Table 3. *In vivo* **tumorigenicity of CD44 variant 6 (CD44v6)-positive and CD44v6-negative cells**

	No. of transplanted cells			Frequency of metastasis-initiating cells (95% CI)
	10, 000	1000	100	
CD44v6-positive cells	6/6	6/6	4/5	62.6** (21.4–185.0)
CD44v6-negative cells	3/12	1/12	0/12	29, 211.2 (10, 813.7–78, 910.0)

CD44v6-positive and -negative cancer cells were separated by FACS, and the indicated numbers of cells were transplanted intraperitoneally into nude mice. The incidence of tumor formation within 8 weeks was scored. Data represent the number of tumors per number of injections. Tumorigenic cell frequencies were estimated with the use of ELDA software for limiting dilution analysis. $^{**}P < 0.01$.

ure 3(e). These results suggested that CD44v6-positive cells play a crucial role in the formation of disseminated tumors in the pelvic peritoneum and have the potential to contain specialized metastasis-initiating cells.

Epithelial–mesenchymal transition (EMT) is an important step in invasion and metastasis of cancer.[32] When the ovarian cancer cells detach and start their metastatic journey, it is believed that they frequently undergo EMT.[3] We therefore hypothesized that CD44v6 has an important role in the EMT phenomenon of ovarian cancer. To investigate the relationship between CD44v6 expression and EMT, we evaluated the expression of EMT regulatory proteins, such as E-cadherin, N-cadherin, fibronectin, and vimentin in FACS-sorted CD44v6-poisitive cells *versus* FACS-sorted CD44v6-negative cells by Western blot analysis. In consequence, E-cadherin expression was downregulated in FACS-sorted CD44v6-positive cells in comparison with FACS-sorted CD44v6-negative cells and concomitant upregulation of N-cadherin, fibronectin, and vimentin was observed in CD44v6 - positive cells (Fig. 3f). These findings suggested that a subpopulation of CD44v6 regulates the metastatic ability of ovarian cancer cells, which is relevant to the process of EMT.

Chemoresistance in a subpopulation of CD44v6-positive ovarian cancer cells. CSCs are inherently responsible for tumor resistance to conventional chemotherapy.[17,18] Given that the primary ovarian tumors containing at least 10% CD44v6-positive cancer cells showed significantly poorer prognosis, we next evaluated the relevance of chemoresistance in CD44v6-positive cells as a potential cause of the poor prognosis. To investigate whether the subpopulation of CD44v6-positive cells correlates with resistance to chemotherapy, ES-2 ovarian cancer cells were exposed to paclitaxel or cisplatin *in vitro*. Flow cytometric analysis showed that treatment with paclitaxel or cisplatin results in enhanced expression of CD44v6 in residual cancer cells as compared to untreated cells (Fig. 4a,b). Furthermore, FACS-sorted CD44v6-positive ovarian cancer cells showed significantly higher viability compared to FACS-sorted CD44v6-negative cells in MTS assay (Fig. 4c,d), indicating that a subpopulation of CD44v6-positive cells is associated with tumor resistance to chemotherapy.

Discussion

We have identified that disseminated tumors in the pelvic peritoneum are highly enriched in CD44v6-positive cancer cells, which prominently contributes to peritoneal metastasis of advanced epithelial ovarian cancer. Of particular interest in this study was that an increased number of CD44v6-positive cancer cells were associated with a shortened OS in the evaluation of the sites of primary tumors. Furthermore, we showed that a subpopulation of CD44v6-positive ovarian cancer cells possesses a strong ability to initiate tumor metastasis in the pelvic peritoneum in an *in vivo* mouse model, indicating that CD44v6-positive cells have the potential to serve as metastasis-initiating cells.

Epithelial ovarian cancer is a highly lethal malignancy that represents a great clinical challenge in gynecologic oncology.[4] Given that peritoneal dissemination and metastasis is responsible for most cancer-related deaths in patients with advanced ovarian cancer, the elucidation of molecular mechanisms underlying the peritoneal metastasis and the characteristics of ovarian CSCs is essential to combat this fatal disease. Although CD44v6 plays an important role in the tumor growth and metastasis of several types of tumors,[24,25] the functions of CD44v6 have not been completely characterized in ovarian cancer metastasis. In the current study, we showed that CD44v6 expression is increased in tumor tissues at the peritoneal metastasis sites compared with those at the corresponding primary tumors, indicating that CD44v6 is clinically associated with the induction of metastasis in the pelvic peritoneum.

Although previous studies have focused on the potential correlation of CD44v with ovarian cancer survival to address the diagnostic and prognostic values of CD44v, there is no unified view on this issue.[33] Some authors suggested that the expression of the CD44v6 is not correlated with tumor development and prognosis of epithelial ovarian cancer,[12,34] whereas others showed that CD44v6 expression levels are involved in ovarian cancer progression, metastasis, and relapse.[35] Taken together, several questions regarding the relationship between CD44v6 expression and prognosis remain to be resolved. In the light of these unanswered questions, we evaluated the association between CD44v6 expression and OS and PFS in the sites of primary lesions. As a result, the tumors containing at least 10% CD44v6-positive cancer cells showed significantly poorer prognosis in terms of OS than those containing less than 10% CD44v6-positive cells in the evaluation of the sites of primary tumors. Furthermore, the multivariate Cox proportional hazards model showed that the expression of CD44v6 is an independent prognostic factor for the OS of patients with advanced ovarian cancer.

In recent years, emerging evidence has provided support for the existence of CSCs in various cancers, including epithelial ovarian cancer.[17,20] Even though previous studies indicated that a CD44v6-positive cell population possesses CSC properties in several types of tumors,[24,25] the correlation between CD44v6-positive cells and ovarian CSCs remained unclear. To investigate whether a subpopulation of CD44v6-positive cancer cells manifest highly metastatic activity, we compared the tumorigenic and peritoneal metastatic potential of CD44v6-positive and CD44v6-negative cells in an *in vivo* mouse model. Consistent with our clinical observations, we found that a subpopulation of CD44v6-positive cells is prominently involved in peritoneal metastasis in a mouse model. In a set of experiments, we also showed that CD44v6 expression demarcates a highly tumorigenic ovarian CSC population with peritoneal metastatic potential and CD44v6-positive cells possess the potential to serve as metastasis-initiating cells. Recent evidence indicates the existence of a "CSC niche," a specialized

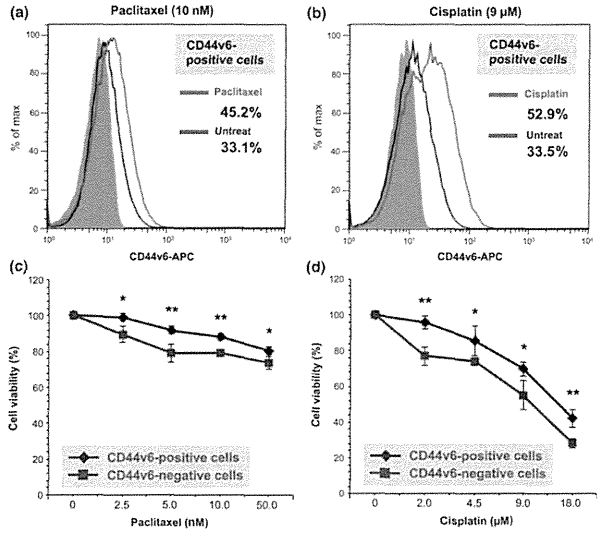

Fig. 4. CD44 variant 6 (CD44v6)-positive ovarian cancer cells are associated with chemoresistance. (a) Flow cytometric analysis of CD44v6 expression in ES-2 ovarian cancer cells treated with paclitaxel and untreated ES-2 cells. (b) Flow cytometric analysis of CD44v6 expression in ES-2 ovarian cancer cells treated with cisplatin and untreated ES-2 cells. (c) Chemosensitivity assay in FACS-sorted CD44v6-positive and FACS-sorted CD44v6-negative cells. Cells were subjected to MTS assay to evaluate viability in the presence of paclitaxel. $^{*}P < 0.05$, $^{**}P < 0.01$. (d) Chemosensitivity assay. FACS-sorted CD44v6-positive and FACS-sorted CD44v6-negative cells were subjected to MTS assay to assess the viability in the presence of cisplatin. $^{*}P < 0.05$, $^{**}P < 0.01$.

