A Randomized Consent Design Trial of Neoadjuvant Chemotherapy with Tegafur Plus Uracil (UFT) for Gastric Cancer – A Single Institute Study

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Abstract. Objective: Various forms of neoadjuvant chemotherapy (NAC) have been applied in the treatment of gastric cancer. The present study was designed to assess the survival benefits of NAC with UFT (tegafur plus uracil) for gastric cancer, as a randomized consent trial as described by Zelen. Patients and Methods: The present study included 295 patients with resectable gastric cancer between 1991 and 1999. After the patients had been pre-randomized into two groups, a control (no-NAC) group (n=120) and a treatment group (n=175), the treatment group patients were then further stratified into two groups, namely those who wished to join the control group and those who wished to receive NAC with UFT (NAC-UFT group). Patient outcome was surveyed in January 2003. Results: Randomization did not necessarily result in an appropriate registration of the patients, and ultimately 193 patients were included in the control group and 102 patients received NAC-UFT. The NAC-UFT was well tolerated by the patients and side-effects were not severe. However, the NAC-UFT group included the patients with significantly higher stages of cancers than the control group. The survival benefit of NAC-UFT was seen in stage 2 or 3 patients, and multivariate analysis also revealed that NAC-UFT was a significant prognostic variable, as were pT, pN, M and the level of nodal dissection, but patient age, gender and histological grade were not significant variables. Conclusion: NAC-UFT may be beneficial in the improvement of survival rate after gastric cancer surgery and this treatment modality is worthy of further study with a larger patient sample size.

In order to improve patient survival after gastric cancer surgery, neo-adjuvant chemotherapy (NAC) has been applied during the last decade. The major aim of NAC is preoperative down-staging to enable more curative surgery. Recently, NAC has become an important option among therapies for gastric cancer. Most NACs have employed intensive regimens including cisplatin (CDDP, P), Adriamycin (ADR, A), 5-fluorouracil (5-FU, F), etoposide (VP-16, E) and leucovorin (LV, L), such as the EAP, FP, PLF and P-ELF regimens (1-5). These NACs have resulted in a 20% - 40% response rate (RR), however they frequently cause serious side-effects and result in the interruption or postponement of surgery. Although it has been reported that the response to NAC was shown by analysis of sequential phase II studies to be the most important independent predictive factor for survival (6), the true effects of NAC, especially patient survival benefits, are still unclear. Furthermore, there have been only a few randomized studies of NAC, all with a relatively small sample size (7-9).

In Japan, NAC for gastric cancer has differed from that in Western countries, because many NAC regimens have included oral fluoropyrimidines such as 5-FU and UFT (10-12). Among these oral fluoropyrimidines, UFT, a mixture of uracil and tegafur (FT) at 4:1, is the most popular agent in Japan. The RR to UFT alone in gastric cancer patients has been reported to be 27.7% in Japan (14). The present study was designed to evaluate the clinical benefits, especially survival benefits, of NAC with UFT (NAC-UFT). This study was designed as a prospective study, but it was not a standard randomized control one. In accordance with the advice of the ethical committee, the randomized consent design devised by Zelen was applied (15) and the application of NAC-UFT was selected according to each patient’s wish. After pre-randomization of the patients
Study design. This study was designed to assess the survival benefits of NAC-UFT for patients with resectable gastric cancer. The study was first designed as a standard randomized control study, however discussion with the ethical committee (Dr. Kazuhisa Ohgaki, President of Kyoto Police Hospital, Kyoto, Japan; Professor Tsuyoshi Yamamoto, Asahi University, Gifu, Japan; Dr. Kazuhiko Tsuboi, President of Sato Hospital, Hirakata, Japan) revealed that it is difficult to apply standard randomized control methods to NAC, because it is difficult to evaluate the clinical stage of gastric cancer before surgery, and NAC might change the clinical features of the gastric cancer. The ethical committee did not approve a randomized study for NAC, for the following reasons: if unexpected side-effects occurred and the surgery had to be postponed, or if the tumor did not respond to the NAC-UFT and the disease progressed, the patients might lose a chance to undergo curative surgery and these kinds of risks and disadvantages would necessarily be divided among the respective patients by randomization. Therefore, we designed this study as a randomized single-consent trial, as proposed by Zelen (15), in which the patients decided which groups they wished to be enrolled into. After enrolment, the patients were pre-randomized into two groups, a control group and a treatment group. In accordance with Zelen’s method, the consent of the patients in the control group was not sought because no-NAC is the standard treatment for curative resection of gastric cancer. The patients in the treatment group were then further stratified into two groups, a control group and a NAC-group, according to the patients’ wishes. Furthermore, the study was performed in a single institute, because the clinical benefits and side-effects of NAC were unclear and the patients required careful monitoring. The survival benefits were evaluated by comparing the survival rate at each stage after surgery between the control group and the NAC group and then the prognostic significance was analyzed by a multivariate analysis, because it is difficult to evaluate the clinical stage of gastric cancer before surgery.

