Comparative Effects of the Administration Period of Adjuvant Chemotherapy using Doxifluridine (5'-DFUR) for 1 Year *Versus* 3 Years after Breast Cancer Surgery by the Shimane Breast Cancer Study Group

SHIMANE BREAST CANCER STUDY GROUP, JAPAN*

Abstract. *Background: The present study investigated the efficacy of oral doxifluridine (5'-DFUR) by comparing the survival between patients who received 5'-DFUR at 800 mg/body daily for 1 or 3 years after surgery for stage 1, 2 or 3 breast cancer. Patients and Methods: Ninety-two patients were enrolled from January 1995 to December 1997, of whom 87 were eligible. The patients were stratified into pre-menopausal and post-menopausal groups, and then each group was further stratified into 1-year or 3-year administration groups. All patients were given endocrine therapy, with gosereline acetate (3.6 mg/body, monthly) for the pre-menopausal patients and tamoxifen (20 mg/day, daily) for the post-menopausal patients for 3 years. Results: The median follow-up duration was 9.5 years. Although no differences were found in the overall or disease-free survivals between the administration groups, subset analysis demonstrated that, in the pre-menopausal patients, the 3-year administration group showed a significantly higher overall survival rate than the 1-year administration group, but not in post-menopausal patients. A multivariate analysis also indicated that the administration duration of 5'-DFUR was a significant factor for disease-free survival. Conclusion: The present study supports the usefulness of 5'-DFUR for adjuvant chemotherapy against breast cancer, especially for pre-menopausal patients; however, further clinical study with a much larger sample size is necessary to reach a conclusive result.*

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Abbreviations: ACT, adjuvant chemotherapy; DFS, disease-free survival; 5'-DFUR, doxifluridine; ER, estrogen receptor; 5-FU, 5-fluorouracil; GA, gosereline acetate; OS, overall survival; RR, response rate; TAM, tamoxifen; UFT, tegafur plus uracil.

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Key Words: Breast cancer, adjuvant chemotherapy, doxifluridine, Furtulon.

Chemotherapy and endocrine therapy play very important roles in the treatment of breast cancer. Previous reports have demonstrated that adjuvant endocrine therapies with LH-RH analogs for pre-menopausal patients or estrogen-receptor (ER) inhibitors for post-menopausal patients may improve the treatment results after breast cancer surgery (1-4).

On the other hand, in Western countries, cyclophosphamide, doxorubicin, 5-fluorouracil (5-FU) or methotrexate have been widely used for adjuvant chemotherapy (ACT) after breast cancer surgery. However, in Japan, oral fluoropyrimidines have also been widely used

for chemotherapy against breast cancer. Doxifluridine (5'-DFUR, Furtulon) is one of these oral fluoropyrimidines. It has been reported that 5'-DFUR generated a 36% response rate (RR) against advanced or recurrent breast cancers (5), but its role in ACT after breast cancer surgery remains unclear. A previous clinical study, in which survival was compared in early stage breast cancer patients after surgery between no ACT and ACT with 5'-DFUR for 6 months, resulted in no difference in the 8-year survival between them (6). However, 6 months might be too short for adjuvant therapy, because in gastric or colorectal cancers, ACT with 5'-DFUR for 1 or 2 years after surgery resulted in an improvement in survival in comparison with ACT with oral 5-FU (7,8). The related phase III study demonstrated that 5'-DFUR at 460 mg/m^2/day, daily for 2 years, was more effective in reducing peritoneal recurrence than oral 5-FU at 115 mg/m^2/day, daily for 2 years, and that 5'-DFUR showed a more favorable disease-free survival (DFS) and overall survival (OS) rates than 5-FU (7). Furthermore, the results of a randomized controlled study indicated that, in stage II or III colorectal cancers, oral 5'-DFUR at 460 mg/m^2/day significantly reduced the risk ratio in comparison with oral 5-FU at 160 mg/m^2/day, in which ACT was administered for 1 year, in combination with the polysaccharide PSK at 3 g/day, daily (8). Since the prognosis of breast cancer is better and the clinical course is longer than these gastrointestinal cancers, ACT should be administered for a longer period in breast cancer than in these gastric or colorectal cancers. Therefore, the administration duration is one of the most important issues for the ACT of breast cancer.