microenvironment that regulates CSC properties and contributes to tumor initiation, growth, and metastasis.[36,37] The present study revealed the close relationship between CD44v6 expression and the pelvic peritoneum and thereby, raises the possibility that the microenvironment of the pelvic peritoneum forms a possible CSC niche for epithelial ovarian cancer.[38]

Recent evidence suggested that CD44v manifests enhanced protection against species (ROS), rendering them resistant to chemotherapy in several types of solid tumors.[22,23] In the current study, we showed that a subpopulation of CD44v6-positive cancer cells is correlated with tumor resistance to chemotherapy. In view of this, the results of our present study raise the possibility that CD44v6 potentiates the ability of ovarian cancer cells to defend themselves against chemotherapy-induced ROS.

In conclusion, the biological and molecular heterogeneity of ovarian CSCs represents a highly promising area of research that may provide new insights that could lead to prognostic and therapeutic breakthroughs for advanced epithelial ovarian cancer. CD44v6-positive cancer cells may be a potential molecular therapeutic target for eliminating ovarian CSCs and metastasis-initiating cells. The finding that a distinct subpopulation of CD44v6-positive CSCs plays a central role in peritoneal metastasis suggests that definitive treatment should target the CD44v6-positive cell population in epithelial ovarian cancer.

Acknowledgments

We thank A. Aoki for technical assistance and Y. Hisako, K. Kawaguchi, S. Miyaji, and R. Tanaka for help in the preparation of the manuscript.

Disclosure Statement

The authors have no conflict of interest.

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Int J Clin Oncol (2015) 20:240–248
DOI 10.1007/s10147-015-0806-7

SPECIAL ARTICLE

Japan Society of Gynecologic Oncology guidelines 2011 for the treatment of uterine cervical cancer

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Received: 5 February 2015 / Accepted: 17 February 2015 / Published online: 24 March 2015

Abstract The second edition of the Japan Society of Gynecologic Oncology guidelines for the treatment of uterine cervical cancer was published in 2011. The guidelines comprise eight chapters and five algorithms. They were prepared by consensus among the members of the Japan Society of Gynecologic Oncology Guidelines Formulation Committee and Evaluation Committee and are based on a careful review of the evidence obtained from the literature, health insurance system, and actual clinical settings in Japan. The highlights of the 2011 revision are (1) the recommended grades have been changed to five stages—A, B, C1, C2, and D; (2) the revisions are consistent with the new International Federation of Gynecology and Obstetrics staging system; (3) the roles are shared between the 'Japanese classification of cervical cancer' and the new guidelines; (4) clinical questions related to adenocarcinoma have been revised; and (5) a clinical question regarding cervical cancer in pregnant patients has been added. Each chapter includes a clinical question, recommendations, background, objectives, explanations, and references. Each recommendation is accompanied by a classification of recommendation categories. The objective of these guidelines is to update the standard treatment strategies for cervical cancer, thus eliminating unnecessary and insufficient treatment.

Keywords Uterine cervical cancer · Clinical practice guidelines · Surgery · Chemotherapy · Irradiation · Recurrence

This article originally appeared in Japanese as *Shikyu keigan chiryo gaidorain 2011 nen ban*, published by Kanehara, Tokyo, 2011.

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Introduction

An estimated 6,000 new cases of invasive cervical cancer were diagnosed in Japan in 2011 [1], and 2,737 women died of the disease [2]. The mortality rate associated with cervical cancer in Japan decreased from the 1960s until 1995; however, the incidence of cervical cancer has slightly increased [2].

The first edition of the Japan Society of Gynecologic Oncology (JSGO) guidelines for the treatment of uterine cervical cancer was published in 2007 [3]; however, some clinical questions (CQs) in the first edition remained unanswered. The second edition, published in 2011, was intended to represent an aggregation of domestic evidence while collecting up-to-date international evidence without providing a new section. For the first time, we accepted specialist physicians engaged in clinical practice in cancer centers or university hospitals as candidates for the committee. Radiation oncologists and pathologists were also members of the guideline committee.

The highlights of the 2011 revision are indicated below.

1. The recommended grades have been changed to five stages—A, B, C1, C2, and D.
2. The revisions are consistent with the new International Federation of Gynecology and Obstetrics (FIGO) staging system. The new FIGO staging system was revised during the creation of these updated guidelines. The new FIGO classification excludes stage 0 carcinoma in situ; however, stage 0 still has high importance in the guidelines because many people, especially young people, have stage 0 disease. Therefore, stage 0 is present in the guidelines. Additionally, stage IIA has been reclassified to stage IIA1 and stage IIA2 in the new FIGO classification. This revision from the Japan Society of Obstetrics and Gynecology 'Japanese classification of cervical cancer' has been adopted, and the reclassification to stage IIA1 and IIA2 is present in the new guidelines.
3. Roles are shared between the 'Japanese classification of cervical cancer' and the new guidelines. A specific radiotherapy technique is detailed in the guidelines.
4. CQs related to adenocarcinoma have been revised. Few clinical trials on adenocarcinoma alone have been conducted; thus, the chapter on adenocarcinoma was deleted and a CQ related to adenocarcinoma is described in each chapter.
5. A CQ regarding cervical cancer in pregnant patients has been added. Because of the increasing incidence of cervical cancer in younger patients and of pregnancy in older patients, the treatment of cervical cancer and its complications owing to pregnancy should be addressed. Therefore, these treatment guidelines are described in detail by increasing the CQs relevant to this topic.

Treatment guidelines for cervical cancer

Chapter 1: Overview of guidelines

1. How to use these guidelines

These guidelines are intended for doctors (general practitioners and specialists) who provide medical care for patients with cervical cancer. The guidelines aim to provide useful treatment methods by integrating previous evidence of treatment benefits. However, the guidelines are not intended to be limited to the therapies listed. Their main purposes are (1) to indicate the current cervical cancer treatments that are considered appropriate, (2) to reduce differences in therapy among various institutions, (3) to improve the prognosis and safety of treatments, (4) to reduce the economic and psychosomatic burden on patients by performing appropriate treatment, and (5) to promote mutual understanding between healthcare professionals and patients.

The JSGO bears the responsibility for the content and descriptions of these guidelines. However, the final decision to use these guidelines should be made by the individual user. Thus, the physicians in charge of treatment are responsible for the outcome of treatment.

2. Method used to prepare these guidelines

To create these guidelines, the Guidelines Formulation Committee and Evaluation Committee were established independently from the Committee for the Treatment Guidelines for Cervical Cancer. The initial draft was created by thoroughly evaluating the various opinions from within and outside the JSGO prior to incorporating them into the final draft. The guidelines were published after approval by the JSGO.

