9 Exophytic with a stalk	8 Broad-based exophytic	0 Invasive
Signal intensity on T1WI	3 High	14 Iso	0 Low
Hemorrhage	Seen in 2 cases	Not seen in 15	
Signal intensity on T2WI	15 High dominant	2 Low dominant	
Pocket like unenhanced area	Seen in 8 case	Not seen in 8	
Strongly enhanced area	Seen in 13 cases	Not seen in 3	
Extrauterine spread	Seen in 2 cases	Not seen in 15	

presentation; however, two cases with stage I disease died of the tumor after initial treatment.

Both benign and malignant MEMTs share some common clinical and pathological features such as the macroscopic findings of the tumors, which usually appear as solitary polypoid gray-tan masses projecting into the endometrial cavity (10).

Some MR characteristics of carcinosarcomas have been reported. Worthington et al (8) first described the MR findings of four cases of carcinosarcoma as large tumors with inhomogeneously low intensity on T1WI and a heterogeneous appearance on T2WI. In their report, three of the four tumors were demonstrated as large masses replacing the normal uterine architecture. Shapeero and Hricak (2) reported a large endometrial mass deeply invading the myometrium, with metastases as a characteristic of carcinosarcomas, which could not be differentiated from invasive endometrial carcinoma. On the other hand, Sahdev et al (6) reported that four of the five tumors showed exophytic endometrial mass and Ohguri et al (7) also reported them as sharply demarcated expanding masses. In our study, all tumors were large and exophytic with or without a stalk in the endometrial cavity. None of our cases showed endophytic growth replacing the uterine architecture. These facts indicate that the older reports tend to describe MR characteristics of the carcinosarcomas as invasive masses. We attribute this to the poor spatial resolution of the MR images at the time of acquisition. As the uterine zonal anatomy was indistinct in older equipment, the border between the tumor and the myometrium might become indistinct. Another reason for the difference in imaging features between older reports and ours is due to the clinical stage of the diseases. Eight of 17 cases of our series were in stage Ia or Ib, in which the tumor did not show deep myometrial invasion. Deep myometrial invasion was seen in larger tumors in our series; therefore, we consider that carcino-

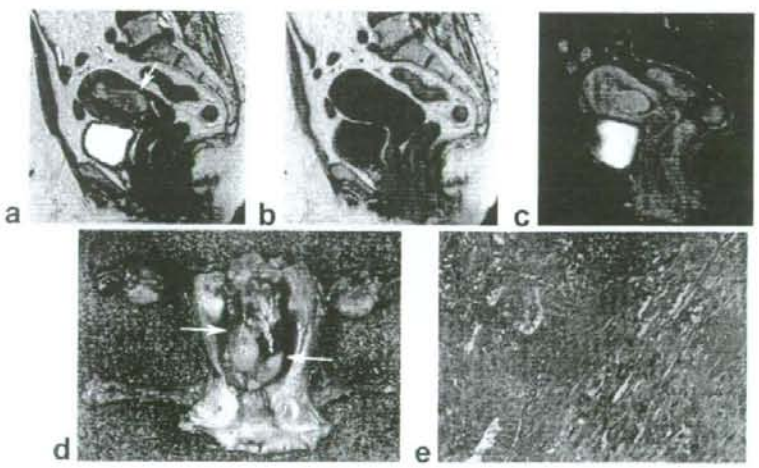

Figure 1. Seventy-three-year-old-woman with vaginal bleeding. Sagittal T2-weighted image **(a)** (TR/TE = 1800/100; echo train length, 16; field of view, 280 mm; matrix, 256 × 256; section thickness, 4 mm; gap, 0.4 mm; two signals acquired) demonstrates a tumor growing exophytically with a stalk within the endometrial cavity (arrows). It is homogeneously hyperintense on the T2-weighted image (A) and isointense to the myometrium on the T1-weighted image **(b)** (TR/TE = 454/13; field of view, 280 mm; matrix, 256 × 192; section thickness, 4 mm; gap, 0.4 mm; two signals acquired). The tumor shows homogeneous enhancement stronger than the outer myometrium (arrows) on the sagittal fat-saturated and contrast-enhanced T1-weighted image **(c)** (575/11; field of view, 280 mm; matrix, 256 × 192; section thickness, 4 mm; gap, 0.4 mm; two signals acquired). The macroscopic view of the resected specimen demonstrates a large exophytic mass drooping from the uterine fundus (**d**, arrowhead). Histological specimen **(e)** (hematoxylin/eosin stain, high-power field) reveals both endometrioid adenocarcinoma and variable types of sarcoma including endometrial stromal sarcoma, leiomyosarcoma, and osteosarcoma within the same specimen. The histopathological diagnosis is carcinosarcoma, heterologous subtype.