The present study was designed to investigate the usefulness of oral 5'-DFUR by comparing the survival between groups which were given 5'-DFUR at 800 mg/body daily for 1 or 3 years after surgery for stage 1-3 breast cancer, especially with regard to the administration duration.

Patients and Methods

Patient registration and randomization. Several basic criteria had to be met before patients were included in the study: i) cytological proof of breast cancer, ii) a curative surgery (mastectomy or breast-conserving surgery), iii) post-surgical TNM stage 1 – 3, iv) performance status <3 (ECOG scale), and v) age under 81.

The contraindications to patient selection included: i) a concomitant malignant disease, ii) prior chemotherapy, endocrine therapy, radiotherapy or immunotherapy for breast cancer, iii) an active infectious disease, iv) severe anemia (hemoglobin <9.0 g/dl), leucopenia (<3,000/mm^3), thrombocytopenia (<100,000/mm^3), azotemia (creatinine >1.5 mg/dl), or liver dysfunction (GOT, GPT >100 U/ml) and v) pregnancy.

This clinical study was carried out by the Shimane Breast Cancer Study Group (SBCSG), Japan, whose members are listed in Table I. The end-point was survival after surgery, and the trial was originally designed to detect a difference in the 5-year OS rate between the 1-year 5'-DFUR and the 3-year 5'-DFUR groups. When the expected difference in OS rates between the groups was estimated at more than 10% (from 80% up to 90%) with 0.05 for alpha-error and 0.20 for beta-error during the 8 years of the study (3 years for recruiting and an additional 5 years for follow-up), the sample size (number of patients) needed in each group was calculated to range between 100 – 165 (210 – 347 in total) (9). Based on these criteria, the study was expected to accumulate 150 patients for each arm (a total of 300). The study was open to patients starting from January 1995. After surgery, the stage of the breast cancer was classified according to the UICC (TNM) stage classification system (10). Within 4 weeks after the surgery, the patients were pre-enrolled into the registration center. At 10 months after surgery, those patients who had received 5'-DFUR at more than 80% of the total protocol dose were randomly assigned into the 4 groups, according to a random number table communicated using a telephone- or fax-based center-call method. The registration center was located at the Department of Cardiovascular and Digestive Surgery, Shimane University School of Medicine, Japan.

According to Zelen's design (11), the patients were pre-randomized with minimization to balance the prognostic factors in individual institutes. Pre-randomization was stratified with respect to ER (+/–), pT (T0/1/2/3/4), nodal involvement (N0/1/2/3), surgery (breast-conserving or mastectomy) and menopause (pre/post).

Treatment protocol. The treatment protocol is summarized in Figure 1. The patients were given 5'-DFUR at 800 mg/body/day daily. The pre-menopausal patients were given gosereline acetate (GA, Zoladex^R) subcutaneously at 3.6 mg/body monthly for 3 years, and the post-menopausal patients received oral tamoxifen (TAM, Norvadex^R) at 20 mg/day, daily for 3 years. The patients were first assigned into the 2 arms: pre-menopausal and post-menopausal groups, and then each group was further classified into 2 arms, respectively. The pre-menopausal patients were classified into group-A (5'-DFUR for 1 year and GA for 3 years) and group-B (5'-DFUR for 3 years and GA for 3 years), whereas the post-menopausal patients were further classified into group-C (5'-DFUR for 1 year and TAM for 3 years) and group-D (5'-DFUR for 3 years and TAM for 3 years). If the patient was more than 70 years old or weighed less than 40 kg, 5'-DFUR was administered at 600 mg/body/day. If grade 2 or worse diarrhea was observed, then the 5'-DFUR administration was interrupted.