(1) Classification of evidence

1. The guidelines were created in accordance with the international standard procedures of evidence-based medicine used for the creation of clinical practice guidelines.
2. In principle, searches of data and published literature were performed prior to December 2009 in Japan and overseas, and evidence was collected.
3. This collected evidence was evaluated for quality using the criteria of the Japan Society of Clinical Oncology and its Formulation Committee on clinical practice guidelines for the use of anticancer agents [4, 5]; however, it was modified to allow some of it to fit into the guidelines (Table 1).

Table 1 Classification of evaluation criteria for evidence quality

Level I Evidence from multiple randomized controlled trials or meta-analyses of multiple randomized controlled trials
Level II Evidence from at least one randomized controlled trial or multiple well-designed controlled studies without randomization
Level III Evidence from at least one other type of well-designed quasi-experimental study or from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies, or case studies
Level IV Expert committee reports, or opinions and/or clinical experiences of respected authorities

Table 2 Classification of recommendation categories

Grade A The treatment is strongly recommended if at least one level I evidence indicates validity
Grade B The treatment is recommended if at least one level II evidence indicates validity
Grade C1 The treatment can be considered, but the evidence is insufficient; for example, there are several reports of level III evidence that show validity with generally consistent results
Grade C2 The treatment is not recommended without sufficient scientific evidence
Grade D The treatment is not recommended because neither utility nor effectiveness has been shown and because the treatment may be harmful

(2) Clinical questions and classification of recommendation categories

As a result of the discussions held by the Guideline Committee, controversial issues were selected as CQs and associated recommendations were made. Each recommendation in response to a CQ is accompanied by a classification of the evidence and a classification of the recommendation categories based on the consensus reached by the Guideline Committee members.

The strengths of the recommendations in our guidelines were also determined by the recommendation criteria of the Japan Society of Clinical Oncology and its Formulation Committee of Clinical Practice Guidelines for the Use of Anticancer Agents [6]. These were modified while referring to the 'Guide 2007 Minds practice guidelines' (Tables 2, 3).

Chapter 2: Primary treatment for stage 0 to IA cervical cancer (Fig. 1)

CQ01. What treatments are recommended for carcinoma in situ?

Recommendations A cervical cone biopsy is recommended (grade B).

Table 3 Classification of risk of postoperative recurrence of cervical cancer

Low-risk group: patients who meet all of the following criteria
Small cervical tumor
Negative pelvic nodes
Negative parametrical invasion
Shallow cervical stromal invasion
No venous or lymphatic infiltration
Intermediate-risk group: patients with negative pelvic nodes and negative parametrical invasion but who meet one of the following criteria
Large cervical tumor
Deep cervical stromal invasion
Positive venous or lymphatic infiltration
High-risk group: patients who meet one of the following criteria
Positive pelvic nodes
Positive parametrical invasion

CQ02. What treatments are recommended for recurrence following conservative treatment?

Recommendations (1) For recurrence following laser cone biopsy or the loop electrosurgical excision procedure, the same procedure should be repeated or a total hysterectomy considered, depending on the patient (grade B). (2) For recurrence following laser ablation or cryotherapy, either a cone biopsy or total hysterectomy is recommended (grade B).

CQ03. What treatments are recommended for stage IA1 disease?

Recommendations (1) It is possible to preserve the uterus by performing a cervical cone biopsy in patients who strongly desire fertility preservation; however, these patients must have no vascular or lymphatic infiltration, negative resection margins, and negative histological results from endocervical curettage (grade B). (2) A total hysterectomy without pelvic lymphadenectomy is recommended for patients with no evidence of vascular or lymphatic infiltration (grade B). (3) Both a modified radical hysterectomy and pelvic lymphadenectomy are sometimes performed for patients with vascular or lymphatic infiltration (grade C1).

CQ04. What treatments are recommended for stage IA2 disease?

Recommendations (1) A modified radical hysterectomy or a more extensive procedure with lymphadenectomy should be considered for stage IA2 disease (grade C1). (2) After thorough histopathological examination of a specimen obtained by diagnostic conization, omission of

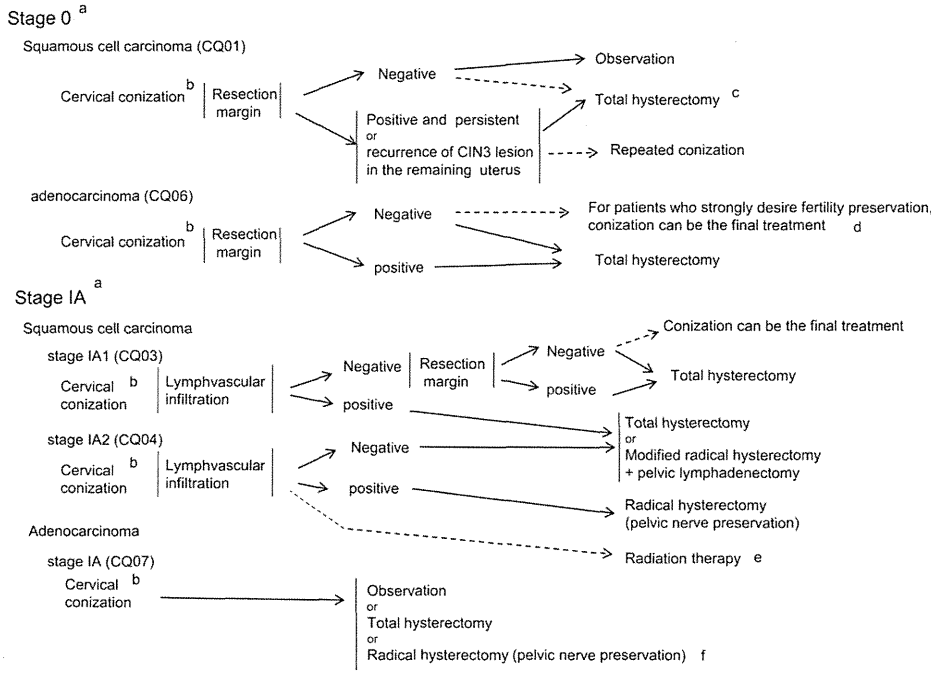

Fig. 1 Primary treatment for stage 0 to IA cervical cancer. **a** If cervical conization is difficult because of atrophy of the cervix, such as in older patients, omission of the conization may be considered. However, prior to surgery, it is necessary to carefully review the cytology, colposcopy, and biopsy tissue findings; this allows for the performance of a hysterectomy suitable for the estimated lesion. **b** Cervical canal curettage should be performed at the time of cervical conization. If cervical curettage is positive, the patient should be treated as if they have positive margins. **c** Hysterectomy may be considered if the patient does not wish to preserve her fertility. **d** Residual lesions are reportedly found in about 20 % of cases involving negative margins. Careful inspection is required to preserve the uterus. **e** In the NCCN clinical practice guidelines in oncology, radiation therapy is also an option for patients with cervical cancer. **f** Operative procedures should be individualized according to the histopathological findings of the conization specimens, namely the extent of invasion and the presence or absence of lymphovascular infiltration

lymphadenectomy in patients with no vascular or lymphatic infiltration can be considered (grade C1).

CQ05. What treatments are recommended if the disease is upstaged to stage IB or higher following total hysterectomy?

Recommendations Adjuvant radiotherapy or concurrent chemoradiotherapy (CCRT) should be considered (grade C1).

CQ06. What treatments are recommended for adenocarcinoma in situ?

Recommendations (1) A total hysterectomy is recommended (grade B). (2) Uterus preservation can be considered with cervical cone biopsy in patients who strongly desire fertility preservation. However, careful management is required (grade C1).

CQ07. What treatments are recommended for stage IA adenocarcinoma?