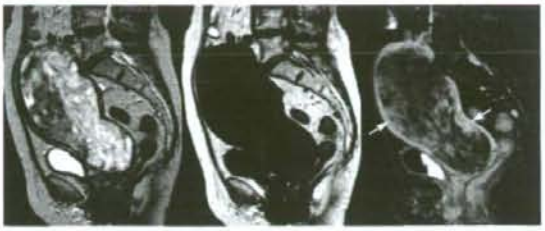

Figure 2. Seventy-one-year-old-woman with enlarged uterus recognized on transabdominal ultrasound for routine check-up for known cholecystolithiasis. Sagittal T2-weight image **(a)** (1800/100; echo train length, 16; field of view, 280 mm; matrix, 256 × 256; section thickness, 5 mm; gap, 0.5 mm; two signals acquired) demonstrates a large broad-based exophytic tumor with high signal intensity. It is isointense to the myometrium on the T1-weighted image **(b)** (545/20; field of view, 280 mm; matrix, 256 × 192; section thickness, 5 mm; gap, 0.5 mm; two signals acquired). The tumor shows heterogeneous enhancement partly stronger than the outer myometrium (arrows) on the sagittal fat-saturated and contrast-enhanced T1-weighted image **(c)** (525/11; field of view, 280 mm; matrix, 256 × 192; section thickness, 5 mm; gap, 0.5 mm; two signals acquired). The histopathological diagnosis is carcinosarcoma, heterologous subtype.

sarcomas initially appear as well-demarcated exophytic masses in the endometrial cavity.

A well-demarcated exophytic mass raises the possibility of submucosal leiomyoma on MR images (14). However, uterine leiomyomas typically show homogeneous low intensity on T2WI (15), which differs from the carcinosarcomas in our series. In this series, they showed a heterogeneous signal and more than half showed a higher signal intensity than the outer myometrium in 15 of 17 cases. On the other hand, uterine leiomyomas can also show heterogeneous signal intensity due to various types of degeneration (16). Therefore, it seems difficult to distinguish carcinosarcomas from leiomyomas when the masses show heterogeneous signal on T2WI.

Worthington et al (8) reported that carcinosarcomas include areas of medium to high signal intensity on T1WI corresponding to hemorrhage and necrosis. Sahdev et al (6) placed importance on necrosis demonstrating as pockets of high signal intensity on T2WI as a sign of uterine sarcomas. They reported that smaller carcinosarcomas showed endometrial masses that cannot be distinguished from endometrial carcinomas, whereas the larger ones were similar to leiomyosarcomas because of the necrosis. It has been reported that hemorrhagic necrosis is commonly seen in uterine leiomyosarcomas (17). In our series, only 8 of the 16 cases with contrast study included an unenhanced area suggesting necrosis and 4 of the 17 cases had an extremely high intensity area suggesting hemorrhage on T1WI. In addition, only two of the eight tumors smaller than 8 cm in maximum diameter included an unenhanced area. Therefore, hemorrhagic necrosis seems to indicate uterine sarcomas making larger masses, although it appears not to be so common in carcinosarcomas as in leiomyosarcomas. This might be due to that carcinosarcomas are really endometrial lesions, which are different from other sarcomatous lesions originating from the myometrium.

Ohguri et al (7) reported that all four carcinosarcomas showed areas of early and persistent marked enhancement similar to that of the myometrium. Yamashita et al (3) also reported that the degree of contrast enhancement differed between carcinomatous and sarcomatous components. As endometrial carcinoma is enhanced homogeneously weaker than the myometrium in general (18), they reported that different patterns of contrast enhancement within an endometrial tumor may raise the possibility of carcinosarcomas. They reported that the carcinomatous component was more strongly enhanced than the sarcomatous component (3); however, Takemori et al (4) reported contrary results. Therefore, different patterns of enhancement within an endometrial mass may represent an admixture of different histopathological components. However, whether a strongly enhanced area corresponds to the epithelial or mesenchymal component is unknown. We tried to clarify the relationship between the histopathological diagnosis and the degree of enhancement. However, we could not identify the exact location of the strongly enhanced area within the resected uterine specimens. The tumors tended to rotate before microscopic examination because the anterior wall of the uterine bodies was usually cut before fixation.

Endometrial carcinomas should be differentiated from carcinosarcomas because their prognosis and treatment strategy differ slightly (13). Endometrial carcinomas are divided into two types: one shows a well-demarcated exophytic mass (Type I) and the other shows invasive endophytic growth toward the myometrium (Type II). The former subtype is considered to be malignancy with favorable prognosis (19). In our study, all of the carcinosarcomas showed well-demarcated exophytic masses similar to Type I endometrial carcinomas. Endometrial tumors are usually diagnosed by endometrial curettage, histopathologically. Nevertheless, histological findings are sometimes misleading, as the biphasic nature may occasionally not be apparent until the entire tumor is studied. As mentioned above, endometrial carcinoma was reported to show weaker enhancement in the delayed phase of contrast MR (18,20). On the other hand, more than 80% of our carcinosarcomas had parts of strong enhancement. Therefore, a strongly enhanced area within the exophytic uterine tumor may suggest the possibility of carcinosarcomas when diagnosing a malignant endometrial tumor.