The endpoint was survival after surgery and the trial was originally designed to detect a difference in 5-year survival rate between the control group and the NAC-UFT group. In our department, the overall 5-year survival rate after gastric cancer surgery between 1982 and 1992 was about 70%. When the expected difference in survival rates between the groups was estimated as more than 10% (from 70% up to 80%), with 0.05 for alpha-error and 0.20 for beta-error during the 10 years of the study (5 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 from 90-213 (totally 189-447) (18). The distribution of the patients was set as 40% for the control group and 60% for the treatment group, respectively, since we expected about 15%-20% of the patients in the treatment group would not wish to receive NAC-UFT and would therefore be enrolled in the control group. As such, the final distribution of the patients was expected to be 50% in each group. Furthermore, it was expected that the patient enrolment target could be achieved in 4 - 7 years, because about 60 patients with gastric cancer undergo gastrectomy annually in our department.

### Table I. Efficacy criteria for primary lesions (Japanese Research Society for Gastric Cancer).

<table>
<thead>
<tr>
<th>Lesions</th>
<th>CR</th>
<th>PR</th>
<th>NC</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Measurable lesions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1) Bidimensionally measurable</td>
<td>Complete disappearance</td>
<td>Decrease ≥ 50%</td>
<td>Decrease &lt; 50% or increase &lt; 25%</td>
<td>Increase ≥ 25%</td>
</tr>
<tr>
<td>(Bidimensional product: Ax B)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2) Unidimensionally measurable Linear measurement</td>
<td>Complete disappearance</td>
<td>Decrease ≥ 50%</td>
<td>Decrease &lt; 50% or increase &lt; 25%</td>
<td>Increase ≥ 25%</td>
</tr>
<tr>
<td>b. Evaluable but not measurable lesions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unidimensionally measurable Linear measurement</td>
<td>Complete disappearance</td>
<td>Marked (estimated decrease ≥ 50%)</td>
<td>No changes or estimated decrease &lt; 50%</td>
<td>Progression or new lesions</td>
</tr>
<tr>
<td>c. Diffusely infiltrating lesions:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric lumen of the affected region</td>
<td>Complete disappearance</td>
<td>Enlargement ≥ 50%</td>
<td>No changes or enlargement &lt; 50%</td>
<td>Progression or new lesions</td>
</tr>
</tbody>
</table>

CR, complete response; PR, partial response; NC, no changes; PD, progress of disease.
Patient enrolment. Two basic criteria had to be met before NAC-UFT administration: 1) histological or cytological proof of gastric cancer and preoperative diagnosis to be curatively resectable, and 2) performance status (PS) 0 - 3 (ECOG scale). Contraindications included: 1) total disability (PS=4, ECOG score), 2) prior chemotherapy, radiotherapy or immunotherapy within 4 weeks, 3) an active infectious disease, 4) severe anemia (hemoglobin < 9.0g/dl), leukopenia (< 3,000/mm³), thrombocytopenia (< 70,000/mm³), azotemia (creatinine > 2.0 mg/dl), or liver dysfunction (GOT, GPT and alkaline phosphatase > 4-fold of normal limits), 5) severe heart disease or a concomitant malignant disease, and 6) pregnancy.