Recommendations (1) In cases involving deep invasion, a radical hysterectomy or modified radical hysterectomy with pelvic lymphadenectomy should be considered (grade C1). (2) In cases involving shallow invasion, a hysterectomy without pelvic lymphadenectomy (total hysterectomy or modified radical hysterectomy) can also be considered (grade C1). (3) If the patient strongly desires fertility preservation, a cervical cone biopsy can be performed

to preserve the uterus. Careful case selection is required (grade C1).

Chapter 3: Primary treatment for stage IB to II cervical cancer (Fig. 2)

CQ08. What treatments are recommended for stage IB1 and IIA1 squamous cell carcinoma?

Recommendations A radical hysterectomy or radiation therapy is recommended (grade B).

CQ09. What treatments are recommended for stage IB2 and IIA2 squamous cell carcinoma?

Recommendations A radical hysterectomy (+ adjuvant therapy) or CCRT is recommended (grade B).

CQ10. What treatments are recommended for stage IIB squamous cell carcinoma?

Recommendations A radical hysterectomy (+adjuvant therapy) or CCRT is recommended (grade B).

CQ11. Is neoadjuvant chemotherapy recommended for stage IB and II squamous cell carcinoma?

Recommendations Neoadjuvant chemotherapy can be considered depending on the extent and size of the tumor (grade C1).

CQ12. Is pelvic nerve preservation recommended in radical hysterectomy?

Recommendations Pelvic nerve preservation can be considered when curability is not impaired (grade C1).

CQ13. Is ovary preservation possible in radical hysterectomy?

Recommendations (1) Ovary preservation is possible without compromising curability if appropriate case selection is performed by considering the patient's histological type or stage (grade B). (2) If the ovaries are to be preserved, ovarian transposition and fixation outside of the pelvic radiation field can be considered (grade C1).

CQ14. Is para-aortic lymphadenectomy recommended in radical hysterectomy?

Recommendations If diagnostically useful, para-aortic lymphadenectomy can be considered to search for metastasis or determine the irradiation field (grade C1).

CQ15. What treatments are recommended for stage IB and II adenocarcinoma?

Recommendations In principle, surgery should be considered for stage IB and II disease (grade C1).

Chapter 4: Postoperative therapy for stage IB to II cervical cancer (Fig. 3)

CQ16. What is the recommended postoperative adjuvant therapy?

Recommendations (1) CCRT is recommended for patients at high risk of recurrence (grade B). (2) Radiation therapy is recommended for patients at intermediate risk of recurrence. However, CCRT can be considered depending on the number and extent of risk factors (grade C1).

CQ17. What irradiation methods are recommended when performing postoperative adjuvant radiotherapy for a patient at high risk of relapse?

Recommendations (1) Whole-pelvis irradiation is recommended (grade B). (2) Three-dimensional treatment planning is recommended (grade B). (3) The addition of intracavitary irradiation is not recommended with the exception of cases involving positive margins (grade C2).

CQ18. For whom is prophylactic para-aortic irradiation indicated?

Recommendations Para-aortic irradiation can be considered for patients with a high risk of recurrence in the para-aortic lymph nodes (grade C1).

CQ19. Are oral anticancer drugs and immunotherapy recommended as maintenance therapies?

Recommendations (1) Oral anticancer agents are not recommended because their usefulness is unclear (grade C2). (2) Immunotherapy is not recommended because its usefulness has not been fully verified (grade C2).

Chapter 5: Primary therapy for stage III to IV cervical cancer (Fig. 4)

CQ20. Which is the recommended radiotherapy for stage III and IVA disease: definitive radiotherapy or CCRT?

Recommendations CCRT is recommended rather than radiation monotherapy (grade B).

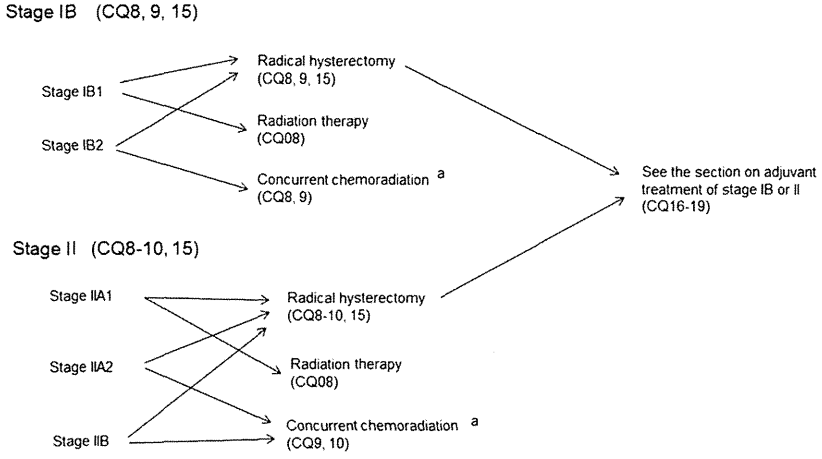

Fig. 2 Primary treatment for stage IB to II cervical cancer (including squamous cell carcinoma and adenocarcinoma). **a** Primary treatment for stage IB to II cervical cancer should be performed with caution because the tolerability of concurrent chemoradiation therapy among Japanese women has not been sufficiently tested

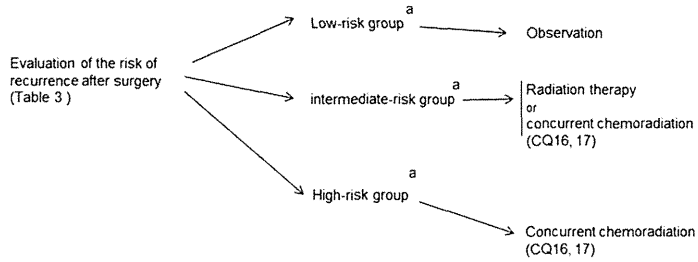

Fig. 3 Postoperative therapy for stage IB to II cervical cancer (including squamous cell carcinoma and adenocarcinoma). **a** There are many discussions and various reports on risk assessment for postoperative recurrence. Postoperative therapy must be considered according to the individual case

CQ21. What CCRT regimens are recommended for stage III and IVA disease?

Recommendations Regimens that include cisplatin are recommended (grade A).

CQ22. Is chemotherapy recommended prior to principal treatment for stage III and IVA disease?

Recommendations (1) Chemotherapy is not recommended before radiotherapy (grade D). (2) Chemotherapy is not recommended before surgery (grade C2). (3) For adenocarcinoma, chemotherapy is not recommended before primary treatment (grade C2).

CQ23. Is surgery recommended for stage III and IVA disease?

Recommendations Surgery is not recommended (grade C2).

CQ24. What treatments are recommended for stage IVB disease?

Recommendations (1) Systemic chemotherapy can be considered for patients with a good performance status and preserved organ function (grade C1). (2) Surgery, radiotherapy, chemotherapy, or a combination of these treatments can be selected for patients with distant metastatic lesions, such as resectable lung metastases, or with lymph

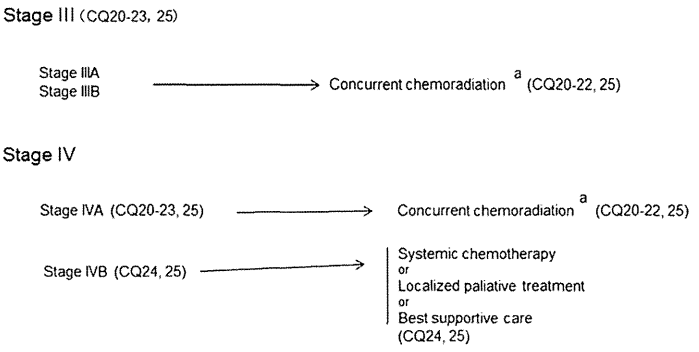

Fig. 4 Primary treatment for stage III to IV cervical cancer (including squamous cell carcinoma and adenocarcinoma). **a** Primary treatment for stage III to IV cervical cancer should be performed with caution because the tolerability of concurrent chemoradiation therapy among Japanese women has not been sufficiently tested

node metastases only (grade C1). (3) If the patient has severe symptoms accompanying oncological complications, palliative radiotherapy of the causal lesion is recommended (grade B).