Endometrial polyps is a common pathology that exophytically occupies the endometrial cavity. Imaoka et al (21) and Park et al (20) reported that benign endometrial polyps showed higher signal intensity than the surrounding myometrium in a contrast-enhanced study. Then, endometrial polyps can show the polypoid lesions with an admixture of high and low signal intensity on contrast-enhanced study. However, endometrial polyps are characterized by a central fibrous core with low signal intensity and intratumoral cysts with high signal intensity on T2WI (22). Therefore, we consider

that endometrial polyps can be distinguished from carcinosarcomas before contrast enhancement.

In conclusion, uterine carcinosarcomas showed large exophytic hyperintense masses on T2-weighted MR images, which are slightly different from MR features of other uterine sarcomas. It might be partly due to the fact that they are really endometrial in origin (1). These exophytic features tend to lead to the possibility of Type I endometrial carcinoma. However, carcinosarcomas have a poorer prognosis than those of Type I endometrial carcinomas. Therefore, radiologists should be aware that strongly enhanced areas within the exophytic endometrial lesion suggests the possibility of carcinosarcomas.

REFERENCES

1. McCluggage WG, Haller U, Kurman RJ, Kubik-Huch RA. Mixed epithelial and mesenchymal tumours. In: Tavassoli F, Devilee P, editors. Pathology and genetics, tumors of the breast and female genital organs. World Health Organization Classification of Tumors. Lyon, France: World Health Organization; 2003:245–249.
2. Shapeero LG, Hricak H. Mixed mullerian sarcoma of the uterus: MR imaging findings. AJR Am J Roentgenol 1989;153:317–319.
3. Yamashita Y, Takahashi M, Miyazaki K, Okamura H. Contrast-enhanced MR imaging of malignant mixed mullerian tumor of the uterus. AJR Am J Roentgenol 1993;160:1150–1151.
4. Takemori M, Nishimura R, Yasuda D, Sugimura K. Carcinosarcoma of the uterus: magnetic resonance imaging. Gynecol Obstet Invest 1997;43:139–141.
5. Umesaki N, Tanaka T, Miyama M, Ogita S, Ochi H. Combined diagnostic imaging of uterine carcinosarcoma: a case report. Int J Gynecol Cancer 2000;10:425–428.
6. Sahdev A, Sohaib SA, Jacobs I, Shepherd JH, Oram DH, Reznek RH. MR imaging of uterine sarcomas. AJR Am J Roentgenol 2001; 177:1307–1311.
7. Ohguri T, Aoki T, Watanabe H, et al. MRI findings including gadolinium-enhanced dynamic studies of malignant, mixed mesodermal tumors of the uterus: differentiation from endometrial carcinomas. Eur Radiol 2002;12:2737–2742.
8. Worthington JL, Balfe DM, Lee JK, et al. Uterine neoplasms: MR imaging. Radiology 1986;159:725–730.
9. Announcements. Gynecol Oncol 1989;35:125–127.
10. Silverberg SG, Kurman RJ. Mixed epithelial-nonepithelial tumors. In: Tumors of the uterine corpus and gestational trophoblastic disease. Third series Fascicle 3. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1991:153–179.
11. Zaloudek C, Norris HJ. Mesenchymal tumors of the uterus. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. 4th ed. New York: Springer; 1994:487–528.
12. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, Epidemiology, and End Results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol 2004;93:204–208.
13. Vaidya AP, Horowitz NS, Oliva E, Halpern EF, Duska LR. Uterine malignant mixed Mullerian tumors should not be included in studies of endometrial carcinoma. Gynecol Oncol 2006;103:684–687.
14. Panageas E, Kier R, McCauley TR, McCarthy S. Submucosal uterine leiomyomas: diagnosis of prolapse into the cervix and vagina based on MR imaging. AJR Am J Roentgenol 1992;159:555–558.
15. Hricak H, Tscholakoff D, Heinrichs L, et al. Uterine leiomyomas: correlation of MR, histopathologic findings, and symptoms. Radiology 1986;158:385–391.
16. Okizuka H, Sugimura K, Takemori M, Obayashi C, Kitao M, Ishida T. MR detection of degenerating uterine leiomyomas. J Comput Assist Tomogr 1993;17:760–766.
17. Tanaka YO, Nishida M, Tsunoda H, Okamoto Y, Yoshikawa H. Smooth muscle tumors of uncertain malignant potential and leiomyosarcomas of the uterus: MR findings. J Magn Reson Imaging 2004;20:998–1007.
18. Hricak H, Hamm B, Semelka RC, et al. Carcinoma of the uterus: use of gadopentetate dimeglumine in MR imaging. Radiology 1991; 181:95–106.
19. Kurman RJ, Zaino RJ, Norris HJ. Endometrial carcinoma. In: Kurman RJ, editor. Blaustein's pathology of the female genital tract. 4th ed. New York: Springer; 1994:439–486.
20. Park BK, Kim B, Park JM, et al. Differentiation of the various lesions causing an abnormality of the endometrial cavity using MR imaging: emphasis on enhancement patterns on dynamic studies and late contrast-enhanced T1-weighted images. Eur Radiol 2006; 16:1591–1598.
21. Imaoka I, Sugimura K, Masui T, Takehara Y, Ichijo K, Naito M. Abnormal uterine cavity: differential diagnosis with MR imaging. Magn Reson Imaging 1999;17:1445–1455.
22. Grasel RP, Outwater EK, Siegelman ES, Capuzzi D, Parker L, Hussain SM. Endometrial polyps: MR imaging features and distinction from endometrial carcinoma. Radiology 2000;214:47–52.

