例）であり、組織型別にみると、扁平上皮癌 28 例では 89.3%、腺扁平上皮癌 7 例では71.4%であった。

合併症については、腸閉塞は 1 例（1.5%）にみられたが、外科的治療を要するものではなかった。下肢の重篤な浮腫とほう窩織炎も 1 例（1.5%）に認めただけであった。

D. 考察

5 年無再発生存率は、中等度危険群と高危険群との間に有意差は無かった（p=0.3122、log-rank test)。特に、高危険群 35 例には 31 例のリンパ節転移陽性例が含まれていたが、その 5 年無再発生存率は 85.7%と一般的な報告（60%前後）に比べて極めて良好と考えられた。また、根治手術後に照射した場合に比較的高頻度に見られる腸閉塞や下肢の重篤な浮腫とほう窩織炎が極めて少なかったことは、私たちの治療戦略が有用である事を示すと考えた。

E. 結論

今回の検討により、子宮頸部扁平上皮癌、腺扁平上皮癌に対して、根治手術後に全身的化学療法を行うという治療方針は成績がよく、患者の QOL も良い事が判明した。私たちは、今後、この治療方針の有用性を前方視的に検証する予定である。

なお、この成績は文献 2 に詳述されている-2)。

F. 健康危険情報

特記すべきことなし

G. 研究発表

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H. 知的財産権の出願・登録状況（予定含）

なし。

厚生労働科学研究費補助金（がん臨床研究事業）
分担研究報告書

進行・再発子宮頸がんに対する標準的治療体系の確立に関する研究

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研究要旨

子宮頸癌に対する放射線治療における高線量率腔内照射の最適線量スケジュールを明らかにする目的で、多施設共同前向き臨床試験を計画した。

I, II 期子宮頸癌に対する放射線治療単独の臨床第 II 相試験を遂行し順調に症例を登録した。

III, IVA 期子宮頸癌に対する同時化学放射線療法の臨床第 II 相試験の研究計画書案を策定した。

A. 研究目的

子宮頸癌に対する高線量率腔内照射（HDR-ICBT）を用いた根治的放射線治療の線量スケジュールにおいて、日米間には大きな差異が認められる。本邦の線量スケジュールの妥当性（安全性、有効性）を多施設共同前向き臨床試験により、科学的に明らかにする。

B. 研究方法

1．I, II 期子宮頸癌に対する HDR-ICBT を用いた根治的放射線治療に関する多施設共同前向き試験

- 対象：I, II 期子宮頸部扁平上皮癌、腫瘍径 40mm 未満かつ骨盤内リンパ節転移なし（MRI にて測定/判定）
- 治療内容：放射線治療単独、全骨盤照射 50Gy/25 回（中央遮蔽 20Gy より）+ HDR-ICBT 6Gy x 4 回
- 主要評価指標：2 年骨盤内無増悪割合
- 目標症例数：60 例（3 年間）

2．局所進行子宮頸癌に対する HDR-ICBT を用いた同時化学放射線療法（CCRT）に関する多施設共同前向き臨床試験

- 対象：III, IVA 期子宮頸癌（扁平上皮癌、腺癌、腺扁平上皮癌）、CT 上短径 10mm 以上の傍大動脈リンパ節腫大なし
- 治療内容：同時化学放射線療法、全骨盤照射（中央遮蔽適用）+HDR-ICBT（合計 BED=72-86Gy$_{10}$）、CDDP 40mg/m^2, weekly 投与 x 5 コース
- 主要評価指標：2 年無増悪生存割合
- 目標症例数：70 例（2 年間）

C. 研究結果（研究の進捗状況）

1. I, II 期子宮頸癌に対する HDR-ICBT を用いた根治的放射線治療に関する多施設共同前向き試験

2004 年 9 月より登録を開始し、2007 年 1 月 31 日現在まで 11 施設より 49 例が登録された。データセンターは大阪大学大学院医学研究科医用物理学講座内においた。今年度定期モニタリングは 2 回行われ、順調な症例集積と重篤な有害事象の

報告がないことが確認された。今年度メモランダムの発行はなかった。2006年12月に第2回QA委員会（放射線治療品質評価）を行い、評価基準に基づき19例について16項目の評価を行った。

2. 局所進行子宮頸癌に対するHDR-ICBTを用いた同時化学放射線療法（CCRT）に関する多施設共同前向き臨床試験

JGOG（婦人科悪性腫瘍化学療法研究機構）での試験実施に向けてプロトコル案の策定作業を行った。喜多川（研究分担者）らとともに化学療法の投与法、休止/中止基準等を検討し策定した。JGOG放射線治療委員会委員が中心となり、厚生労働省がん研究助成金研究班小口班（放射線治療における臨床試験の体系化に関する研究）の協力で、放射線治療に関してのアンケート収集作業を行いそれらの結果をもとに放射線治療内容の策定を行った。2006年11月米国Radiation Physics Center（RPC)の視察を行い、放射線治療QA/QCプログラムの作成を開始した。今後JGOGにて正式な承認を得て試験開始予定である。

D. 考察（本研究の意義と今後の見通し）

I, II期子宮頸癌に対する試験は順調に進行していると考えられる。2007年9月までに症例登録を終了する予定である。2年後に行われる解析の結果、早期子宮頸癌に対する本邦の線量スケジュールの妥当性が明らかになることが期待される。

局所進行子宮頸癌に対する同時化学放射線療法（CCRT）の研究計画はほぼ順調に進んでいると考えられる。次年度にはJGOGにて試験開始の予定である。本研究は本邦におけるCCRTの認容性と有効性を科学的に証明するのみならず、子宮頸癌の集学的治療における標準的放射線治療の確立に寄与すると思われる。

E. 結論

子宮頸癌に対する放射線治療における、本邦の線量スケジュールの妥当性を探索する多施設共同臨床試験を策定、遂行した。

F. 健康危険情報

特記すべきことなし

G. 研究発表

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H.知的財産権の出願・登録状況(予定含)

なし

研究成果の刊行に関する一覧表

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Fertility-preserving treatment for patients with malignant germ cell tumors of the ovary

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Abstract

Aim: The aim of this study was to investigate whether fertility preservation influences the clinical outcome in patients with malignant germ cell tumors of the ovary (MGCTO).