Examinations of the hematology, serum biochemistry, serum tumor markers, and evaluation of the symptomatic and performance status were routinely performed. If a recurrence appeared, the patients were offered alternative regimens.

Informed consent and the Ethics Committee. All patients and their families in the treatment group were fully informed with regard to the study aim, treatment program, expected side-effects and clinical benefits of the study, and informed consent was then obtained. The study was supervised by the supervisor and extramural reviewer, and the protocol was reviewed by the Ethics and Safety Committee.

Evaluation of side-effects. The patients underwent hematology, serum biochemistry and tumor marker examinations, and had their symptomatic status and performance status routinely reviewed at bimonthly intervals, and sometimes more frequently. Toxicity was evaluated according to the WHO standard criteria (12). If the toxicity was detected, the dose of 5'-DFUR was decreased

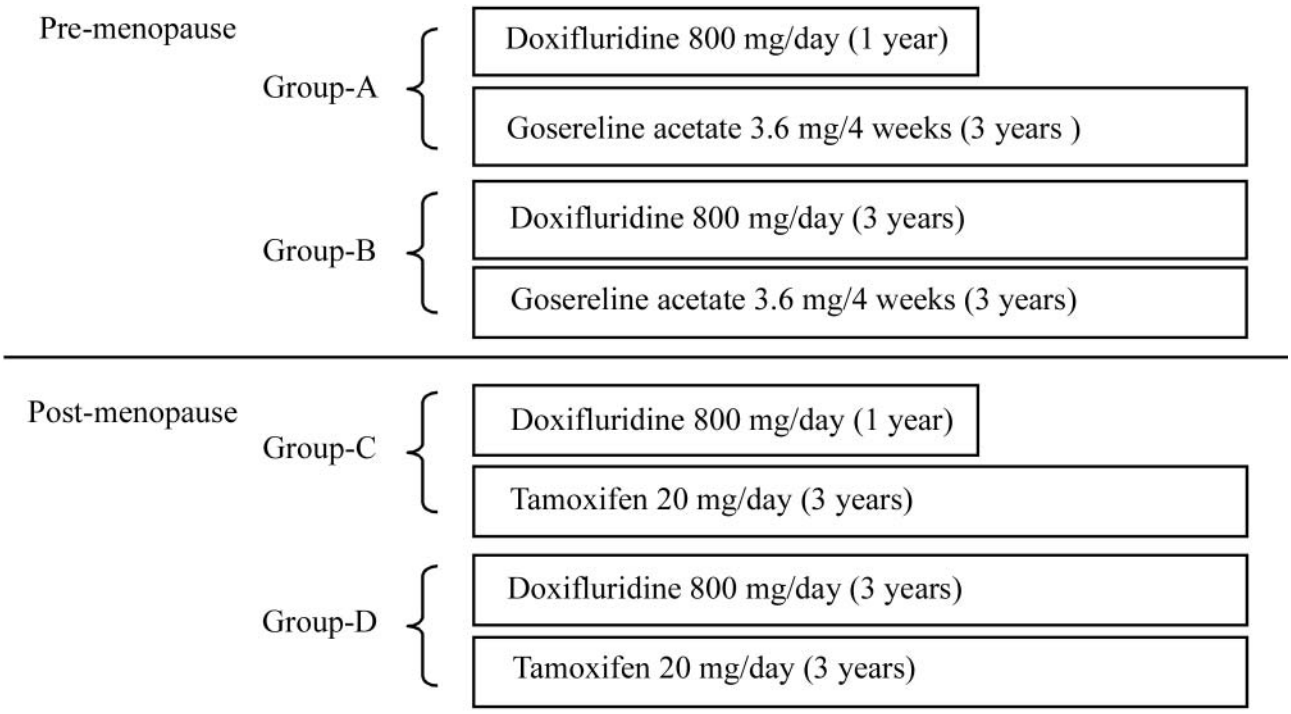

Figure 1. *Treatment protocol.*

according to each patient's condition (performance status, body weight, age, hematology and serum biochemistry).