Radiat Med (2008) 26:526–532
DOI 10.1007/s11604-008-0268-1

ORIGINAL ARTICLE

Comparison of tumor regression rate of uterine cervical squamous cell carcinoma during external beam and intracavitary radiotherapy

Kiyoshi Ohara · Yumiko Oishi Tanaka · Akinori Oki
Yoshikazu Okamoto · Toyomi Satoh · Koji Matsumoto
Hiroyuki Yoshikawa

Received: February 26, 2008 / Accepted: June 26, 2008

Abstract
Purpose. We compared the radioresponse of cervical carcinoma that was closely related to local disease control by the tumor regression rate (RR) during intracavitary radiotherapy (ICRT) and external beam radiotherapy (EBRT) on the presumption that ICRT has a stronger treatment impact than EBRT because of its specific dose distribution.
Materials and methods. A total of 37 patients were treated by EBRT at 45.0 Gy over 5 weeks, followed by high-dose-rate ICRT at 6.0 Gy per weekly insertion at point A three to five times and by boost EBRT. RR was defined as the slope (day^{-1}) of the tumor-volume shrinkage curve fit to an exponential regression equation. Assuming that the tumors were ellipsoid, the tumor volume was estimated using magnetic resonance (MR) images obtained before treatment, after 45.0 Gy of EBRT, and after the third ICRT insertion. RRs were compared based on the radiotherapy method.
Results. RR ranged between –0.008 to 0.093 day^{-1} (median 0.021 day^{-1}) during EBRT and –0.001 to 0.097 day^{-1} (median 0.018 day^{-1}) during ICRT, showing no significant difference or correlation between treatments.
Conclusion. Contrary to expectations, RR did not directly relate to the impact of physical treatment. RR could be related to biological factors, such as the amount of tumor clearance and changes in tumor consistency during treatment.

Key words Cervical cancer · Radioresponse · Tumor clearance · Minimum target dose · Tumor geometry

K. Ohara (✉)[1]
Department of Radiation Oncology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Y.O. Tanaka · Y. Okamoto
Department of Diagnostic Radiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

A. Oki · T. Satoh · K. Matsumoto · H. Yoshikawa
Department of Obstetrics and Gynecology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan

Present address:
[1]Department of Radiation Oncology, Tsuchiura Kyodo General Hospital, 11-7 Manabeshinmachi, Tsuchiura 300-0053, Japan
Tel. +81-29-823-3111; Fax +81-29-823-1160
e-mail: ki-ohara@md.tsukuba.ac.jp, ki-ohara@tkgh.jp

Introduction

Radiotherapy (RT) remains a mainstay of the locoregional treatment of invasive uterine cervical cancer. It normally consists of a combination of two methods: external beam radiotherapy (EBRT) and intracavitary radiotherapy (ICRT). Concurrent use of chemotherapy (chemoradiotherapy) is believed to enhance the effect of RT, and use of this combination is now regarded as the standard treatment strategy for locally advanced cervical cancer. For RT of cervical cancer, major predictable prognostic factors include clinical stage, tumor size, and tumor geometry (exophytic or endophytic).[1,2] In addition, the tumor radioresponse, which comprises tumor cell radiosensitivity but cannot be predicted before RT, is also prognostic of local disease control[3,4] and may be the most powerful among the factors.[5] In clinical practice, residual tumor mass assessed by pelvic examination[6,7] and more recently by objective magnetic resonance (MR) imaging[8,9] is often used as a prognostic factor that

incorporates all these factors. Residual tumor mass is, however, assessed only immediately before or after the end of RT.