Methods: A case study analysis was performed on patients with MGCTO treated at Kurume University Hospital between 1986 and 2004. Thirty-five patients were included in the study, 14 with immature teratoma, 11 with dysgerminoma, eight with endodermal sinus tumor, and two with mixed germ cell tumor. Twenty-three patients had International Federation of Gynecology and Obstetrics stage I (Ia, 11; Ib, 2; Ic, 10), one had stage II, seven had stage III, and four had stage IV disease.

Results: Five patients with stage III or IV disease received radical surgery. Thirty patients underwent conservative surgery. As the adjuvant treatment, 30 patients received chemotherapy, while five patients did not receive any chemotherapy. The overall survival rate was 97.1%. One patient died of the disease. She was 13 years old with a stage IV endodermal sinus tumor. Twelve have attempted conception, and eight have achieved at least one pregnancy (66.7%).

Conclusions: Irrespective of the stage of the disease, conservative surgery and adjuvant chemotherapy for MGCTO can achieve a favorable outcome in terms of survival and fertility.

Key words: chemotherapy, fertility preservation, malignant germ cell tumor, surgery.

Introduction

Malignant germ cell tumors of the ovary (MGCTO) account for 5% of all ovarian malignancies in Western countries.[1] MGCTO mainly occur in adolescents and young women. The prognosis for patients with ovarian non-dysgerminomatous germ cell malignancies was bleak before the introduction of modern combination chemotherapy. The evolution of modern chemotherapy transformed these poor prognosis malignancies into highly curable ones. In the early 1970s, the combination of vincristine, actinomycin D, and cyclophosphamide (VAC) emerged as the first effective therapy.[2] The efficacy of cisplatin, vinblastine, and bleomycin (PVB) was documented in the treatment of males with testicular cancer and subsequently became the standard treatment for females with ovarian germ cell malignancies.[3] Bleomycin, etoposide, and cisplatin (BEP) have been shown to have equal efficacy and less toxicity in the treatment of ovarian germ cell malignancies.[4] Prompt initiation of appropriate chemotherapy after surgery is critical for young patients with an advanced MGCTO.[5] Contemporary principles of surgery for MGCTO dictate that fertility-

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preserving surgery is appropriate even in the case of extensive metastatic disease, because removal of the uninvolved ovary had little impact on the patients' survival. The objective of this study was to evaluate the clinical outcome and fertility of patients with MGCTO who received fertility-preserving treatment.

Patients and Methods

From 1986 to 2004, 35 patients diagnosed with MGCTO were registered for treatment at Kurume University Hospital. The tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) 1987 staging system for primary ovarian carcinoma. Histopathology was classified according to the World Health Organization criteria. The serum tumor markers (α-fetoprotein [AFP], β-human chorionic gonadotropin [β-HCG], lactate dehydrogenase [LDH], and CA125) were calculated during treatment. Data were obtained from the patients' medical records. The median age of these 35 patients was 22 years, with a range of 8–34 years. Seven patients (20%) were younger than 15 years old, and 21 patients (60%) were younger than 25 years old. There were 14 patients (five, grade 1; five, grade 2; four, grade 3) with immature teratoma (IMT) (40%) 11 with dysgerminoma (DSG) (31.4%), eight with endodermal sinus tumor (EST) (22.9%), and two with mixed germ cell tumor (MGT) (5.7%). Twenty-three patients had Stage I (Ia, 11; Ib, 2; Ic, 10) tumors (65.7%), one patient had a Stage II tumor (2.9%), seven patients had Stage III tumors (20%), and four patients had Stage IV tumors (11.4%). The serum tumor markers AFP, β-HCG, LDH, and CA125 were elevated in 16 patients (45.1%), three patients (8.6%), 11 patients (31.4%) and 22 patients (62.9%), respectively. Eight patients (22.9%) were negative for tumor markers (Table 1).

Table 1 Patient characteristics

Characteristics	No. patients ($n = 35$)
Median age at diagnosis (range)	22 (8–34)
Median month of follow up (range)	84 (6–442)
Histopathologic types	
Immature teratomal	14 (40.0%)
Dysgerminoma	11 (31.4%)
Endodermal sinus tumor	8 (22.9%)
Mixed germ cell tumor	2 (5.7%)
Clinical stage (FigO)	
I	23 (65.7%)
a	11
b	2
c	10
II	1 (2.9%)
III	7 (20.0%)
IV	4 (11.4%)
Tumor marker	
α-fetoprotein	16 (45.7%)
β-human chorionic gonadotropin	3 (8.6%)
Lactate dehydrogenase	11 (31.4%)
CA125	22 (62.9%)
Negative	8 (22.9%)

Surgery

All patients underwent laparotomy as an initial treatment. Up to 1993, we performed bilateral salpingo-oophorectomy, hysterectomy, omentectomy, pelvic lymphadenectomy, washing cytology of the pelvis and paracolic gutters, and metastasectomy in patients with advanced disease. Five patients (14.3%) who had Stage III or Stage IV disease underwent bilateral salpingo-oophorectomy and hysterectomy. Regardless of the stage of the disease after 1993, conservative surgery was performed. A unilateral salpingo-oophorectomy, washing cytology of the pelvis and paracolic gutters cytology, and if it was needed, pelvic and paraaortic nodes biopsy were performed for 30 patients (85.7%). Among these, a contralateral wedge resection was performed in eight patients (22.9%). Up to 1990, second-look operations (SLO) were performed in 13 patients, seven of whom had residual lesions at primary surgery.

Chemotherapy

All patients with Stage I DSG and grade 1 of IMT and were treated by surgery alone. The other 30 patients (85.7%) received adjuvant chemotherapy. From 1986 to 1988, seven patients received VAC: vincristine (1–1.5 mg/m^2 on day 1 every 4 weeks), actinomycin D (0.5 mg/day × 5 days every 4 weeks), and cyclophosphamide (150 mg/m^2/day × 5 days every 4 weeks). From 1986 to 1991, five patients received PVB: cisplatin (20 mg/m^2/day × 5 days every 3 weeks), vinblastine (0.15 mg/kg on days 1 and 2 every 3 weeks), and bleomycin (20 mg/m^2 on days 2, 9, and 16 every 3 weeks). From 1992 to 2004, 18 patients received BEP: bleomycin (30 mg/body on days 2, 9, and 16 every 3 weeks), etoposide (100 mg/m^2/day × 5 days every 3 weeks), and cisplatin (20 mg/m^2/day × 5 days every 3 weeks) (Table 2). Regarding the course of chemotherapy, at least one more course would be given after tumor markers normalized. Two or three courses of consolidation

Table 2 Treatment

Treatment	No. patients ($n = 35$)
Surgery	
TAH + BSO	5 (14.3%)
USO only	22 (62.8%)
USO with contralateral wedge resection	8 (22.9%)
Chemotherapy	
VAC	7 (20.6%)
PVB	5 (14.7%)
BEP	18 (50%)
None	5 (14.7%)

BEP, bleomycin, etoposide, and cisplatin; BSO, bilateral salpingo-oophorectomy; PVB, cisplatin vinblastin, and bleomycin; TAH, total abdominal hysterectomy; USO, unilateral salpingo-oophorectomy; VAC, vincristine, actinomycin D, and cyclophosphamide.