All patients and their families in the treatment group were fully informed with regard to the study aim, treatment program and expected side-effects and clinical benefits of the study, and informed consent was obtained. After surgery, the stage of gastric cancer was classified according to the UICC (TNM) stage classification system (19).
Treatment protocol for NAC with UFT. The patients were administered UFT orally within 1 hour after meals. The administration usually started from the day of the first visit to the outpatient ward and the patients were given the last UFT at 6 p.m. on the day before surgery. The administration period was dependent on the waiting period for surgery, which was usually more than 2 weeks. UFT is a mixture of uracil and FT, but the dose of UFT is usually expressed as the dose of FT and the dose of UFT was set at 8 mg/kg/day for the patients under 70 years and at 6 mg/kg/day for those over 71 years. UFT is an oral agent and usually administered in capsules or as granules. One capsule contains 100mg of FT and one granule package includes 150 mg of FT.

Evaluation of side-effects. Before surgery, the patients in the NAC-UFT group were examined regarding hematology, serum biochemistry and tumor markers, plus symptomatic status and performance status, routinely at biweekly intervals, or sometimes more frequently. Toxicity was evaluated according to the WHO standard criteria (20). If toxicities occurred, the dose of UFT for each patient was decreased according to each patient’s condition (PS, body weight, age, hematology and serum biochemistry).

Evaluation of objective response (OR). The objective response (OR) was evaluated as complete response - progress of disease (CR – PD) by endoscopy, upper gastrointestinal examination and CT scan, according to the criteria of the Japanese Gastric Cancer Association (21), which is summarized in Table I. If possible, the size of the primary lesion was assessed before and after UFT administration (usually 1 or 2 days before surgery). Assessments were made more frequently in some patients. If the tumor was evaluated to be progressive, NAC-UFT was interrupted. The duration of the response was not included in the evaluation of the objective response because all patients underwent surgery.

Post-surgical adjuvant chemotherapy (ACT). The patients were treated with ACT according to their post-surgical stage classification. Stage 1-3 patients received ACT with UFT for 1-3 years. Stage 4 patients received intensive chemotherapy with 1-4 courses of CDDP, 5-FU and Epirubicin (Epi) (FPEPIR regimen) (22,23) and then received oral UFT daily as long as possible.

Follow-up of patients. All the patients were followed-up by physical examination, general X-ray examination, ultrasonography (US), computed tomography (CT), routine hematological and biochemical examinations and serum tumor marker assays. The post-surgical status of all patients was surveyed on January 15, 2003. The median follow-up period was 83 months.

Statistical evaluation. The Mann-Whitney U-test was used to compare patient backgrounds among the groups. The cumulative survival rates were calculated according to the Kaplan-Meier method and were compared by the generalized-Wilcoxon test. A multivariate analysis of Cox’s proportional hazard risk model was used to obtain the conditional risk of gastric cancer-related death. Statistically significant differences were defined at \( p < 0.05 \). The statistical analysis was carried out using SAS computer software.

Results

Patient enrolment. Between 1991 and 1999, a total of 295 patients with gastric cancer were enrolled in the study, of whom 120 patients were initially pre-randomized into the control group and 175 patients were assigned into the treatment group. However, randomization according to the patients’ will resulted in an unbalanced distribution of the patients: a total of 73 patients in the treatment group did not wish to receive NAC-UFT and were subsequently enrolled in the control group. Overall, a total of 102 patients were registered in the NAC-UFT group and a total of 193 patients...
were registered in the control group (Figure 1). The number of patients enrolled in the NAC-UFT group was much smaller than expected. One major reason for patients not wishing to receive NAC-UFT was that many whose cancers were diagnosed as early stage cancer hoped instead to undergo surgery as soon as possible, although their post-surgical clinical stages were found to range between 1 and 4. The other reason for not wishing to receive NAC-UFT was that patients feared a delay in surgery, if unexpected side-effects associated with NAC-UFT occurred.