It has been reported that tumor radioresponse, as assessed by the regression rate (RR), varies widely and is specific to the individual tumor.[10] In that study, tumors were assumed to regress exponentially with time, and MR imaging was used to define the RR as the speed of shrinkage of the tumor volume. Using this definition, it was hypothesized that if tumors shrink exponentially throughout the course of RT the RR may prove to be valuable tool in the early assessment of tumor radioresponse. For example, tumors assessed as not radioresponsive may be evaluated for a change in the treatment strategy before completing RT. Early-assessed RR (at 3–4 weeks after the start of RT, during EBRT but before ICRT), however, did not show exact correspondence with late-assessed RR (6–7 weeks after the start of RT, during the course of ICRT).[10] One reason for this inconsistency may be the difference between EBRT and ICRT regarding their impact on tumors. Because ICRT, with its characteristic steep dose falloff, delivers a much higher dose to the part of the tumor closest to the source, it should have a stronger impact than EBRT on tumors and accordingly on the RR.

We conducted a clinical study to compare the radioresponse of cervical cancer to the two RT methods based on the presumption that RR is higher during ICRT than EBRT.

Material and methods

Patients

Of 56 consecutive patients with uterine cervical squamous cell carcinoma treated primarily by RT at our institution between January 2006 and December 2007, a total of 42 were eligible for the study. Eligibility criteria included curative treatment under our standard clinical practice of EBRT and ICRT with or without concurrent cisplatin chemotherapy and completion of scheduled MR imaging according to the study protocol. Reasons for noneligibility among the other 14 patients included treatment by neoadjuvant chemotherapy before RT (n = 13) and palliative treatment with EBRT without ICRT (n = 1). Of the 42 eligible patients, 5 could not participate owing to intentionally higher than normal EBRT doses given before ICRT (n = 2) or difficulty with tumor identification (n = 2) or measurement (n = 1) on MR images; however, those with tumor disappearance before ICRT (n = 3) did participate. Thus, 37 patients were eligible for and participated in the study. Clinical stages based on the International Federation of Gynecology and Obstetrics staging system were IB1 (n = 2), IIB (n = 7), IIIB (n = 26), and IVA (n = 2). Patient ages ranged from 28 to 88 years (median 58 years).

Treatment

Patients were treated according to our normal RT protocol, with concurrent use of cisplatin when feasible. Prior written informed consent for the treatment was obtained from all patients. The initial clinical target volume was determined according to radiological nodal status, a variable closely associated with disease-free survival, as assessed by computed tomography (CT).[11] The whole pelvis was selected in patients with negative pelvic and paraaortic lymphadenopathy (n = 21) and the whole pelvis and paraaortic nodes were selected in patients with possible or probable pelvic but negative paraaortic lymphadenopathy (n = 16). Patients with possible or probable paraaortic lymphadenopathy were treated first by neoadjuvant chemotherapy and were excluded from the study.

Radiotherapy was performed according to the American Brachytherapy Society recommendations.[12] EBRT was performed using a CT-based conformal four-field technique with 10-MV X-rays in 1.8-Gy fractions at the isocenter at five fractions per week. When the total dose reached 45.0 Gy, EBRT was directed at the parametrial extension or lymphadenopathy as a boost, and ICRT was initiated. ICRT was performed weekly using a high-dose-rate remote afterloading system with ^{192}Ir. A Henschke-type tandem-ovoid applicator was normally used, although a vaginal cylinder was used for patients with a narrow vagina (n = 10). The prescribed dose to reference point A was 6.0 Gy per insertion. Point A was defined as 2.0 cm cephalic from the external os along a tandem and 2.0 cm lateral to the tandem. The dose of boost EBRT and number of ICRTs were determined individually in accordance with the tumor response. The total EBRT dose ranged from 45.0 to 63.0 Gy (median 54.0 Gy) including the boost dose, and the numbers of ICRTs performed in individual patients were two (n = 1), three (n = 24), four (n = 7), or five (n = 5). The number of ICRTs was normally three; however, a patient whose tumor responded completely after EBRT underwent only two ICRTs, and 12 patients whose tumors were not considered radioresponsive underwent more than three ICRTs. The overall treatment time was 44–71 days (median 54 days), with 9 patients exceeding 8 weeks in association with four or five ICRTs.

Patients were treated by concurrent chemoradiotherapy with cisplatin (n = 22) or by RT alone (n = 15). Cisplatin was given by single weekly intravenous

administration at 35 mg/m^2 starting from the first week of EBRT and continued for as long as feasible until the start of ICRT for a total of two (n = 1), three (n = 2), four (n = 4), five (n = 14), or six (n = 1) times. Those treated by RT alone were generally older (>70 years, n = 11), declined chemotherapy (n = 2), or had stage IB1 disease (n = 2) or associated liver disease (n = 1).