CQ25. What treatments are recommended for stage III and IV adenocarcinoma?

Recommendations CCRT involving external irradiation and intracavitary irradiation is recommended for stage III or VIA adenocarcinoma (grade B). (2) A platinum-based agent other than cisplatin, either as monotherapy or as part of combination chemotherapy, can also be considered for patients with stage IVB adenocarcinoma with preserved organ function (grade C1).

Chapter 6: Therapies for relapsed cervical cancer (Fig. 5)

CQ26. What treatment methods are recommended for recurrence confined to the pelvis if radiotherapy has not been previously performed?

Recommendations (1) Radiotherapy is recommended (grade B). (2) CCRT can also be considered (grade C1).

CQ27. What treatments are recommended for recurrence within the radiation field?

Recommendations (1) Palliative treatment for symptomatic relief is the general rule for treatment (grade C1). (2) Chemotherapy can also be considered, keeping in mind that the response rate is low for recurrence within the radiation field (grade C1). (3) Localized radiotherapy or pelvic exenteration can also be considered for central recurrence in the vaginal stump after a thorough preoperative evaluation (grade C1). (4) Re-irradiation is not recommended (grade C2).

CQ28. What treatments are recommended for recurrence outside the radiation field or for extrapelvic recurrence if radiotherapy has not been previously performed?

Recommendations (1) Para-aortic metastasis: radiation therapy or CCRT can be considered for solitary metastasis (grade C1). (2) Brain metastasis: (a) stereotaxic radiosurgery along with whole-brain radiation therapy (WBRT) or WBRT alone is recommended for metastases of up to three sites (grade B). (b) WBRT is recommended for more than four metastases (grade B). (3) Bone metastasis: (a) single-fraction or multi-fraction radiotherapy is recommended for pain relief (grade B). (b) Bisphosphonates are recommended for symptom relief (grade B). (c) Strontium chloride can be considered for multiple bone metastases if medical therapy is ineffective (grade C1). (4) Lung metastasis: resection or stereotactic body radiotherapy can be considered for one to three localized metastases (grade C1).

CQ29. Is systemic chemotherapy recommended for recurrence?

Recommendations Systemic chemotherapy is recommended for patients with disease that is difficult to control by surgery or radiotherapy as well as for patients with a good performance status and preserved organ function (grade B).

CQ30. What systemic chemotherapy regimens are recommended to treat recurrent disease?

Recommendations (1) Cisplatin as either monotherapy or part of two-drug combination chemotherapy is

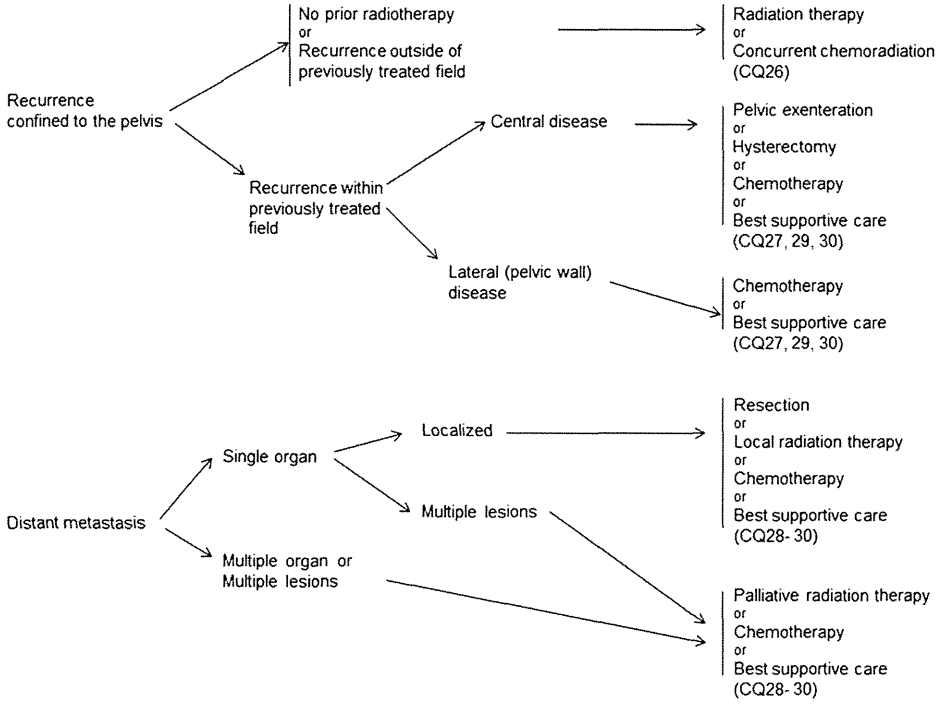

Fig. 5 Therapy for relapsed cervical cancer (including squamous cell carcinoma and adenocarcinoma)

recommended (grade B). (2) A platinum-based agent other than cisplatin, as either monotherapy or part of two-drug combination chemotherapy, can also be recommended (grade B). (3) Cisplatin as either monotherapy or part of two-drug combination chemotherapy is preferable for recurrent adenocarcinoma (grade C1).

Chapter 7: Management of cervical cancer during pregnancy

CQ31. What treatments are recommended for stage 0 disease during pregnancy?

Recommendations (1) Cone biopsy may be delayed until after delivery as long as the diagnosis is stage 0 disease based on consistent cytology, colposcopy, or biopsy analysis results (grade C1). (2) If adenocarcinoma in situ is suspected, a cone biopsy should be performed to determine the diagnosis during pregnancy (grade C1).

CQ32. What treatments are recommended for stage IA disease during pregnancy?

Recommendations If stage IA or higher disease is suspected, a cervical cone biopsy should be considered to determine the diagnosis during pregnancy (grade C1).

CQ33. What treatments are recommended for invasive cancer during pregnancy?

Recommendations If the diagnosis made during the gestational period (usually during the 3rd trimester) indicates that the fetus can survive outside the uterus, standard treatment after delivery can be considered (grade C1).

Chapter 8: Surveillance after treatment for cervical cancer

CQ34. What intervals are recommended for post-treatment surveillance?

Recommendations The following intervals are recommended for standard surveillance (grade C1):

For the first 1–2 years: every 1–3 months
For the 3rd year: every 3–6 months
For the 4th and 5th years: every 6 months
From the 6th year: every 12 months

CQ35. What investigations and examinations should be performed during post-treatment surveillance?

Recommendations (1) A physical examination (including pelvic and rectal examination), cytological examination, chest radiography, measurement of tumor markers, and diagnostic imaging should be performed (grade C1). (2) Any complications associated with surgery, radiotherapy, or chemotherapy should be noted (grade C1).

Acknowledgments We thank the Japan Society of Obstetrics and Gynecology, the Japan Association of Obstetricians and Gynecologists, the Japanese Gynecologic Oncology Group, the Japan Society of Clinical Oncology, and the Japanese Society for Therapeutic Radiology and Oncology for their comments and contributions throughout the project. We also acknowledge support by grants from the Ministry of Health, Labour and Welfare; H24-Clinical Cancer Research-001 (chief researcher, Koichi Hirata).