Table 3 Comparison of survival rates after conservative surgery versus radical surgery

Survival outcome	Alive	Dead	Total
Conservative Surgery (fertility preserving surgery)	30	0	30
Radical Surgery (not fertility preserving surgery)	4	1	5
Total	34	1	35

Malignant germ cell tumors of the ovary recurred in no patients. The survival rate after 5 years was 97.1%. Normal menstrual cycle was observed in all patients after conserving surgery.

would be given if gross residual disease was present after primary surgery.

Results

Follow up and recurrence

The median follow-up period was 84 months (range 6–432 months). Twenty-three cases (65.7%) have been followed longer than 60 months. No recurrence was observed in any patients, whether fertility was preserved or not preserved, except one patient with stage IV EST. The overall survival rate was 97.1% (Table 3). In eight patients who received wedge resection, no occult metastasis was found in any contralateral ovaries.

Through October 2004, 30 patients receiving chemotherapy had been followed with sustained remission for at least 36 months. Thirteen patients received SLO after finishing chemotherapy. No tumor was found at SLO, regardless of the size of residuals. No secondary malignancy has been documented in any of the patients who received chemotherapy.

There was only one patient who died of disease. She was 13 years old with Stage IV EST. Her chief complaints were acute abdominal pain and a feeling of abdominal distension. Computed tomography (CT) showed a huge pelvic tumor, massive ascites, and disseminated tumor to the peritoneum and liver surface. The serum tumor marker of AFP was elevated to 60 959 ng/mL. She was given a preliminary diagnosis of an ovarian yolk sac tumor. Exploratory surgery revealed a 5×10 cm tumor on the right ovary and disseminated tumors on the left ovary, Douglas cavity, peritoneum and liver surface were found (maximum 3 cm). Bilateral salpingo-oophorectomy, hysterectomy, omentectomy, and metastasectomy of the liver surface were performed as primary surgery and a suboptimal debulking surgery. After surgery AFP was decreased to 15 104 ng/mL. Post-operatively, the patient was given six cycles of the BEP regimen of chemotherapy. After one cycle of chemotherapy the AFP had decreased to 192 ng/mL. After six cycles of chemotherapy it had decreased to 1.5 ng/mL and there was no evidence of disease. However, 1 month later AFP was re-elevated to 40.8 ng/mL. The patient developed further progression of her disease, and a CT revealed ascites, a large tumor (>5 cm) at the pelvic cavity, and metastasis to multiple lymph nodes. We considered secondary surgery, but it was difficult to achieve optimal cytoreduction. The patient was given four cycles of irinotecan hydrochloride and cisplatin, but the chemotherapy was not effective. She died 11 months after the initial diagnosis.

Ovarian function and reproductive outcome

Among the 30 patients who received fertility-preserving treatment, 12 had attempted conception, and eight (66.7%) achieved at least one pregnancy. Seven offspring were born of five patients without any neonatal disorder. All five of the patients who had offspring had received chemotherapy. Four patients were treated before puberty. These four patients subsequently experienced normal menarche. Twenty patients experienced amenorrhea during chemotherapy, but 18 patients resumed regular menses on completion of chemotherapy (Table 4).

Discussion

The development of combination chemotherapy for the treatment of malignant germ cell tumors of the

Table 4 Reproductive status of patients who received conservative surgery

Status	No. patients ($n = 30$)
Potentially fertile	30
Not attempting conception	18
Attempting conception	12
Pregnancy	8*
Labor	4
Failures	4

*Six patients received chemotherapy.

ovary (MGCTO) has been one of the true success stories in medicine. With excellent survival rates now possible, resent studies have focused on the preservation of reproductive potential. The standard treatment for malignant tumors of the ovary has generally been surgery consisting of bilateral salpingo-oophorectomy, total hysterectomy, and omentectomy. A unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is now considered the appropriate surgical treatment for patients with MGCTO. Even in patients with advanced disease, preservation of reproductive function is possible, particularly if the contralateral ovary is normal.[6] In the current study there was no macroscopic bilateral involvement in any of the patients with early stage disease. Furthermore, in the eight patients who had biopsy of a contralateral ovary that was either macroscopically normal or had a suspicious-looking lesion, no occult malignancy was found.

The results of several large studies suggest at least equivalent survival after conservative surgery (i.e. unilateral salpingo-oophorectomy) when compared with bilateral salpingo-oophorectomy with or without hysterectomy.[7–9] Review of the data from the Gynecologic Oncology Group showed that 44 of 70 primary lesions treated with VAC were Stage I and none were Stage IB.[2] Removing both ovaries did not appear to improve survival.

During surgery, routine biopsy of the normal-appearance contralateral ovary should be avoided. Biopsy of the contralateral ovary could lead to future infertility related to peritoneal adhesions or ovarian failure.[10] Buttram *et al.* reported 59 patients with previous ovarian wedge resection, 40 of whom were found to have pelvic adhesions.[10]

An SLO for MGCTO is not necessary in most contemporary situations.[11] Unlike epithelial ovarian cancer, the incidence of positive SLO and recurrence after negative SLO were extremely low.[12] In the present study, no persistent lesions were performed in 13 SLO, despite seven of these patients having had residuals at primary surgery.