Tumor measurement and geometry typing

Magnetic resonance imaging was performed with 1.5-Tesla units. Images were obtained before RT (pre-RT), after EBRT at 45.0 Gy but before ICRT (pre-ICRT), and immediately after completion of the third ICRT application (post-ICRT). Tumors were identified as high-intensity lesions on T2-weighted images. As a clinical convenience, tumor volume was calculated assuming an ellipsoid mass by measuring three-dimensional maximum sizes of a tumor (i.e., lateral and anteroposterior sizes on axial images and the cephalocaudal size on a sagittal image). Tumors that had disappeared, were recognized as a remnant only, or remained as a small, high-intensity "scar" that was difficult to measure were regarded as 0.1 cm^3 in volume.

In addition to the RT method as a physical factor, we included tumor geometry as a biological factor. Tumor geometry, a prognostic factor estimable by routine pelvic examination and MR imaging, was classified according to pre-RT MR image observations rather than pelvic examination owing to the ease with which the former allows estimation of the proportion of exophytic to endophytic components. Tumors were classified as predominantly exophytic or predominantly endophytic (or intermediate when classification into either of the first two categories was difficult).

Response assessment

Tumor shrinkage curves were estimated by plotting tumor volumes on a semilogarithmic graph, with the start of RT set as day 0. RR was defined as the slope of the curve (day^{-1}) by fitting to an exponential regression equation. RR during EBRT was determined from the pre-RT and pre-ICRT volumes; and the RR during ICRT was determined from the pre-ICRT and post-ICRT volumes.

Statistical analysis

Comparison of each tumor's RR during EBRT and ICRT was done using the paired t-test, and correlation was analyzed by regression analysis. Differences in RR according to geometry type were tested using the Mann-Whitney U-test. StatView 5.0 (SAS Institute, Cary, NC, USA) was used for all analyses. $P < 0.05$ was considered statistically significant.

Results

To determine tumor volumes, MR images were obtained 3–32 days before RT (n = 37; median 17 days), 29–39 days after the start of EBRT but before ICRT (n = 37; median 34 days), and 46–63 days after the start of EBRT immediately after the third ICRT insertion (n = 34; median 55 days). Pre-RT volumes ranged from 1.3 to 88.2 cm^3 (median 23.7 cm^3); post-EBRT volumes from 0.1 to 56.7 cm^3 (median 4.3 cm^3), including three complete responders; and post-ICRT volumes from 0.1 to 26.4 cm^3 (median 0.8 cm^3), including another seven complete responders. Ten tumors had thus achieved a complete response after the third ICRT insertion (Fig. 1).

The RR ranged from –0.0083 to 0.0934 day^{-1} (n = 37; median 0.0205 day^{-1}) during EBRT and from –0.0113 to 0.0967 day^{-1} (n = 34; median 0.0181 day^{-1}) during ICRT; there was no significant difference between them (P = 0.3692) (Fig. 2). RR showed no significant correlation between the two treatments (n = 34) (R = –0.104, P = 0.8323) (Fig. 3). However, a strong correlation was seen between post-ICRT and post-EBRT volumes (n = 34) (R = 0.925, P < 0.0001) (Fig. 4), whereas pre-RT volumes showed a weak correlation with post-EBRT volumes (n = 37) (R = 0.378, P = 0.0203) or no significant correlation with post-ICRT volumes (n = 34) (R = 0.313, P = 0.0712).

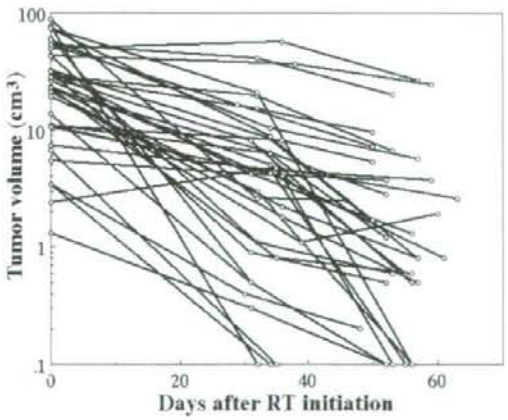

Fig. 1. Tumor shrinkage curves determined from tumor volumes before radiotherapy (day 0), preintracavitary radiotherapy after pelvic external beam radiotherapy (45.0 Gy), and postintracavitary radiotherapy following the third insertion. *RT*, radiotherapy