Patient follow-up. All of the patients were followed by physical examination, general X-ray examination, ultrasonography, computed tomography, routine hematological and biochemical examinations, and serum tumor marker assays. The post-surgical status of all patients was surveyed in December 2004. The median follow-up period was 9.5 years.

Statistical evaluation. The Chi-square and Mann-Whitney *U*-tests were used to compare the backgrounds of patients between each group. The OS and DFS were the true end-points. Survival was calculated by the Kaplan-Meier method. A statistical comparison of the survival rates among the three groups was made by the generalized-Wilcoxon test and the log-rank test. Multivariate analysis of the maximum likelihood estimates using Cox's proportional hazard model was used to obtain the conditional risk of breast cancer-related death. All analyses were performed using StatView software (SAS Institute Inc., Cary, NC, USA), with a *p*-value less than 0.05 being considered statistically significant.

Results

The present study did not achieve the scheduled number of registrations, because the study-related rules and regulations, such as good post-marketing surveillance practice and the pharmaceutical manufacturers' association promotion code for prescription drugs, were changed (13, 14). Therefore, the support system and most of the institutes involved in the study could not accommodate the criteria from these regulations 2 years after the start of the study. However, during these 3 years, a total of 103 patients were tentatively enrolled. Most of these patients were enrolled during the first year, and 92 out of 103 patients were actually registered. Of the 92 registered patients, 1 was not given 5'-DFUR and 4 were given other kinds of chemotherapy, so ultimately 87 patients were eligible. Furthermore, 22 patients (25%) changed their administration groups after registration according to their own choice (Table II). The backgrounds are summarized in Table III, but there were significant differences in age and clinical stage: the 3-year administration group included significantly younger and lower stage patients.

Toxicities due to 5'-DFUR were seen in 8 patients: 3 liver dysfunction (grade 1 - 2), 2 gastric ulcer (grade 2), 1 diarrhea (grade 1), 1 leucopenia (grade 1) and 1 purpura (grade 1), respectively. 5'-DFUR was continued in 1 patient, interrupted for 1-3 months in 6 patients and discontinued in 1 patient. Furthermore, 2 patients with stomach ulcer and 1 with liver dysfunction were treated with medications.

The median follow-up duration was 9.5 years. The 5- and 10-year OSs were 95% and 89% for stage 1; 95% and 88% for stage 2; and 67% and 44% for stage 3, respectively. The 5- and 10-year DFSs were 90% and 82% for stage 1; 87% and 80% for stage 2; and 67% and 44% for stage 3, respectively.

Table II. *Registration and stratification.*

Pre-registered (n=103)	Registered (n=92)	Ineligible (n=5)	Eligible (n=87)	Cross-over of therapy groups (n=22)	Final stratification (n=87)
11 elimination *	Group-A (n=14)	3 other drugs	n=11	A → B n=2	n=15
	Group-B (n=23)	1 other drug	n=22	B → A n=6	n=18
	Group-C (n=28)	1 no-drug	n=27	C → D n=2	n=37
	Group-D (n=27)		n=27	D → C n=12	n=17

*7 withdrawal of consent, 3 recurrences within 1 year after surgery, and 1 death due to cerebral apoplexy.

Table III. *Comparative backgrounds of the patients.*

	1-year administration (Group-A and -C)	3-year administration (Group-B and -D)	
Number	52 (A=15, C=37)	35 (B=18, D=17)	*p*-value
Age	58.4±10.6	52.2±12.4	0.0156 (*t*-test)
Stage			
1	30	11	
2	20	20	0.0115 (*t*-test)
3	2	4	
pT			
1	35	15	
2	16	18	0.0216 (*U*-test)
3	1	1	
4	0	1	
pN			
n0	32	17	
n1	18	15	N.S. (*U*-test)
n2	2	2	
n3	0	1	
ER			
+	22	17	
–	16	12	N.S. (χ^2-test)
unclear	14	6	
Surgery			
Breast conserving	29	20	N.S. (χ^2-test)
Mastectomy	23	15	

The OS and DFS curves are shown in Figure 2. Although no differences were found in the OS or DFS between the administration groups, subset analysis demonstrated that, in pre-menopausal patients, the 3-year administration group showed a significantly higher overall survival rate than the 1-year administration group (Figure 3), but not in the post-menopausal patients.