Many combination chemotherapy regimens for MGCTO have arisen from the studies of testicular carcinoma, the male counterpart that is 10 times more common than MGCTO. The first effective combination chemotherapy regimen for advanced MGCTO was the VAC regimen. Although VAC achieved a high response rate, 50% of patients with advanced MGCTO died of the disease.[2] The introduction of cisplatin-based chemotherapy led to a significant improvement in survival for patients with testicular tumors.[13,14] The PVB regimen proved to be active and more effective than the VAC regime in women with MGCTO.[15–17] Subsequently, the substitution of etoposide for vinblastine proved to be equally effective but less toxic.[14] This regimen has been incorporated into the treatment of MGCTO that is widely used.[18,19] The overall survival of patients treated with platinum-based chemotherapy ranges from 87%[3] to 98%.[18,19]

In the present study, the type of surgical procedure was not an important prognostic factor for patients with MGCTO at all clinical stages. This may indicate that conservative surgery is appropriate for the treatment of germ cell tumors as long as appropriate chemotherapeutic regimens are employed. Conceiving after finishing treatment is an important goal of many of these patients. Low *et al.* reported on 74 patients with malignant germ cell tumors of the ovary who underwent conservative surgery, 47 of whom (63.5%) received adjuvant chemotherapy.[20] Of these, 20 attempted conception and 19 were successful (95%). Zanetta *et al.* reported on 81 patients who were treated conservatively and received adjuvant chemotherapy.[21] Twenty patients attempted to conceive and 16 were successful (80%), compared with 12 of 12 in the group not treated with chemotherapy.

In many cases of MGCTO, only three or four courses of chemotherapy have placed patients into remission with long-term survival.[18,19] For patients with dysgerminoma, three cycles seem to be adequate therapy for patients with Stage I disease, whereas a minimum of four cycles may be indicated for patients with advanced or recurrent disease, although these patients may require four to six cycles.[19] For patients of EST, serum AFP is an extremely sensitive tumor marker. Decreasing of the AFP value below the normal range is recognized as an indication of remission. Two more cycles after clinical remission would be encouraged as the adjuvant chemotherapy.[22] The long-term toxicity of

antineoplastic chemotherapy on ovarian function has been studied extensively.[23,24] The reported histologic changes in the ovaries of patients receiving chemotherapy include cortical fibrosis, reduction in number of follicles, and impaired follicular maturation.[25,26] These changes may lead to hypogonadism. Excessive chemotherapy may be harmful for the function of the preserved ovary.

In present study one patient died of disease. Generally patients who are frankly platinum resistant, that is, they showed no response primary treatment and progression occurred within 6 weeks following treatment, will have a poorer prognosis, and treatment options are limited. Regarding prognostic factors of MGCTO, Lai *et al.* found in the series presented in their article that stage III/IV and non-DSG/IMT were significant poor features associated with treatment failure, and that non-DSG/IMT histology, residual tumor ≥1 cm after salvage surgery, and not receiving high-dose chemotherapy after primary chemotherapy failed were significant poor features associated with death.[27] Nawa *et al.* stated that the prognostic factors of patients with EST were that the residual tumor was <2 cm and ascites were either absent or <100 mL in volume.[28]

High-dose chemotherapy (HDC) with carbopatin and etoposide and stem cell support have been shown in some studies to have 30–50% response rates and 20–34% sustained response rates in testicular germ cell tumors.[29,30] Phase II studies of paclitaxel, gemcitabine, and oxalipatin have been performed on male patients with germ cell tumors that are platinum resistant, with response rates of 15–20%.[31–33] There are individual case reports of treatment with EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) or a combination of etoposide, doxorubicin, and cyclophosphamide as salvage for MGCTO.[34]

Meanwhile the role of secondary cytoreductive surgery in the management of persistent or recurrent MGCTO is unclear. Few studies have addressed this question. Munkarah *et al.* reviewed 20 patients who underwent salvage surgery for chemorefractory MGCTO.[35] While not statistically significant, increased survival was correlated with residual disease <2 cm in diameter. In our patient who died, we had considered attempting secondary cytoreductive surgery, but CT revealed ascites and a large tumor (>5 cm) at the pelvic cavity and metastasis to multiple lymph nodes, so we did not perform the surgery.

In conclusion, although one stage IV EST died of disease in our study, fertility-preserving surgery followed by appropriate chemotherapy should be advocated as the standard of treatment for women with MGCTO, even in advanced stages. Because of the rarity of these tumors and the difficulty of treating them, gynecologic oncologists should make an initial diagnosis and resolution regarding the treatment of MGCTO, and cooperative study is required for the improvement of the results.

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5013 Poster Discussion, Sun, 8:00 AM - 12:00 PM

Phase III randomized trial of neoadjuvant chemotherapy (NAC) followed by radical hysterectomy (RH) versus RH for bulky stage I/II cervical cancer (JCOG 0102). *N. Katsumata, H. Yoshikawa, T. Hirakawa, T. Saito, K. Kuzuya, T. Fujii, M. Hiura, R. Tsunematsu, H. Fukuda, T. Kamura; National Cancer Center, Tokyo, Japan; University of Tsukuba, Tsukuba, Japan; Kyushu University, Fukuoka, Japan; Kyushu Cancer Center, Fukuoka, Japan; Aichi Cancer Center, Nagoya, Japan; Kure Medical Center, Kure, Japan; Shikoku Cancer Center, Matsuyama, Japan; Kurume University Hospital, Kurume, Japan*

Background: NAC may represent an alternative to conventional RH for locally advanced cervical cancer. We compared NAC followed by RH with RH for bulky stage I/II cervical cancer. **Methods:** Patients (pts) with stage IB2, IIA (> 4 cm), or IIB squamous cell carcinoma of the uterine cervix were randomly assigned to receive either BOMP (bleomycin 7mg day 1–5, vincristine 0.7mg/m^2 day 5, mitomycin 7mg/m^2 day 5 and cisplatin 14 mg/m^2 day 1–5,) q21 days, 2 to 4 cycles followed by radical hysterectomy (NAC arm) or undergo RH (RH arm). Pts with positive surgical margins, metastatic nodes, infiltration to parametrium, and/or deep myometrial invasion received postoperative irradiation. Eligibility included preserved organ function, aged 20–70, and Performance Status 0 or 1. Primary endpoint was overall survival (OS) to be compared by log-rank test. Assuming 100 eligible pts in each arm, the study had 80% power to detect a 15% increase in 5-year survival at 0.05 one-sided alpha. **Results:** 134 pts (67 NAC, 67 RH) were randomized between 12/01 and 08/05. The first planned interim analysis was performed in July 2005 using data from 108 pts registered as of 11/04. Data and Safety Monitoring Committee recommended to terminate the study because overall survival in NAC arm was inferior to that in RH arm (HR 2.11, multiplicity adjusted 99% CI 0.34 to 13.2) and the predictive probability of significant superiority using Spiegelhalter's method of NAC arm was extremely low (6.4%). No increase of operability and no decrease of surgery-related morbidity were observed in NAC arm. Response Rate of NAC was 61% (33 of 54) using RECIST criteria. One-year progression-free survival and overall survival, updated as of 05/05, were 69.9% and 91.8% (95% CI 84.1–99.6) in NAC arm and 78.6% and 95.4% (95% CI 89.1–100) in RH arm respectively. **Conclusions:** Neoadjuvant chemotherapy with BOMP regimen followed by radical hysterectomy did not demonstrate clinical benefit, and conventional radical hysterectomy still remains to be a standard treatment option for bulky stage I/II cervical cancer.