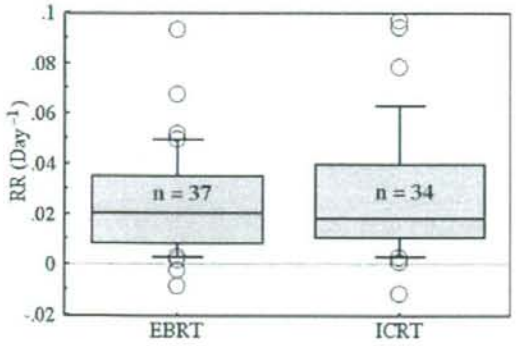

Fig. 2. Box plots of the tumor regression rate (*RR*) during external beam radiotherapy (*EBRT*) and intracavitary radiotherapy (*ICRT*) ($P = 0.3692$). The *box* indicates the range of the 25th and 75th percentiles with the median value, and the *bars* indicate the 10th and 90th percentiles

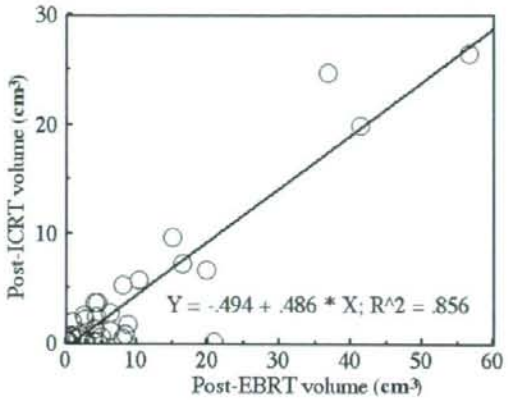

Fig. 4. Relation of the tumor volume after pelvic external beam radiotherapy (*post-EBRT volume*) to that after the third intracavitary radiotherapy insertion (*post-ICRT volume*) ($n = 34$). $P < 0.0001$

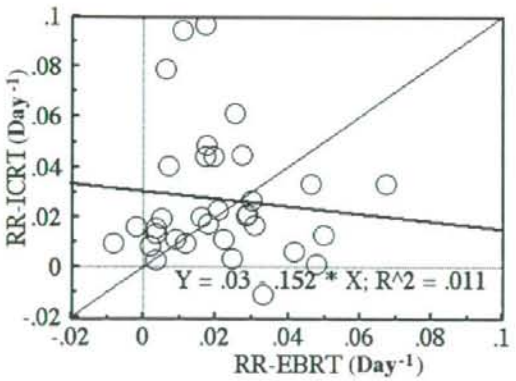

Fig. 3. Tumor regression rate (*RR*) with external beam radiotherapy (*EBRT*) versus that with intracavitary radiotherapy (*ICRT*) ($n = 34$). $P = 0.8323$

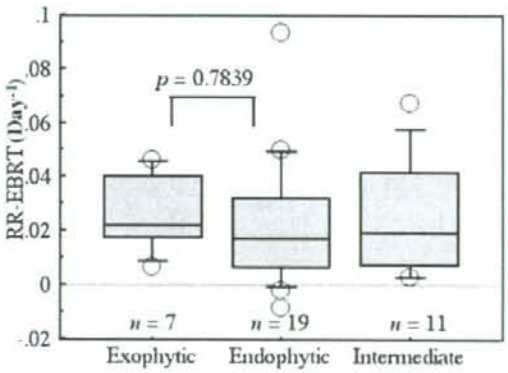

Fig. 5. Box plots of the tumor regression rate with external beam radiotherapy (*RR-EBRT*) according to tumor geometry (exophytic, endophytic, intermediate). The *box* indicates the range of the 25th and 75th percentiles with the median value, and the *bars* indicate the 10th and 90th percentiles

No significant correlation was seen between pre-RT volumes and RR during EBRT ($n = 37$) ($R = 0.317$, $P = 0.0556$).

Tumor geometry was classified as exophytic ($n = 7$), endophytic ($n = 19$), or intermediate ($n = 11$). Pre-RT volumes were 1.3–74.4 cm^3 (median 13.8 cm^3) in the exophytic group, 3.4–77.8 cm^3 (median 23.7 cm^3) in the endophytic group, and 5.4–88.2 cm^3 (median 26.8 cm^3) in the intermediate group, with no significant difference between the exophytic and endophytic types ($P = 0.5171$). The RR during EBRT did not significantly differ among the exophytic (range 0.0172–0.0465 day^{-1}, median 0.0223 day^{-1}), endophytic (range –0.0083 to 0.0934 day^{-1}, median 0.0174 day^{-1}), and intermediate (range, 0.0034–0.0676 day^{-1}, median 0.0195 day^{-1}) groups (Fig. 5). Furthermore, the RR during ICRT did not differ significantly among the tumor types.