Conflicts of interest None of the members of the committee in charge of the preparation of these guidelines has any conflict of interest with entities such as a specific profit or nonprofit organization. The board of the Society Conflict of Interest Committee confirmed the self-reported absence of any conflicts of interest by the Guideline Committee members.

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Original Article

J Gynecol Oncol Vol. 26, No. 3:193-200
http://dx.doi.org/10.3802/jgo.2015.26.3.193
pISSN 2005-0380 · eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

High-dose oral tegafur-uracil maintenance therapy in patients with uterine cervical cancer

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Objective: The aim of this study was to determine the efficacy and toxicity of oral administration of tegafur-uracil (UFT) at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

Methods: This study consisted of a retrospective analysis. From April 1986 to March 1997, 309 patients with uterine cervical cancer were registered. Oral UFT was administered to 162 patients for maintenance therapy after an initial treatment (the UFT group). The other 147 patients were not treated with UFT (the control group). The survival rate was calculated for both groups and statistically analyzed using the log-rank test. Adverse events were compared between the UFT and control groups.

Results: In the UFT group, 103 patients (63.6%) received UFT for ≥90 days. The drug dose was 600 mg/day for 137 patients (84.6%) and 300 to 400 mg/day for the remainder. The overall survival rate was significantly higher in the UFT group than in the control group ($p<0.05$). The prognosis was particularly favorable in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated by radiotherapy. The most frequent side effects were nausea/vomiting (12.2%), appetite loss (10.1%), and leukopenia/neutropenia (5.8%).

Conclusion: High-dose oral UFT maintenance treatment prolonged the disease-free survival and overall survival of patients with uterine cervical cancer, particularly of those with advanced disease.

Keywords: Follow-up Studies; Maintenance Chemotherapy; Survival Rate; Tegafur; Uterine Cervical Neoplasms

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide. There are approximately 530,000 new cases and 275,000 associated deaths each year [1]. In advanced uterine cervical cancer, the addition of chemotherapy to external pelvic radiation has been proposed because systemic chemotherapy further enhances local control and improves the overall survival. The main agents are cisplatin and 5-flurouracil (5-FU), concurrent chemoradiotherapy with either weekly cisplatin or monthly cisplatin and 5-FU are recommended for patients with advanced uterine cervical cancer. Oral 5-FU is also a mainstay in the maintenance therapy for cervical cancer in most cases in Japan. Among 5-FU derivative chemotherapeutic agents, tegafur-uracil (UFT) is an oral antineoplastic drug consisting of tegafur and uracil in a fixed 1:4 molar ratio. Tegafur is an oral prodrug of 5-FU and is slowly metabolized by cytochrome P450 to 5-FU [2-4]. Uracil competitively inhibits

Received Nov 24, 2014, Revised Jan 8, 2015, Accepted Jan 22, 2015

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dihydropyrimidine dehydrogenase (DPD), which results in increased and sustained plasma and tumor 5-FU concentrations. The 5-FU that results from the metabolism of tegafur is modulated by formyltetrahydrofolic acid (folic acid). More recently, studies that have compared adjuvant chemotherapy with UFT after surgery and surgery alone have been reported and clearly proved a survival benefit of adjuvant UFT treatment for lung, gastric, colorectal, and breast cancer [5-11]. In early-stage uterine cervical cancer, oral 5-FU after surgery with radiotherapy appears to be useful for patients who have some risk factors but not for those with pelvic lymph node metastases [12]. However, the extent of impact of adjuvant treatment with oral UFT on patients with advanced cervical cancer remains unclear. Although the amount of UFT per day was high in the above-described trial, it was standardized at 300 to 400 mg/day for adjuvant therapy of advanced cervical cancer. It remains unclear whether the high dose of this oral compound will become tolerable with infrequent observation of toxic effects and result in a significant improvement in the survival rate.

This study was conducted to determine the efficacy and toxicity of adjuvant and maintenance therapy with oral administration of UFT at a high dose, 600 mg/day, based on the tegafur dose, against uterine cervical cancer.

MATERIALS AND METHODS

1. Study design

This retrospective study was planned in a total of five institutions in Kumamoto, Japan. In these five institutions, between April 1986 and March 1997, patients with advanced cervical cancer were enrolled. The patients were required to meet the following criteria: histologically confirmed primary uterine cervical carcinoma; International Federation of Gynecology and Obstetrics (1988 FIGO) stages Ib to IV; performance status of 0 to 2; adequate bone marrow, renal, and hepatic function as evidenced by a white blood cell count >3,000 cells/μL, platelet count >100,000 cells/μL, serum creatinine level <2.0 mg/dL, blood urea nitrogen (BUN) level <30 mg/dL, serum bilirubin level <1.5 mg/dL, and serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels <2 times the normal limit; and no serious complicated illness such as renal hepatic, cardiac, or pulmonary disease. Patients also could not have previously received any biochemical modulation.

In total, 309 patients with advanced cervical cancer were allocated to either the UFT-treated group (the UFT group) or the UFT-untreated group (the control group). The study group consisted of 162 selected consecutive patients with advanced cervical cancer who were enrolled in this study at five institutions in Kumamoto between August 1992 and March 1997. The patients were treated by oral administration of UFT at a dose of 600 mg/day for maintenance therapy after an initial treatment. A group of 147 similar patients who had received the same treatment in five institutions in Kumamoto between December 1986 and March 1997 was used as an external control group. These patients were required to meet the criteria mentioned above and not treated with UFT. In the UFT and control groups, 43 patients (26.5%) and 41 patients (27.9%) received radical hysterectomy combined with pelvic lymph node dissection; 58 (35.8%) and 65 (44.2%) received radiotherapy; 26 (16.0%) and 29 (19.7%) received radiotherapy and radical surgery; and 14 (8.6%) and six (4.1%) received a combination of surgery, radiotherapy, and chemotherapy, respectively. Postoperative pelvic radiotherapy was advocated for patients with pelvic lymph node metastasis, deep stromal invasion, and parametrial invasion. Toxicity was recorded by grade according to the National Cancer Institute Common Toxicity Criteria ver. 2.0. Monthly complete blood counts,

Table 1. Patient characteristics and treatment

Characteristic	Control group (n=147)	UFT group (n=162)
Median age (yr)	62.0±14.1	61.0±14.1
FIGO stage		
I	58 (39.5)	64 (39.5)
II	37 (25.2)	42 (25.9)
III	40 (27.2)	39 (24.1)
IV	12 (8.1)	17 (10.5)
Histologic type		
Squamous cell carcinoma	134 (91.2)	133 (82.1)
Adenocarcinoma	9 (6.1)	17 (10.5)
Adenosquamous carcinoma	4 (2.7)	6 (3.7)
Undifferentated carcinoma	0	1 (0.6)
Others	0	5 (3.1)
Primary treatment		
RT alone	65 (44.2)	58 (35.8)
Surgery alone	41 (27.9)	43 (26.5)
Surgery/RT	29 (19.7)	26 (16.0)
Surgery/RT/chemotherapy	6 (4.1)	14 (8.6)
RT/chemotherapy	4 (2.7)	11 (6.8)
Surgery/chemotherapy	2 (1.4)	10 (6.3)

Values are presented as mean±SD or number (%). Chemotherapy means cispatin based therapy, not included the oral administration of UFT. Chemotherapy regimens were given to patients before the oral administration of UFT.
FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy; UFT, tegafur-uracil.

http://dx.doi.org/10.3802/jgo.2015.26.3.193

including white blood cell, red blood cell, and platelet counts, were performed to assess myelosuppression. A complete chemistry panel, including serum creatinine, BUN, bilirubin, AST, and ALT levels, was also obtained. The UFT treatment was continued for up to 2 years until side effects became intolerable. In some cases, the dose was reduced from 600 mg/day to 300 to 400 mg/day when side effects were beyond control. Severe (grade 3/4) toxicity related to chemotherapy resulted in dose reduction.