The multivariate analyses are summarized in Table IV, and indicated that stage and administration duration of 5'-DFUR were significant variables for OS and that the administration duration of 5'-DFUR was a significant variable for DFS.

Discussion

As described above, the present study did not achieve the scheduled number of registrations, due to the changes in study-related rules and regulations. Although the number of registered patients was much smaller than initially expected, a significant result that the OS of the 3-year administration group was significantly higher than that of the 1-year administration group was obtained. Furthermore, multivariate analyses also demonstrated that the administration period of 5'-DFUR was a significant variable for improving the OS and DFS, and suggested that the long-term administration of 5'-DFUR may inhibit recurrence and improve the survival after breast cancer surgery.

The significance of these results, despite the small sample size, can be attributed to two factors. First, the follow-up duration was prolonged from 5 years to 10 years. The progression and clinical course of breast cancer are slower than those of gastrointestinal cancers, and 5 years may be too short to compare the OS or DFS between the treatment groups; 10 years may be the minimum. In fact, the recurrences in the stage 3 patients were seen within 5 years after surgery, but those in stage 1 or 2 patients were seen later than 5 years after surgery. These findings suggest that, in studies on breast cancer, the follow-up duration may need to be 10 years or more. The second factor is that 5'-DFUR was administered for 3 years. As described above, in clinical studies on gastric or colorectal cancers, the 1- or 2-year

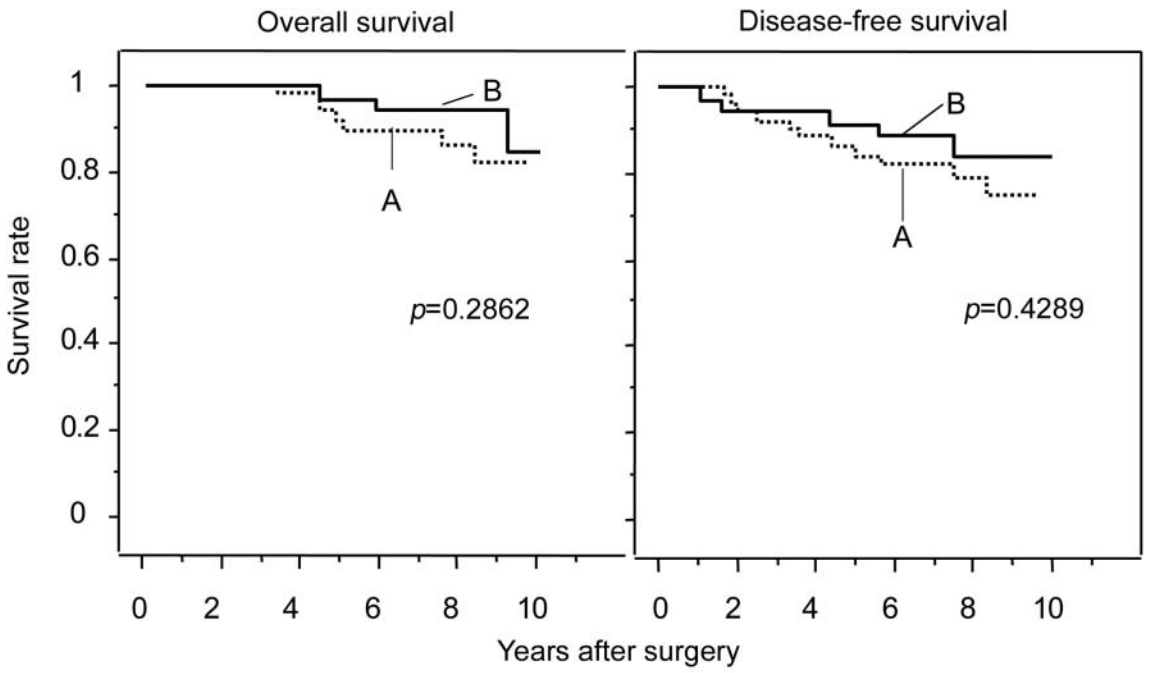

Figure 2. *Overall and disease-free survival curves. A. 1-year administration of 5'-DFUR (groups-A and -C, n=52). B. 3-year administration of 5'-DFUR (groups-B and -D, n=35).*