Discussion

Our presumption that RR is significantly higher during ICRT than during EBRT was based on two major hypotheses: (1) The treatment impact is physically

greater with ICRT than with EBRT; and (2) RR is proportional to the treatment impact. The first hypothesis is based on the physical facts that ICRT delivers extremely high doses of more than several tens of Gray units to parts of a tumor close to the source, and that the smaller the tumor the higher the dose delivered to the part of a tumor distant to the source (minimum target dose). The treatment impact would thus be higher with ICRT than with EBRT, particularly in small tumors, although the treatment fractionation differs between the RT methods. In addition, the minimum target dose increases with ICRT in accordance with tumor shrinkage, whereas it is constant with EBRT irrespective of tumor size. The second hypothesis is based simply on the biological basis that the higher the impact, the greater the rate of tumor cell death, which directly relates to the RR. Another hypothesis of the exponential shrinkage of tumors was based on the findings of Gong et al., whose meticulous weekly MR measurement of cervical tumor volume over 5 weeks identified exponential shrinkage during EBRT.[13]

Contrary to our expectations, however, the study did not show that RR was significantly higher during ICRT than EBRT. Indeed, the RR was lower during ICRT than EBRT in 11 of 34 tumors (32.4%) (Fig. 3). In addition, RR did not significantly correlate with the tumor geometry, which is considered a significant prognosticator of tumor response. These inconsistent results could be due in part to error-causing factors such as the approximate tumor-volume estimation made on the assumption that tumors are ellipsoid,[14] the inconsistent period of time between the pre-RT MR imaging and the initiation of RT, and protraction of the EBRT effect on RR during ICRT. In addition to these error-causing factors, biological factors that concern RR could participate in the process of tumor shrinkage.

A hypothetical mechanism of tumor clearance may be a biological factor that accounts for the difference. Tumor clearance involves two mechanisms: biological clearance (phagocytic scavenging) and mechanical clearance (exfoliation).[15] Clearance of tumors located on an outer tissue surface (e.g., esophageal and pharyngeal tumors) involves the participation of both mechanisms. For tumors surrounded by normal tissue, on the other hand (e.g., metastatic lymph nodes and pancreatic tumors), mechanical clearance is blocked by surrounding tissues, leaving biological clearance as the only mechanism involved. Cervical cancer involves both mechanisms, but mechanical clearance is less efficient for endophytic than exophytic tumors. Endophytic infiltrating tumors are largely surrounded by normal cervical stroma or parametria, whereas exophytic tumors are largely exposed to the vaginal cavity. However, the proportion of exophytic and endophytic components in cervical tumors varies; and in any case tumors are difficult to classify under this simple classification.

As a further complication, the activity of each clearance mechanism is difficult to predict. Mechanical clearance may occur unpredictably with time. Tumor volume reduction may occur even before treatment (e.g., via tumor ulceration caused by spontaneous disruption to the integrity of the tumor stroma). Biological clearance may be hampered by radiation-induced damage to the integrity of surrounding normal tissues, which could preferentially occur during the late period of RT (i.e., ICRT). In addition to these tumor clearance mechanisms, many other biological factors are likely to be closely involved in tumor response (e.g., intrinsic tumor cell radiosensitivity[16] and oxygen status[17]). Tumor characteristics identified on MR imaging should be altered by RT; in other words, tumors after RT are qualitatively different from those before RT. The physical impact of treatment does not directly account for tumor response, which is assessed only quantitatively. Moreover, the aggregate impact of these multiple biological factors are difficult to estimate individually, and their individual impact during RT may be inconsistent. Positron emission tomography with ^{18}F-fluorodeoxyglucose may be useful in the qualitative assessment of tumor response.[18]

Bulky endophytic tumors that often leave a residual mass are generally managed by intensifying the treatment. This is done by either adjuvant hysterectomy or increasing the ICRT dose. Paley et al. identified residual tumor cells in 61% of stage IB–IIB cervical cancers hysterectomized because of a residual tumor mass after treatment by EBRT and low-dose-rate ICTR.[19] They used low doses, indicating the possibility of adjuvant surgery when necessary. Consequently, residual tumor cells were subsequently identified in 78% of patients receiving target doses that were less than the mean dose at point A (79.7 Gy), but in only 47% of those receiving higher target doses. Moreover, hysterectomy after RT is reported to heighten the incidence of complications.[20] Eifel et al. reported that the treatment of patients with stage IB–IIB bulky endophytic tumors using EBRT and low-dose-rate ICTR resulted in a significantly higher 5-year local recurrence rate in patients receiving low doses (33%) than in those receiving high doses (16%), but there was no significant difference in the 5-year rate of major complications (23% and 10%, respectively).[21] Delivery of low doses that were nevertheless sufficient to preclude the possibility of adjuvant surgery resulted from restricted dose delivery due to unfavorable (narrow) vaginal anatomy or from historical institutional differences in prescription of the ICRT dose.