2. Statistical analysis

Survival was estimated as the time of study entry until death as a result of any cancer. Progression-free survival was defined as the time from study entry to the initial observation of disease progression or death as a result of any cancer. The survival rate was statistically analyzed using the log-rank test. No patients were lost to follow-up in this study. Each patient was followed until death or is alive with the disease status being known. This study was approved by the Institutional

Table 2. Efficacy of UFT in the patients with cervical cancer

Variable	Overall survival (%)			Disease-free survival (%)		
	Control group	UFT group	p-value	Control group	UFT group	p-value
All patients	60.8	73.8	0.049	59.8	68.5	0.076
FIGO stage						
I	88.9	91.5	0.665	89.2	91.6	0.661
II	46.7	71.3	0.644	61.6	71.6	0.855
III	34.9	62.1	0.012	38.3	62.5	0.026
IV	20.8	35.3	0.318	10.4	37.6	0.204
Histologic type						
Squamous cell carcinoma	60.7	74.1	0.062	64.6	75.2	0.083
Adenocarcinoma	85.7	80.6	0.764	85.7	80.8	0.694
Adenosquamous carcinoma	25	62.5	0.29	25	62.5	0.242
Primary treatment						
Radiotherapy alone	48.7	64.3	0.068	48.9	65.6	0.082
Surgery alone	94.7	92.7	0.746	94.9	92.7	0.701
Surgery/radiotherapy	53.5	82.7	0.193	59.5	83.2	0.093

The effect of UFT administration on overall survival rate was analyzed according to FIGO staging, histological type, and primary treatment. A p-value between patients with and without UFT administration.
FIGO, International Federation of Gynecology and Obstetrics; RT, radiotherapy; UFT, tegafur-uracil.

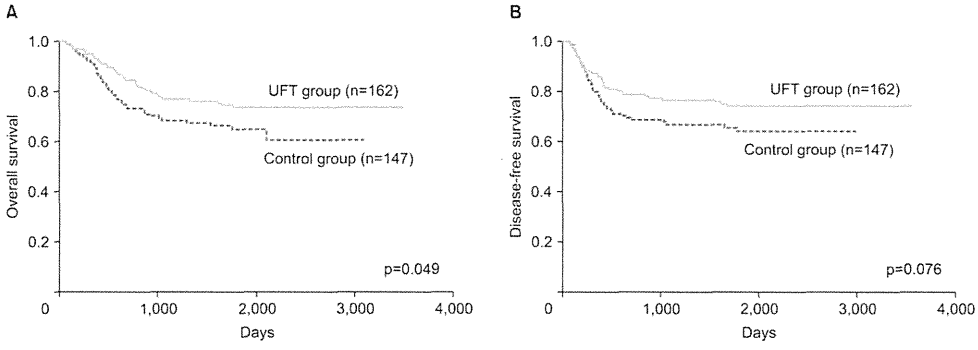

Fig. 1. Survival curves among 309 patients with uterine cervical cancer in the tegafur-uracil (UFT) and the control group. Kaplan-Meier estimates of (A) the overall survival (p=0.049), (B) the disease-free survival (p=0.076).

Table 3. Efficacy of long-term oral administration of UFT in the patients with cervical cancer

Variable	Overall survival (%)			Disease-free survival (%)		
	Administration period <90 days	Administration period ≥90 days	p-value	Administration period <90 days	Administration period ≥90 days	p-value
All patients	59.6	81.4	0.001	62.2	81.4	0.001
FIGO stage						
I	84.4	94.9	0.13	84.4	94.9	0.134
II	54.8	79.8	0.072	58.7	79.3	0.063
III	55.3	66.8	0.334	61.1	64.8	0.467
IV	17.1	57.1	0.001	17.1	60	<0.001
Histologic type						
Squamous cell carcinoma	59.6	81	0.003	62.2	81	0.003
Adenocarcinoma	71.4	87.5	0.416	71.4	87.5	0.361
Adenosquamous carcinoma	66.7	50	0.081	66.7	66.7	0.715
Primary treatment						
Radiotherapy alone	44.7	74.9	0.01	49.1	75.3	0.006
Surgery alone	88.9	93.6	0.594	88.9	93.5	0.594
Surgery/radiotherapy	87.5	80.4	0.759	88.9	80.8	0.761

We compared the disease free survival rate in the patients who received the drug for ≥90 days with those who received the drug for <90 days. A p-value between patients received the drug for 90 days or more, and for less than 90 days.
UFT, tegafur-uracil; FIGO, International Federation of Gynecology and Obstetrics.

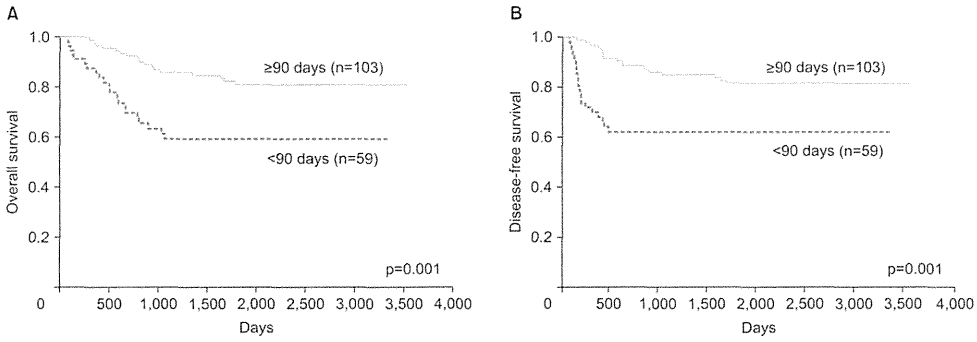

Fig. 2. Survival curves of the tegafur-uracil (UFT)-treated patients between those who received the drug for ≥90 days and <90 days. Kaplan-Meier estimates of (A) the overall survival (p=0.001), (B) disease-free survival (p=0.001).

Review Board of Kumamoto University (Japan).

RESULTS

The patient characteristics of the two groups are listed in **Table 1**. The median follow-up period was 52 months (range, 1 to 119 months). The patient characteristics, including background factors such as age, FIGO stage, histological type, and therapeutic modality, were well balanced between the UFT and control groups. In the UFT group, 108 patients (63.5%) received UFT for ≥90 days, and the average duration was 217.2 days. The average total dose was 120.2 g (range, 1.0 to 544.0 g).

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1. Response, survival, and disease-free survival

The overall survival rate was significantly higher in the UFT group (73.8%) than in the control group (60.8%; p<0.05) (**Table 2**, **Fig. 1A**). Next, the effect of UFT administration on survival was analyzed according to FIGO staging, histological type, and primary treatment (**Table 2**).

There was a significant difference in survival between the UFT group and the control group among the stage III patients (UFT group, 62.1%; control group, 34.9%; p=0.012) (**Table 2**, **Supplementary Fig. 1A**). Among the patients with squamous cell carcinoma, the overall survival was 74.1% in the UFT group and 60.7% in the control group (p=0.062) (**Table 2**, **Supplementary Fig. 1B**). The patients who were treated by radiotherapy tended to have a favorable prognosis (p=0.068) (**Table 2**, **Supplementary Fig. 1C**). However, the difference in the disease-free survival rates was not statistically significant (**Table 2**, **Fig. 1B**).