Patient background. Comparative profiles of the patients in the two groups are summarized in Table II. The statistical analyses revealed that there were significant differences in several background factors of the patients: the NAC-UFT group included patients with significantly higher stages of cancer ($p=0.0042$): the mean stage was $1.81 \pm 1.14$ for the control group and $2.14 \pm 1.26$ for the NAC-UFT group. Furthermore, the NAC-UFT group tended to include higher histological grades of cancers ($p=0.0570$).

Dose and period of NAC-UFT. The dose and period of drug administration are summarized in Table III. In 14 patients, the dose and period were reduced due to the side-effects such as anorexia, myelo-suppression or liver dysfunction: 10 patients were administered UFT at $4.0 \text{ mg/kg/day}$ and 9 patients were administered UFT for less than 9 days. The mean administration dose and totally administered dose were $6.9 \pm 2.0 \text{ mg/kg/day}$ and $7.67 \pm 3.80 \text{ g}$, respectively, and the mean administration period was $20.8 \pm 8.8$ days.

Figure 2. Representative cases responding to NAC-UFT.
A. H.K., 70-year-old male patient. He had a IIc-like advanced gastric cancer at stomach angle, which was proved to be a moderately-differentiated adenocarcinoma by biopsy. He was administered UFT at $300 \text{ mg/day}$ ($5.7 \text{mg/kg}$) for 15 days. A-1. Before UFT: ulcerative lesion at stomach angle. A-2. After UFT: scar formation of ulcerative lesion and the objective response was evaluated as PR.
B. K.S., 58-year-old male patient. He had two ulcerative lesions at stomach angle, which were proved to be poorly-differentiated adenocarcinomas by biopsy. He was administered UFT at $300 \text{ mg/day}$ ($6.8 \text{mg/kg}$) for 14 days. B-1. Before UFT: two ulcerative lesions at stomach angle. B-2. After UFT: scar formation of ulcerative lesions and the objective response was evaluated as PR.
Side-effects of NAC-UFT. The NAC-UFT was well tolerated by the patients and the side-effects were not serious before surgery (Table V): anorexia in 14 patients (13.7%), leukopenia in 3 patients (2.9%), thrombocytopenia in 2 patients (2.0%) and slight liver dysfunction in 2 patients (2.0%). Three patients suffered from bleeding from the stomach due to the necrosis of the cancer and one of them received an emergency gastrectomy. Postoperative complications were seen in 15 patients (14.7%): suture insufficiency in 4 cases, perforative peritonitis in 1 case, enteritis due to MRSA in 2 cases and liver dysfunction (serum GOT level > 50 IU/L) in 8 patients (7.8%), in 2 of whom serum GOT levels increased to higher than 500 IU/L. All of these patients were cured by conservative therapy or re-operation. The frequencies of these post surgical complications were higher in the NAC-UFT group than in the control group.

Objective response (OR) to NAC-UFT. OR was evaluated in 87 patients. In no patients did disease appear to progress during NAC-UFT treatment and 2 CRs and 27 PRs were observed.
Table VI. Multivariate analysis by Cox's proportional hazard risk model. *

<table>
<thead>
<tr>
<th>Variables</th>
<th>Conditional risk ratio (95% confidence limit)</th>
<th>p-value (Chi-square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distant metastasis</td>
<td>5.178 (3.042-8.814)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PT (primar tumor)</td>
<td>1.914 (1.520-2.408)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>pN (nodal involvement)</td>
<td>1.448 (1.170-1.794)</td>
<td>0.0007</td>
</tr>
<tr>
<td>NAC-UFT</td>
<td>0.531 (0.327-0.862)</td>
<td>0.0105</td>
</tr>
<tr>
<td>Nodal dissection</td>
<td>0.690 (0.501-0.949)</td>
<td>0.0224</td>
</tr>
<tr>
<td>Histological grade</td>
<td>1.248 (0.986-1.580)</td>
<td>0.0658</td>
</tr>
<tr>
<td>Age</td>
<td>1.003 (0.982-1.025)</td>
<td>0.7646</td>
</tr>
<tr>
<td>Gender</td>
<td>1.070 (0.634-1.805)</td>
<td>0.7996</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>1.067 (0.604-1.885)</td>
<td>0.8231</td>
</tr>
</tbody>
</table>

* dependent variable, month; censoring variable, gastric cancer-related death

observed (response rates, 33.3%) (Table VI). The representative cases are shown in Figure 2. Statistical analyses revealed that there was no correlation between the OR and clinicopathological factors such as age, gender, clinical stage, histology and dose or administration period of UFT (data not shown).