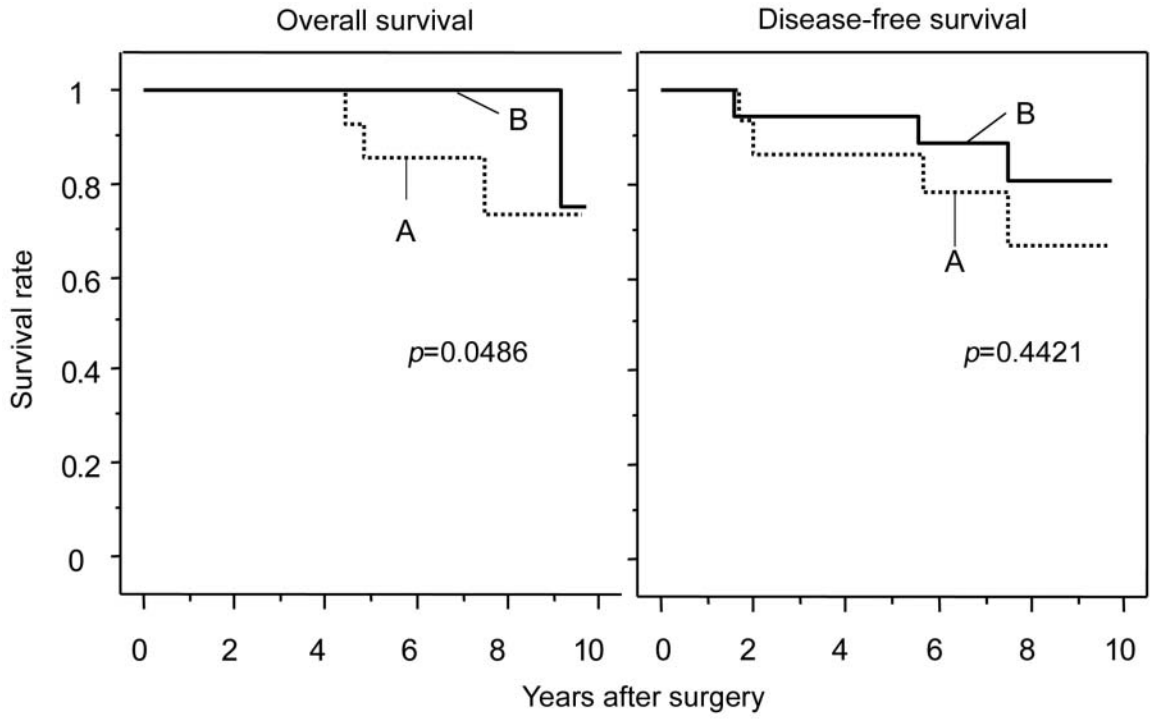

Figure 3. *Overall and disease-free survival curves in pre-menopausal patients. A. 1-year administration of 5'-DFUR (groups-A and -C, n=15). B. 3-year administration of 5'-DFUR (groups-B and -D, n=18).*