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CLINICAL INVESTIGATION **Cervix**

EARLY DETERMINATION OF UTERINE CERVICAL SQUAMOUS CELL CARCINOMA RADIORESPONSE IDENTIFIES HIGH- AND LOW-RESPONSE TUMORS

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Purpose: To investigate whether early-assessed radioresponse of tumors corresponds with late-assessed radioresponse, which is associated with local disease control in radiotherapy (RT) for cervical cancer.
Methods and Materials: This prospective study included 12 patients with cervical squamous cell carcinoma treated by RT with or without concurrent cisplatin. Tumor volume was estimated by scheduled magnetic resonance imaging before (preRT), 3 to 4 weeks after (early assessment), and 6 to 7 weeks after (late assessment) RT initiation. Radioresponse was assessed with tumor shrinkage curves based on these volumes. Radioresponse for each tumor was calculated as the slope (day^{-1}) of the shrinkage curve by fitting to an exponential equation.
Results: Early-assessed radioresponse ranged from 0.001 to 0.106 day^{-1} (median, 0.021 day^{-1}) and late-assessed radioresponse from 0.009 to 0.091 day^{-1} (median, 0.021 day^{-1}), with no significant difference between them (p = 0.1191). The early-assessed radioresponse correlated with the late-assessed radioresponse (R^2 = 0.714, p = 0.0005).
Conclusions: Correspondence between early- and late-assessed radioresponse in a series of tumors showing a wide range of radioresponse was not particularly close overall. However, early assessment of radioresponsiveness did seem to be useful for characterizing those tumors with high or low radioresponsiveness. © 2006 Elsevier Inc.

Radiosensitivity, Intracavitary radiotherapy, Minimum target dose, Chemoradiotherapy.

INTRODUCTION

In radiotherapy (RT) for uterine cervical cancer, significant predictors of local disease control include not only clinical stage but also pretreatment tumor size and tumor radioresponse (1–5). Of the latter two, radioresponse is of greater practical importance because whereas pretreatment tumor size is deterministic, radioresponse is subject to modification, for example by concurrent chemotherapy. The degree of tumor shrinkage is commonly used as an index of radioresponse (6, 7)—for example, complete response (disappearance, 100% decrease in volume), partial response (≥65% decrease), and stable disease (<65% decrease). A complete response at the end of RT, which is assessed by subjective pelvic examination, is usually associated with local disease control (3–5). It would therefore be valuable to be able to predict early in the course of RT whether a tumor is to achieve a complete response; if not, intensification of treatment or the use of additional treatment could be considered earlier than otherwise possible. However, because the degree of tumor shrinkage is categorical and independent of time, it is not suitable as an index for the early estimation of radioresponse. In contrast, the speed of tumor shrinkage, another expression of radioresponse, is continuous and a function of time and pretreatment tumor size and should therefore serve as a useful index for prediction of posttreatment size.

Here, we prospectively investigated whether the speed of tumor shrinkage as assessed in the early phase of RT corresponds with that assessed in the late phase of RT, under conditions of standard clinical practice for concurrent chemoradiotherapy as proposed by the U.S. National Cancer Institute (8).

METHODS AND MATERIALS

Patients

The study group consisted of 12 patients with cervical squamous cell carcinoma selected from 19 consecutive cervical squamous cell carcinoma patients treated primarily by RT with or without concurrent cisplatin chemotherapy between December 2003 and

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December 2004. Following normal clinical practice, patients were scheduled to undergo magnetic resonance imaging (MRI) of the pelvis in three phases of RT, namely before and at 3 to 4 weeks (early phase) and 6 to 7 weeks (late phase) after the start of RT. The accuracy and clarity of MRI in demonstrating cervical tumors has been confirmed (9, 10). Seven patients were excluded from the study because not all MR images were available or because the images did not clearly identify the tumor. Clinical disease stages according to the International Federation of Gynecology and Obstetrics staging system were IB1 (n = 1), IIB (n = 1), and IIIB (n = 10). Patients ranged in age from 37 to 81 years (median, 51 years).

Treatment

Radiotherapy consisted of external and intracavitary RT. External RT was performed with a 10-MV X-ray in 1.8-Gy fractions at 5 fractions per week. Clinical target volume was the pelvis (n = 5) or the pelvis plus para-aortic nodes (n = 7), with para-aortic nodes treated prophylactically. A conformal box-field technique was used for all but 1 patient, in whom anterior–posterior opposing portals were used. A central block was placed in the pelvic RT field for the start of intracavitary RT after a total dose of 45.0 Gy (stage IIIB) or 36.0 Gy (stages IB1 and IIB) was reached. Total dose to the pelvis ranged from 50.4 to 66.6 Gy (median, 54.0 Gy), including boost doses to parametrial induration or lymphadenopathy, and total dose to the para-aortic nodes was 45.0 Gy. Intracavitary RT was performed with a high-dose-rate remote afterloading system. The prescribed dosage to reference point A was 6.0 Gy per insertion at three (n = 10) or four (n = 2) weekly insertions per patient. One patient underwent an interstitial implant after three intracavitary insertions. Thus, overall RT treatment duration ranged from 42 to 63 days (n = 11; median, 50 days) and was 70 days for the patient treated by interstitial implant.

Ten patients were treated by concurrent chemotherapy with cisplatin, and 2 (both aged 81 years) were treated by RT alone. Cisplatin was given by single weekly i.v. administration at 35 mg/m^2 (n = 3), 30 mg/m^2 (n = 6), or 20 mg/m^2 (n = 1, aged 72 years) for 3–6 weeks, starting from the first (n = 5), second (n = 4), or third week (n = 1) of RT. Delayed chemotherapy (n = 5) was due to renal dysfunction caused by hydronephrosis, which was managed by nephrostomy.

