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進行・再発子宮頸癌に対する標準的治療体系の確立に関する研究

平成１８年度～２０年度　総合研究報告書

研究代表者　嘉村　敏治

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目　　次

厚生労働科学研究費補助金（がん臨床研究事業）

総合研究報告書

進行・再発子宮頸癌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

子宮頸がんは婦人科で取り扱うがんの中では最も頻度が高いがんである。これまで手術療法、放射線療法単独、あるいはこの２者を組み合わせた治療法が標準治療として用いられてきたが、進行期別に５年生存率の経時的変化をみてみると、この 20 年間改善が認められていない。このことは手術療法と放射線療法の限界を示すものであり、新しい治療法を取り入れる必要がある。現在この２者の治療法以外の治療法としてその効果が期待されるものとして抗がん剤を用いた化学療法がある。米国ではいくつかの第 3 相試験の結果 cisplatin と paclitaxel の 2 剤併用療法(TP 療法)が子宮頸がんの標準的化学療法として行われている。しかしながら本療法は神経毒性が高く、また大量の輸液等が必要であり、患者さんの QOL を損なう可能性がある。このような副作用を軽減し、かつ高い抗腫瘍効果を期待して cisplatin のかわりに carboplatin を使用した TJ 療法を新たな化学療法レジメンとして確立することを目的とした。第 2 相試験を行ったが安全性には問題がなく、奏功率も 59%と TP 療法比べて遜色がなかった。そこで TP 療法と TJ 療法の比較を行う臨床第三相試験を行うこととし、プロトコールを作成し、平成 18 年 2 月より 250 例を目標に症例集積を開始した。平成 20 年 1 月に中間評価が行われ、21 年 2 月現在 214 例の症例の集積を行っている。

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A. 研究目的

現在本邦にはエビデンスレベルが高い子宮頸癌に対する化学療法は存在しない。米国ではいくつかの第 3 相試験の結果 cisplatin と paclitaxel の 2 剤併用療法(TP 療法)が標準的化学療法として行われている。しかしながら本療法は神経毒性が高く、また大量の輸液等が必要であり、患者さんの QOL を損なう可能性がある。このような副作用を軽減し、かつ高い抗腫瘍効果を期待して cisplatin のかわりに carboplatin を使用した TJ 療法を新たな化学療法レジメンとして確立することを目的とした。

B. 研究方法

再発進行子宮頸がんを対象として TJ 療法について第 2 相試験を分担研究者の施設で行い、その結果により現在米国で子宮頸がんに対する標準化学療法である TP 療法との間で非劣性試験としての第 3 相試験を JCOG 研究として行う。

(倫理面への配慮)

TJ 療法の安全性については卵巣がん患者への使用で確立されている。また全ての症例にインフォームドコンセントをとりカルテに記載した上で治療を実行した。

C. 研究結果

研究期間中に再発・進行子宮頸癌を対象とした TJ 療法の第 2 相試験を行った。40 例を目標として研究分担施設の中でプロトコールが IRB で承認された順に目標症例に達するまで症例集積を行ったが、41 例がエントリーされた。最終解析では 59%(95%CI:40.7-74.5%)の、無増悪生存期間の中央値 4.9 ヶ月(1.0-18.7 ヶ月)、全生存期間の中央値 9.4 ヶ月(2.6-22.9 ヶ月)と米国の TP 療法のデータ(36%、4.8 ヶ月、9.7 ヶ月)に匹敵する結果が得られた。このデータをもとに JCOG 運営委員会でコンセプトが承認された TP 療法、TJ 療法の無作為化比較試験(第 3 相試験)を行うこととした。厳密なプロトコールの元に平成 18 年 2 月より症例登録を開始した。平成 20 年 1 月に JCOG 効果安全委員会にて中間評価が行われ、安全性、効果よりみて研究続行が決定された。以後実地臨床に合わせたプロトコールの軽微な改訂を加えながら平成 21 年 2 月現在 214 例の症例が登録されている。

D. 考察

進行あるいは再発子宮頸がんはその発生部位の特性により尿路系の閉塞をきたすことが多く、腎機能の低下を招いている症例も少なくない。そこで cisplatin に比較して腎毒性が低い carboplatin は治療の compliance が高いことは、第 2 相試験でもその可能性が確かめられ、しかも高い奏功率が得られた。この結果は米国の結果に匹敵しており、本研究成果は 2004 年の ASCO 演題として採用されている。TP 療法、TJ 療法の無作為化比較試験(第 3 相試験)については平成 18 年 2 月末に JCOG30 施設で研究開始した。残念ながら本研究期間内に結論を出すことはできないが、平成 21 年 2 月現在 214 例の症例が登録されている。本研究で標準的化学療法が確立されれば、次のステップとして他の手術療法や放射線療法と組み合わせ新たな集学的治療が展開可能となる。

E. 結論

第 2 相試験を経て、非劣性試験である第 3 相試験のプロトコールの作成、臨床試験開始までに至った。compliance を含めた feasibility に関して TJ 療法の方が TP 療法よりも高い有用性を示すことが期待される。本研究によってもたらされる新規化学療法は、従来の子宮頸がんの集学的治療に導入されることとなり、より良好な予後をもたらす可能性が高いと考えられる。

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G. 知的財産権の出願・登録状況（予定含）

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

研究成果の刊行に関する一覧表

雑誌

平成18年度

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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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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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