Next, we investigated the effect of long-term oral administration of UFT in the patients with cervical cancer. Among the UFT-treated patients, those who received the drug for ≥90 days had significantly higher overall and disease-free survival rates than those who received the drug for <90 days (p=0.001) (**Table 3**, **Fig. 2**). Long-term oral administration of UFT in patients with cervical cancer was associated with a decreased risk of recurrence and death. There was a significant difference in survival with the stage IV patients (57.1% in the patients who received the drug for ≥90 days vs. 17.1% in the patients who received the drug for <90 days) (**Table 3**). The difference in survival was significant in the patients with squamous cell carcinoma (81.0% in the patients who received the drug for ≥90 days vs. 59.6% in the patients who received the drug for <90 days) (**Table 3**). In the patients treated by radiotherapy, the overall survival rate was 74.9% for the long-term administration group and 44.7% for the shorter-term administration group (**Table 3**). Squamous cell carcinoma and radiotherapy had a significant effect on disease-free rates (p<0.05) (**Table 3**).

2. Toxicity

In total, 139 of the 162 patients enrolled in the UFT group were assessable for toxicity. Fifty-six patients (40.3%) showed ≥1 adverse reactions; overall, high-grade toxicities were infrequently observed. The toxicities are summarized according to the worst grade per patient for all treatment courses in **Table 4**. Nausea and vomiting (17/139, 12.2%), appetite loss (14/139, 10.1%), leukopenia/neutropenia (8/139, 5.8%), elevation of serum transaminases (7/139, 5.0%), diarrhea (7/139,

Table 4. Adverse events in the tegafur-uracil (UFT) group

Toxicity	Grade				
	1	2	3	4	Unknown
Hematological adverse events					
Leukopenia/neutropenia	1	6	1	0	0
Thrombocytopenia	0	1	0	0	0
Anemia	0	1	0	0	0
Elevation of serum transaminases	2	2	0	0	3
Non-hematological adverse events					
Nausea/vomiting	12	2	2	0	1
Loss of appetite	7	3	4	0	0
Diarrhea	3	3	1	0	0
Abdominal discomfort	2	0	0	0	0
Abdominal pain	1	1	1	0	0
Rash	4	0	0	0	0
Skin/nail pigmentation	3	2	0	0	0
Stomatitis	2	0	0	0	1
Itching	1	0	0	0	0
Tremor	1	1	0	0	0
Dysgeusia	3	0	0	0	0
General fatigue	0	0	0	0	1
Bloody stool	0	0	0	0	1
Total	42	22	9	0	7

5.0%), and skin/nail pigmentation (5/139, 3.6%) were the most commonly observed toxicities (**Table 4**). No patients developed grade 4 hematological or nonhematological adverse events. Overall, eight patients experienced grade 3 nonhematological adverse events in the study group. Gastrointestinal toxicity was not manageable for most patients. In particular, grade 3 hematological toxicity was observed in one patient.

DISCUSSION

This is the first report to investigate the efficacy of oral administration of a high dose (600 mg/day) of UFT in uterine cervical cancer patients. In this study, we elucidated that UFT maintenance treatment might lead to a favorable prognosis in stage III cases, in cases of squamous cell carcinoma, and in cases that were treated by radiotherapy.

One particular limitation of this study warrants mention. Owing to its small sample size, this study did not have sufficient statistical power to demonstrate the effect of UFT treatment in uterine cervical cancer patients. However, the overall survival rate was significantly higher in the UFT group than in the control group. This difference might indicate the possibility of using UFT as a treatment option in uterine cervical cancer patients.

DPD is the initial rate-limiting enzyme in the catabolism of 5-FU and plays a critical role in regulating the availability of 5-FU for anabolism. In the treatment of advanced colorectal cancer, orally administered prodrugs of 5-FU were introduced as DPD inhibitory fluoropyrimidine drugs, including UFT. UFT can maintain a higher 5-FU plasma level for a longer period through the inhibition of 5-FU degradation [2-4,13].

Adjuvant chemotherapy can offer clinical benefits for patients receiving primary radiation therapy because 5-FU is a radiation sensitizer. Theoretically, possible mechanisms such as the inhibition of repair of radiation damage, cell synchronization, recruitment of nonproliferating cells into the cell cycle, and reduction of the hypoxic fraction are promoted. In this study, we showed that the prognosis was favorable in the UFT group that was treated by radiotherapy. Compared with continuous infusion of 5-FU and capecitabine, the combination of UFT and radiotherapy has several clinical benefits. Chemoradiotherapy that includes UFT is efficacious against solid tumors, including those in head and neck cancer [14] and non-small cell lung cancer [15]. Recently, in the treatment of resectable rectal cancer, preoperative chemoradiotherapy consisting of UFT with leucovorin plus radiotherapy was well tolerated and effective, and it represents a convenient alternative to 5-FU-based chemoradiotherapy [16]. This study showed a correlation between the potential role of UFT and radiotherapy in uterine cervical cancer. There are some studies to evaluate the effect of adjuvant chemotherapy after chemoradiotherapy for locally advanced cervical cancer [17,18]. However, the evidence was insufficient to support the use of adjuvant chemotherapy after chemoradiotherapy in locally advanced cervical cancer. Future large trials are required to demonstrate a correlation between adjuvant chemotherapy including UFT and radiotherapy in uterine cervical cancer.

The effect of UFT has been suggested to be influenced by tumor angiogenesis and the status of angiogenesis-related factors as well as by the status of enzymes involved in 5-FU metabolism, such as TS and DPD [19-23]. In uterine cervical cancer, UFT and its metabolite gamma-butyrolactone inhibit angiogenesis induced by vascular endothelial growth factor, which causes an antitumor effect [24]. Metronomic therapy, which is continuously administered systemically at close to non-toxic doses, involves multiple mechanisms that include antiangiogenesis and antivasculogenesis. In this study, patients who received UFT administration for ≥90 days had significantly higher survival and disease-free rates than those who received the drug for <90 days. Long-term administration of UFT after primary treatment can be a key factor for improving the prognosis in uterine cervical cancer.

Our study suggested that high-dose oral UFT maintenance treatment might prolong the disease-free survival and overall survival of patients with uterine cervical cancer. However, adverse events are likely to be more frequently observed in patients treated with high-dose UFT (600 mg/day) than in those treated with low-dose UFT (300 to 400 mg/day). Although significant myelosuppression, mucositis, or alopecia was infrequently encountered, the incidence of gastrointestinal toxicity was shown to be approximately 32% in the present study, and most of these patients were not able to continue self-administration by mouth beyond 90 days. Recently, a weekday-on/weekend-off oral UFT schedule has been frequently proposed as outpatient adjuvant chemotherapy with good tolerability.

Future studies that investigate new treatment schedules should be considered to reduce the frequency of nausea/vomiting and loss of appetite while achieving an excellent rate of compliance in self-administering high-dose UFT therapy. High-dose UFT oral administration provides a springboard from which we expect to launch better adjuvant and maintenance chemotherapy in advanced cervical cancer. Our present regimen is a potentially attractive alternative to palliative treatments for recurrent and incurable cervical cancer.

http://dx.doi.org/10.3802/jgo.2015.26.3.193

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We wish to thank the participating patients and their families to all other co-investigators who contributed to and were recruited to the study.

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