Tumor measurement with MR images

Magnetic resonance imaging was performed with 1.5-T units. The preRT images were obtained from 1 to 26 days (median, 11 days) before RT, with early-phase images obtained from 18 to 34 days (median, 24 days) and late-phase images obtained from 36 to 59 days (median, 46 days) after the start of RT, the latter being before (n = 1) or during (n = 11) the intracavitary RT course. Tumors identified as high-intensity lesions on T2-weighted images were measured three-dimensionally by width, thickness, and length for each tumor, and tumor volume was calculated on the assumption that the tumor mass was ellipsoid. The volume of tumors that disappeared or were recognized as only a remnant was regarded as 0.01 cm^3, whereas that of those remaining as a small, high-intensity "scar" that was difficult to measure was regarded as 0.05 cm^3.

Radioresponse assessment

Estimated tumor volumes were plotted on a semilogarithmic graph, with the start of RT set as Day 0. The early-phase shrinkage curve was calculated from the preRT and early-phase volumes, the late-phase shrinkage curve from the early-phase and late-phase volumes, and the through-phase shrinkage curve from the preRT and late-phase volumes. The slope of the curve (day^{-1}) (i.e., the speed of shrinkage per day) was determined by fitting an exponential regression equation to the respective curve. Radioresponse was defined as the speed of shrinkage, with radioresponsive tumors thus characterized by steep slopes. With the equation of the through-phase shrinkage curve, the tumor volume at the end of RT (postRT volume) was duly calculated for each tumor and categorized according to the degree of shrinkage. For this, either shrinkage to $\leq$0.05 cm^3 or to <1% of the preRT volume was regarded as complete response, whereas shrinkage to <35% of the preRT volume and shrinkage confined to $\geq$35% of the preRT volume were defined as partial response and stable disease, respectively.

Statistical analysis

The early-assessed radioresponse was compared with the late-assessed and with the through-assessed radioresponse. Differences in response between phases were analyzed by the Wilcoxon signed rank test. Correlation between the early-assessed and through-assessed radioresponses was analyzed by regression analysis. Radioresponse was compared between the speed of shrinkage (through-assessed radioresponse) and the degree of shrinkage. StatView 5.0 (SAS Institute, Cary, NC) was used for all analyses. P values of <0.05 were considered statistically significant.

RESULTS

The preRT volume ranged from 2.3 to 301.6 cm^3 (median, 95.5 cm^3). Complete response was observed in the early phase in one tumor and in the late phase in two (Fig. 1). Radioresponse ranged from 0.001 to 0.106 day^{-1} (median, 0.021 day^{-1}) in the early phase, from 0.013 to 0.121 day^{-1} (median, 0.025 day^{-1}) in the late phase, and from 0.009 to 0.091 day^{-1} (median, 0.021 day^{-1}) in the through phase. Radioresponse did not differ significantly between the early and late phases or between the early and through phases (p = 0.1361 for both). When the tumor that achieved a complete response in the early phase was excluded, however, the difference in response between the early and late

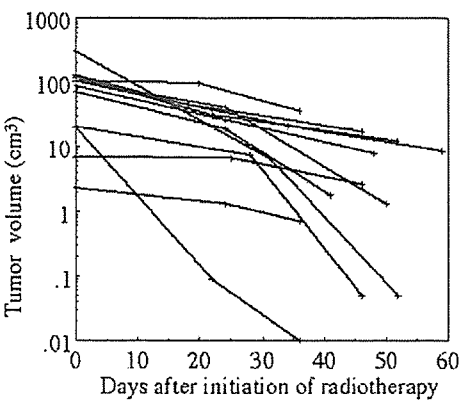

Fig. 1. Tumor shrinkage curves composed of three-phase volumes of preradiotherapy, early phase (3 to 4 weeks), and late phase (6 to 7 weeks) (n = 12).

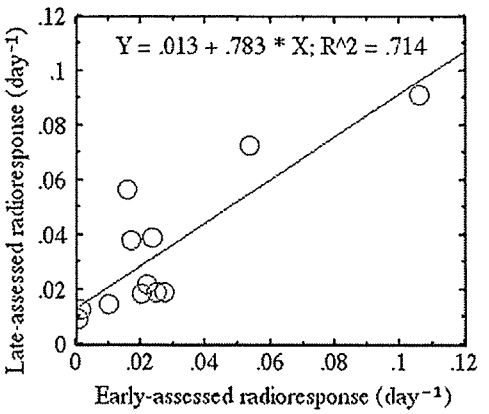

Fig. 2. Correlation between early-assessed and late-assessed radioresponse (n = 12, p = 0.0005).

phases approached significance, with radioresponse greater in the late (range, 0.013–0.121 day^{-1}; median, 0.022 day^{-1}) than in the early phase (range, 0.001–0.054 day^{-1}; median, 0.021 day^{-1}) (n = 11, p = 0.0505).

The early-assessed radioresponse correlated with the late-assessed radioresponse (Fig. 2; R^2 = 0.714, p = 0.0005). This correlation remained significant even when the tumor that achieved a near-complete response was excluded (n = 11, R^2 = 0.496, p = 0.0155).

The postRT volume ranged from 0.01 to 21.95 cm^3 (median, 0.41 cm^3) and was ≤0.05 cm^3 in three tumors. The postRT volume as a percentage ranged from 0 to 17.8% (median, 4.5%) of the preRT volume. Response category was complete response for five tumors and partial response for the remaining seven (Fig. 3). None was categorized as stable disease.

DISCUSSION

Characterization of radioresponse is particularly important for large tumors, from the standpoint of not only radiosensitivity but also dose delivery by intracavitary RT, which is characterized by steep dose fall-off within the tumor. Given that radioresponse normally implies generic radiosensitivity of tumor cells, tumors with low radioresponsiveness require larger doses for local disease control than those with high radioresponsiveness. Nevertheless, large tumors with low radioresponsiveness receive smaller target doses at the tumor periphery (minimum target doses) by intracavitary RT than large tumors with high radioresponsiveness, because the latter undergo significant shrinkage subsequent to the preceding external RT (11). Compared with large tumors, small tumors receive substantially higher minimum target doses irrespective of tumor shrinkage induced by external RT, and these high doses are considered to effectively overcome any radioresistance.