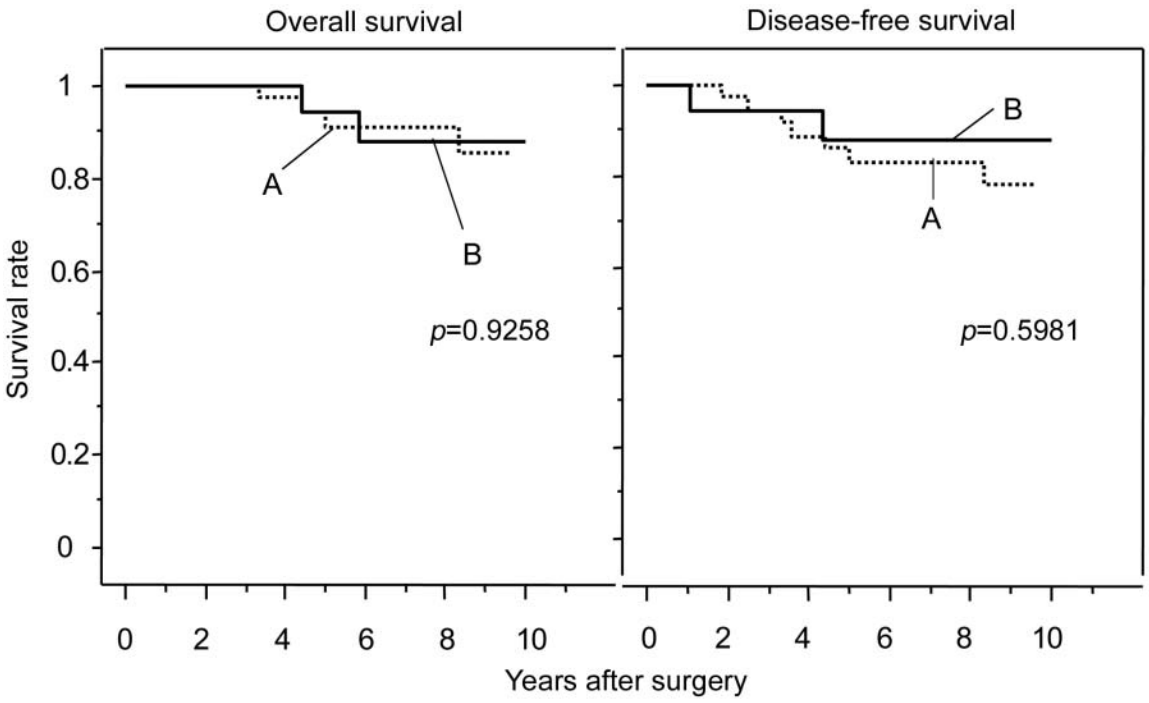

Figure 4. *Overall and disease-free survival curves in post-menopausal patients. A. 1-year administration of 5'-DFUR (groups-A and -C, n=37). B. 3-year administration of 5'-DFUR (groups-B and -D, n=17).*

administration of 5'-DFUR resulted in a significant improvement in survival in comparison with ACT with other chemotherapies (7, 8). Furthermore, a meta-analysis of five studies on tegafur plus uracil (UFT) (an oral fluoropyrimidine similar to 5'-DFUR) as a post-surgical ACT for breast cancer demonstrated that 2 years of administration significantly reduced the risk of recurrence (15). Accordingly, ACT with oral fluoropyrimidines may require an administration period of 2-3 years.

Since the present study was a doctor-conducted clinical study, which respected the patients' freedom of choice, the patients could change the treatment group even after registration. Therefore, about 25% of the patients changed their administration period, and the 3-year administration group included significantly younger and more advanced stage patients. These results suggest that those patients with a relatively high risk of recurrence (young and advanced stage) hoped to be given 5'-DFUR for 3 years rather than 1 year. On the other hand, the older and relatively early stage patients hoped to be given ACT for 1 year. These results imply that both the patients and doctors believed that the long-term administration of 5'-DFUR might be more beneficial to reduce recurrence.