Survival rate. The median follow-up period was 83 months, ranging between 37 and 140 months. The overall survival curves after gastrectomy are shown in Figure 3. There were no significant differences in survival rates between the control group and the NAC-UFT group in patients overall (p=0.6878). At each stage, the survival rate of the NAC-UFT group was higher than that of the control group and the differences were statistically significant in stages 2 and 3 (p=0.0486) (Figure 4). Further survival analyses revealed that survival benefits of NAC-UFT tended to be seen in the patients with nodal involvement (pN1-2) (p=0.0065) (Figure 5), but there were no differences in survival in each pT category between the NAC-UFT group and the control group (data not shown). On the other hand, in the NAC-UFT group, a survival benefit was seen in the patients whose primary tumors responded to UFT, especially in stage 2 or 3 patients (Figure 6).

Multivariate analysis. Since the statistical analyses revealed that the NAC-UFT group included the patients with significantly more advanced stages of cancers (Table II), a multivariate analysis by Cox's proportional hazard risk model was applied to evaluate the real implication of NAC-UFT for patient survival. The results are summarized in Table VI, demonstrating that NAC-UFT was one of the significant variables affecting survival, as were pT, pN, M and the level of nodal dissection, but patient age, gender, histological grade and post surgical adjuvant chemotherapy were not significant variables.

Discussion

It is still unclear whether NAC contributes to improved survival after surgery or not. To our knowledge, there have been only three reports on this subject, perhaps because it is difficult to define the effect of NAC in a phase III setting. The present study was designed as a so-called randomized consent-design, as devised by Zelen (15), because it is difficult to evaluate the clinical stage of gastric cancer before surgery and to randomize the patients for NAC from an ethical viewpoint, as explained in the study design. Therefore, in the present study, multivariate analysis and the survival rates at each stage were used to screen the survival benefits of NAC-UFT in gastric cancer surgery.

In the present study, the patient distribution was quite unbalanced; among the enrolled patients, about one-third received NAC-UFT and the other two-thirds did not. In addition, the stage distribution was significantly different between the control group and the NAC-UFT group, the NAC-UFT group including the patients with higher stages of cancer. In the process of obtaining informed consent, the patients, who had been diagnosed to have advanced stages of cancer, tended to hope for a down-staging of cancer by receiving NAC treatment to achieve a more curative surgery. In contrast, those who had been diagnosed to have early stage cancer were not so interested in preoperative down-staging, but most of them hoped to receive surgery as soon as possible. As a result, the first pre-randomization (40% for control and 60% for the treatment group) was poor and we should have researched the patients' wishes and study trends for NAC before planning the study. Although the present study did not obtain an appropriate distribution of patients registered, it may be the first clinical study using Zelen's randomized consent-design to evaluate the benefits of NAC and we believe that valuable information regarding patients' wishes with respect to treatment in case of gastric cancer was obtained for application in future clinical studies. Furthermore, although it was difficult to set up an appropriate pre-randomization, Zelen's randomized consent-design seemed to be useful from an ethical viewpoint, because it minimized the stress associated with obtaining informed consent. Accordingly, if the subjective patients had been strictly restricted, for example preoperative stage 2 or 3, and the pre-randomization had been more carefully set-up, this consent trial design would be beneficial in the evaluation of the phase III study of NAC.