Tumors were categorized by the degree of shrinkage into either complete response or partial response only. Whereas complete response is characterized by shrinkage within a very narrow range (99–100% decrease), partial response is characterized by a wide range of shrinkage (65%–99% decrease) and is therefore not suitable for differentiating tumors at the respective ends of this range. In contrast, the speed of shrinkage is shown as a variable specific to the individual tumor and is therefore useful for differentiating partial response tumors by calculation, if the shrinkage is fitted well by a regression equation.

Our results showed that the early-assessed radioresponse corresponded with the late-assessed radioresponse, although not particularly closely. In contrast, Gong *et al.* (12), who used frequent, rigidly scheduled MRI (four to eight times per patient) and sophisticated tumor measurement methods, reported that the radioresponse of cervical tumors is exponential. Several possible reasons for this apparent discrepancy can be suggested.

First, Gong *et al.* investigated radioresponse during simple treatment with external RT alone, whereas our study involved complex treatment. Second, most of our tumors were treated by concurrent chemotherapy that was nevertheless not always simultaneous with the start of RT and by intracavitary RT that was performed in the late phase. The impact of our treatment might therefore have differed between phases, or even by week. In fact, we previously showed that the use of concurrent chemoradiotherapy tends to increase radioresponse over that achieved with RT alone (13). Further, radioresponse might have been underestimated in our three tumors that achieved a complete response because the response might have occurred before the time of observation. On these bases, we suggest that the lack of a clear exponential radioresponse in the present study was likely due to the complex treatment given, in addition to differences in the accuracy and frequency of tumor measurement.

Although exact correspondence was not obtained, our response assessment, conducted under conditions of stan-

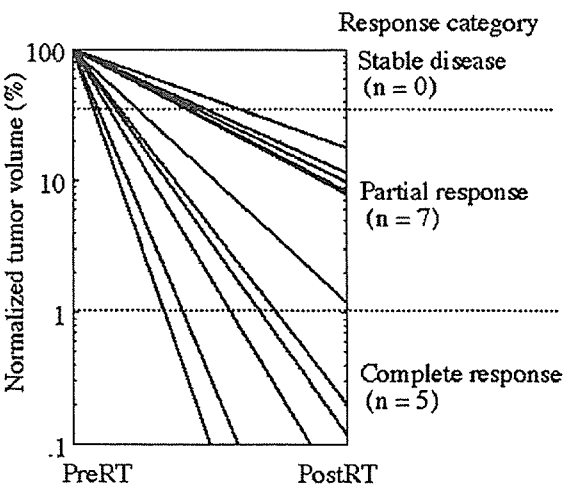

Fig. 3. Comparison of calculated radioresponse at the end of radiotherapy (RT) between the speed of shrinkage (curves) and the degree of shrinkage (response category). The postRT volume was calculated with the regression equation for each tumor at the end of RT for each individual (42–63 days from the start of RT).

dard clinical practice, is considered effective in the differentiation of highly (e.g., >0.05 day^{-1}) and poorly radioresponsive (e.g., <0.02 day^{-1}) tumors, which here represented the upper and lower quartiles of tumors by response, from those moderately radioresponsive, which made up the middle half of tumors. This is because the wide radioresponse seen facilitates the recognition of tumors at the respective ends of radioresponsiveness. Moreover, this finding is consistent between our results and those of Gong *et al.*: radioresponse range from 0.001 to 0.106 day^{-1} (early phase, 106-fold variation) and from 0.009 to 0.091 day^{-1} (through phase, 10-fold variation) in the present study and from 0.007 to 0.182 day^{-1} (26-fold variation, by planimetry) in Gong *et al.* (12).

The U.S. National Cancer Institute has recommended the concurrent use of RT and chemotherapy with cisplatin or cisplatin plus fluorouracil (as radiosensitizers) in place of the conventional use of RT alone to improve survival in patients with locally advanced cervical cancer (8), and the efficacy of this treatment has been confirmed by systematic review and meta-analysis (14). However, this recommendation is based on the assumption that the radioresponse of tumors is unknown. Early knowledge of the radioresponsiveness of tumors during treatment would allow the individualization of treatment. Given that a substantial proportion of patients have been cured by conventional RT treatment alone, those with highly radioresponsive tumors, so-called radiosensitive tumors, might not necessarily require concurrent chemotherapy. Conversely, patients with poorly radioresponsive tumors, so-called radioresistant tumors, might benefit from the intensification of treatment, such as the planned use of interstitial implants and the incorporation of a potent new radiosensitizer (gemcitabine) into concurrent chemotherapy (15).

In conclusion, the early-assessed radioresponse of uterine cervical squamous cell carcinoma corresponded with the late-assessed radioresponse, albeit not particularly strongly. Although it would be premature to incorporate these findings directly into local disease control, early determination might nevertheless be useful for identifying tumors at either extremity of the wide radioresponse range seen here.

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Treatment with paclitaxel plus carboplatin, alone or with irradiation, of advanced or recurrent endometrial carcinoma

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Abstract

Objectives. The goal of this study was to evaluate the efficacy and toxicity of paclitaxel plus carboplatin in the treatment of primarily advanced or recurrent endometrial carcinoma.

Methods. Thirty-seven consecutive patients with advanced or recurrent endometrial carcinoma were enrolled in this study. Paclitaxel at a dose of 175 mg/m^2 was administered intravenously over 3 h followed by carboplatin with area under the curve of 5 to 6 over 1 h at 4-week intervals. Five patients were received 50 Gy pelvic irradiation, and 7 were received 50 Gy pelvic and 50 Gy paraaortic irradiation, after adjuvant chemotherapy with paclitaxel plus carboplatin. Eighteen patients had evaluable lesions. Responses were assessed before the use of any irradiation.

Results. Eleven patients (61%) achieved an objective response, including one complete response (5.6%) and 10 partial responses (56%). The most common toxicity was hematologic: grade 3 or 4 leukopenia and neutropenia occurred in 59% and 86% of patients, respectively. Three patients (8%) required granulocyte colony-stimulating factor support. One patient required a platelet transfusion, and four required blood transfusions. There was a single adverse event of anaphylaxis.

Conclusion. The combination of paclitaxel and carboplatin appears to be an effective regimen for the treatment of patients with advanced or recurrent endometrial carcinoma with tolerable toxicity.

Keywords: Paclitaxel; Carboplatin; Endometrial cancer

Introduction

Endometrial carcinoma is one of the most common gynecologic malignancies. A large percentage, approximately 85%, of patients diagnosed as endometrial cancer has shown to have limited disease that can be cured with surgery alone with or without adjuvant radiation [1]. However, for cases of advanced or recurrent disease, there is no consensus regarding the optimal therapy and systemic chemotherapy is required.