In the present study, although the stage of the 3-year administration group was significantly more advanced than that of the 1-year administration group in the pre-menopausal patients, the OS of the 3-year administration group was significantly better than that of the 1-year administration group. These results indicate that the long-term administration of 5'-DFUR is beneficial for improving the survival of pre-menopausal patients. On the other hand, in post-menopausal patients, there were no differences in

Table IV. *Multivariate analyses by Cox's proportional hazard risk model.*

Variable	Overall survival		Disease-free survival	
	Risk ratio (95% confidence)	*p*-value	Risk ratio (95% confidence)	*p*-value
Age	0.989 (0.897 - 1.090)	0.8213	0.952 (0.893 - 1.015)	0.1329
Clinical stage	3.498 (0.940 - 13.018)	0.0618	1.749 (0.679 - 4.506)	0.2467
Duration of 5'-DFUR therapy	0.914 (0.823 - 1.014)	0.0903	0.920 (0.850 - 0.996)	0.0401
Radiation	1.371 (0.157 - 11.978)	0.7755	2.675 (0.624 - 11.467)	0.1850

the OS or DFS between the 1- or 3-year administration groups. Although 5'-DFUR is widely used for chemotherapy against breast cancer, especially in Japan, its role in ACT has remained unclear. To our knowledge, the present study is the first report demonstrating the significant improvement in the OS of breast cancer patients by ACT with 5'-DFUR. However, the sample size of the present study was too small to allow any definitive interpretations.

In conclusion, the present study supports the usefulness of 5'-DFUR for ACT against breast cancer, especially for pre-menopausal patients. However, a further clinical study with a much larger sample size is necessary to reach a conclusive result.

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References

1 Jakesz R, Hausmaninger H, Kubista E *et al*: Austrian Breast and Colorectal Cancer Study Group Trial 5. Randomized adjuvant trial of tamoxifen and goserelin *versus* cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer. J Clin Oncol *20*: 4621-4627, 2002.

2 Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet *35*: 1451-1467, 1998.

3 Stewart HJ, Prescott RJ and Forrest AP: Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years. J Natl Cancer Inst *93*: 456-462, 2001.

4 Swedish Breast Cancer Cooperative Group. Randomized trial of two *versus* five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. J Natl Cancer Inst *88*: 1543-1549, 1996.

5 Niitani H, Kimura K, Saito T *et al*: Phase II study of 5'-deoxy-5-fluorouridine (5'-DFUR) in patients with malignant cancer – a multi-institutional cooperative study. Gan To Kagaku Ryoho *12*: 2044-2051, 1985 (article in Japanese).

6 Tominaga T, Toi M, Abe O *et al*: 5'-BC Study Group (5'-DFUR Adjuvant Chemotherapy for Breast Cancer Study Group). The effect of adjuvant 5'-deoxy-5-fluorouridine in early stage breast cancer patients: results from a multicenter randomized controlled trial. Int J Oncol *20*: 517-525, 2002.

7 Takiguchi N, Nakajima N, Saitoh N, Fujimoto S and Nakazato H: A phase III randomized study comparing oral doxifluridine and oral 5-fluorouracil after curative resection of gastric cancer. Int J Oncol *16*: 1021-1027, 2000.

8 Koda K, Miyazaki M, Sarashina H *et al*: A randomized controlled trial of postoperative adjuvant immunochemotherapy for colorectal cancer with oral medicines. Int J Oncol *23*: 165-172, 2003.

9 Schoenfeld DA and Richter JR: Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biometrics *38*: 163-170, 1982.

10 TNM Classification of Malignant Tumours. Sixth Edition. International Union Against Cancer. John Wiley & Sons, Inc., 2002.

11 Zelen M: A new design for randomized clinical trials. N Engl J Med *300*: 1242-1245, 1979.

12 Miller AB, Hoogstraten B, Staquet M and Winkler A: Reporting results of cancer treatment. Cancer *47*: 207-214, 1981.

13 Japan Pharmaceutical Manufacturers Association. Japan Regulatory Affairs 2005. http://www.jpma.or.jp/english/library/pdf/2005.pdf

14 Japan Pharmaceutical Manufacturers Association. JPMA promotion code for prescription drugs 2004. http://www.jpma.or.jp/english/library/pdf/2005.pdf

15 Kasumi F, Yoshimoto M, Uchino J *et al*: Meta-analysis of five studies on tegafur plus uracil (UFT) as post-operative adjuvant chemotherapy for breast cancer. Oncology *64*: 146-153, 2003.

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