To our knowledge, there have been only three reports on the randomized setting of NAC. Yonemura et al. reported that the rate of potentially curable cases was higher in the NAC group (n=29) with the PMUE regimen (CDDP + MMC + UFT + VP-16) than in the control group, which received surgery first and thereafter received post-surgical PMUE (n=26) (38% in the former versus 15% in the latter); also in the resection cases, the survival rate was significantly
in overall survival rates. This may be due to the unbalanced consent design seems to be beneficial for clinical trials with larger patient sample size. Furthermore, Zelen’s randomized staging of the gastric cancer. These results suggest some of the difficulties in evaluating the benefits of NAC and establishing a randomized setting. The other previous phase II studies included fewer than 100 patients (1-6) and, to our knowledge, the present study had the biggest sample size and was the second to demonstrate a survival benefit of NAC. The present study used UFT for the NAC regimen. This was a special characteristic of the study because previous studies of NAC have utilized very intensive chemotherapies (1-9). UFT is widely used for the chemotherapy of digestive organ cancers in Japan and the RRs of various cancers to UFT are reported to be comparable to those of intensive i.v. chemotherapies including CDDP, which usually achieve a 20% - 40% RR for gastric cancer (14). In addition, the side-effects of UFT are relatively less severe (14). Recently, it has also been reported that combination regimens with UFT + LV or UFT + LV +CDDP + Epi achieved a high RR in gastric cancer and were well tolerated (24-26). In the present study, NAC-UFT achieved a 33% RR as a final result and the side-effects were not too severe. These results were compatible with the previous report (14). Accordingly, the previous reports and the present results suggest that UFT may be applied for NAC instead of intensive intravenous chemotherapy. In the present study, there were no significant differences in overall survival rates. This may be due to the unbalanced distribution of the stages between control and treatment groups. However, the survival rate of the NAC-UFT group was significantly higher in stages 2 and 3 than that of the control group, and the multivariate analysis also demonstrated that NAC-UFT was a significant variable related to improved survival after gastric cancer surgery. Comparisons of 5-year survival rates with historical survival rates in our department and other institutes are summarized in Table VII (27-30), which indicates that a survival benefit of NAC-UFT was seen in patients with stage 3 gastric cancers. These results suggest that NAC-UFT is one of the beneficial treatment options to improve the survival of gastric cancer patients. However, it is unclear what mechanisms are responsible for the survival benefits of NAC-UFT. In the present study, subcategorized analyses revealed that survival benefits of NAC-UFT tended to be seen in the patients with nodal involvement (pN1-2) (p=0.0665) (Figure 5). On the other hand, in the NAC-UFT group, a survival benefit was seen in the patients whose primary tumors responded to UFT, especially in stage 2 or 3 patients (Figure 6). These results suggest that NAC-UFT improved survival through down-sizing of the primary tumor as well as inhibiting nodal involvement. As previously reported, in the NAC-UFT group, endoscopic examination showed that advanced gastric cancers became early gastric cancers and metastatic lesions in liver or lymph nodes obviously decreased in size in several patients (16,17). The response did not always mean a down-staging, but these observations clearly demonstrated that preoperative down-sizing of the primary and metastatic lesions was achieved by UFT. In conclusion, NAC-UFT may be beneficial in improvement of the survival rate after gastric cancer surgery and this treatment modality is worthy of further study with a larger patient sample size. Furthermore, Zelen’s randomized consent design seems to be beneficial for clinical trials with NAC, if pre-randomization can be appropriately set-up.

Table VII. Comparative 5-year survival rates (%) between patients in the present study and other institutions.

<table>
<thead>
<tr>
<th>Stage</th>
<th>NAC-UFT</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>100.0(39)</td>
<td>95.5(102)</td>
</tr>
<tr>
<td>1B</td>
<td>70.0(8)</td>
<td>77.9(21)</td>
</tr>
<tr>
<td>3A</td>
<td>83.3(9)</td>
<td>41.7(16)</td>
</tr>
<tr>
<td>3B</td>
<td>53.3(6)</td>
<td>33.3(19)</td>
</tr>
<tr>
<td>4</td>
<td>27.4(25)</td>
<td>13.9(27)</td>
</tr>
</tbody>
</table>

* 1982-1999 (n=592)
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References


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