Single-agent chemotherapy regimens including doxorubicin, cisplatin, carboplatin and paclitaxel have been employed in this setting and have been reported to have response rates of 25%, 20%, 33% and 36% [2–6]. Studies examining combination regimens have shown to have higher response rates. The results from a Gynecologic Oncology Group phase III trial showed that the combination of cisplatin and doxorubicin improved response rate (42% vs. 25%) and progression-free survival compared with doxorubicin alone with a negligible impact on overall survival and increased toxicity [2]. Because of its low response rate, cardiac and renal toxicity, and requirement of hydration, identification of new chemotherapy regimens is necessary.

In recent years, several studies demonstrated efficiency of paclitaxel plus carboplatin in the treatment of endometrial cancer [7–11]. The purpose of this study was to evaluate further the efficacy of paclitaxel plus carboplatin, with or without irradiation, in the treatment of primarily advanced or recurrent endometrial carcinoma. We also investigated the adverse effects of this combination chemotherapy.

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Patients and methods

This study includes 37 patients with histologically confirmed endometrial carcinoma treated between 1999 and 2005 at the Department of Obstetrics and Gynecology of the University of Tokyo. Patients were eligible if they met any of the following criteria: (1) newly diagnosed, primarily advanced, i.e. surgical stages IIIB, IIIC, or IV; clinical stage IV; IIIA with macroscopic ovarian involvement; or (2) recurrent after surgery and/or radiotherapy. Additional eligibility criteria included Gynecologic Oncology Group performance status of 2 or better, an interval of 3 weeks or more since any prior tumor-directed therapy, recovery from recent surgery or radiotherapy or chemotherapy, and adequate white blood cell count (≥3000/μl), platelet count (=100,000μl), and renal function test (serum creatinine level ≤ 1.5 mg/dl).

All patients underwent a pretreatment regimen, designed to abrogate hypersensitivity reactions of paclitaxel, which consisted of dexamethasone 20 mg, diphenhydramine 50 mg, and ranitidine 50 mg. Paclitaxel at a dose of 175 mg/m^2 was infused intravenously in 500ml of normal saline over 3 h, followed by carboplatin with an area under the curve (AUC) of 5 (patients who had been previously treated with chemotherapy and/or irradiation) or 6 (patients who had not received any chemotherapy and irradiation) in 250 ml of 5% glucose over 1 h. All treatment was repeated every 28 days. Five to six cycles were administered for patients with recurrent tumor and for primary advanced cases of clinical stage IVb, unless there was documented disease progression, undue toxicity. For primary advanced cases of clinical stage III or IVa, three cycles of chemotherapy were given, followed by whole pelvis 50 Gy irradiation and/or 50 Gy irradiation at the paraaortic nodal region depending on their nodal involvement [12].

Response to the chemotherapy was assessed in those with measurable disease using radiographic and clinical assessment. Responses were assessed before the use of any irradiation. A complete response (CR) required disappearance of all clinically detectable disease for at least 4 weeks. A partial response (PR) required >50% reduction in the sum of the products of the two largest perpendicular dimensions of bidimensionally measurable lesions for at least 4 weeks. Stable disease was defined as a steady state of response, either less than a partial response or progression of less than 25%. All other cases were considered to have progressive disease. Response duration was defined as the time from partial or complete response to the appearance of progressive disease. Time to progression was measured from the time of initiation of treatment to the time of last patient contact or documented progressive disease. Survival was calculated from the time of initiation of therapy to the last patient contact or death [13]. Time to progression and survival curves were constructed using the Kaplan–Meier product limit method [14].

Toxicity was graded according to National Cancer Institute-Common Toxicity Criteria. Toxicity was recorded as the worst ever per patient for this treatment regimen. For the purpose of this report, it is only recorded for the chemotherapy cycles and not for the radiotherapy component.

Table 1
Patient characteristics

Characteristic	No. of patients	
	Primary	Recurrent
Age (years)		
Median	58	62
Range	30–80	42–81
Stage (FIGO)		
IIIa	4	N/A
IIIc	10	N/A
IVb	9	N/A
Histology type		
Endometrioid	17	13
Serous	1	1
Clear cell	2	0
Mixed	1	0
Undifferentiated	2	0
Grade (Endometrioid type)		
G1	2	5
G2	10	6
G3	5	2

N/A: not applicable as recurrent disease.

Table 2
Response rates

	Primary	Recurrent	Total
CR	0	1	1
PR	3	7	10
SD	1	3	4
PD	0	3	3
Response rates	75%	57%	61%

Results

Thirty-seven endometrial cancer patients were treated with paclitaxel and carboplatin during the study period. The median age of the patient population was 59 years (range: 30 to 81 years). The main characteristics of the patients are summarized in Table 1. Twenty-three patients (62%) presented with an advanced FIGO stage (III or IV). Five patients were received 50 Gy pelvic irradiation, and 7 were received 50 Gy pelvic and 50 Gy paraaortic irradiation, after adjuvant chemotherapy with paclitaxel plus carboplatin. One of them received this regimen as a neo-adjuvant chemotherapy. Eighty-one percent of histology of the tumors were endometrioid adenocarcinoma. Ten of 14 recurrent cases had received prior chemotherapy: seven patients had been treated with cyclophosphamide, doxorubicin and cisplatin, one had received cyclophosphamide, doxorubicin and carboplatin, and another two had used paclitaxel and carboplatin. The median number of cycles of paclitaxel plus carboplatin administered was 4 (range: 1 to 9 cycles).

Response

Eighteen patients (49%) had measurable disease. Patients with measurable disease were analyzed for the response assessment. The overall response rate was 61% (95% confidence interval [CI]: 36% to 86%). The great majority of responses were partial (Table 2). Of the 10 patients who had received prior chemotherapy, 5 patients (50%) had a partial response. Because of this small number of patients and the variety of subgroups, it is not possible to perform meaningful subset analysis of response.

Survival

Of 23 primarily advanced patients, 4 individuals have died of progressive cancer and 4 are currently alive with disease. The remaining 15 patients are currently without clinical evidence of disease. The median overall and progression-free survival time for primarily advanced patients has not yet been reached, with a 77% 3-year overall survival rate (Fig. 1). The median progression-free survival time for those with recurrent was 7 months (range: 1 to 33 months). The median overall survival time for those patients has not yet been reached (Fig. 2).