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Safety of Adjuvant Oral Uracil-Tegafur Therapy in Older Patients With Resected Non-small Cell Lung Cancer

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Abstract

Background/Aim: Oral uracil-tegafur (UFT) therapy as adjuvant chemotherapy (ACT) has demonstrated efficacy and is widely used for patients with completely resected early-stage non-small cell lung cancer (NSCLC). However, most previous clinical trials have enrolled patients aged ≤75 years, and evidence regarding the safety of UFT in older patients remains limited. This study aimed to evaluate the safety of adjuvant UFT therapy in older patients.

Patients and Methods: We retrospectively analyzed 101 patients who underwent curative lung resection and were pathologically diagnosed with stage IA3 or IB NSCLC (TNM 8th edition) at our department between January 2017 and January 2023. Patients were stratified into older (aged ≥75 years) and younger (aged <75 years) groups, and the administration rate of UFT therapy was compared. Among patients who received UFT, dose, treatment duration, completion rate of 24 months, and incidence of adverse events were further evaluated.

Results: The older group included 42 patients (42%). The UFT administration rate was 63% in the younger group and 62% in the older group, with no statistically significant difference. UFT dose, completion rate of 24 months, and incidence of adverse events in older patients appeared not to be inferior to those in younger patients. However, in the standard-dose group (400 mg daily), the older group tended to have a lower completion rate and a higher incidence of adverse events.

Conclusion: Adjuvant UFT therapy was generally safe in patients aged ≥75 years. Nevertheless, dose adjustments may be necessary in older patients. In a super-aging society, these findings underscore the importance of considering not only chronological age but also each patient's overall condition when making decisions regarding adjuvant UFT therapy.

Keywords: Aged, antineoplastic agents, adjuvant, carcinoma, non-small-cell lung, uracil.

Introduction

Surgical resection remains the most effective curative treatment for stage I non-small cell lung cancer (NSCLC) (1). However, even in early-stage lung cancers, postoperative recurrence is a common issue, with recurrence rates of approximately 35% for stage IA3 and 40% for stage IB (2).

Adjuvant chemotherapy (ACT) following surgery plays a key role in preventing recurrence. In Japan, the efficacy of uracil-tegafur (UFT) has been demonstrated in several

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randomized controlled trials and meta-analyses, and it has long been adopted as a standard adjuvant regimen (3-5). In particular, the JCOG0707 trial confirmed the validity of UFT even in comparison with S-1 and further established its acceptable safety profile (6). Moreover, despite the widespread use of molecular targeted therapies and immune checkpoint inhibitors, real-world data continue to support the clinical benefit of adjuvant UFT therapy (7).

However, most clinical trials and retrospective studies have primarily enrolled patients younger than 75 years, leaving limited evidence regarding the safety and efficacy of ACT in older patients. Japan entered a super-aging society in 2007, when individuals aged ≥65 years accounted for more than 21% of the population (8). Thus, the aging of patients eligible for ACT is inevitable. Although evidence on the efficacy of UFT continues to accumulate (9, 10), data addressing its safety in older patients remain insufficient.

Therefore, we conducted a retrospective analysis of the administration rate and safety of adjuvant UFT therapy in patients with NSCLC aged ≥75 years who underwent surgery at our institution.

Patients and Methods

Patients. We retrospectively reviewed patients who underwent curative pulmonary resection for primary NSCLC at our institution between January 2017 and January 2023. Eligible patients had a tumor diameter of 21-40 mm and were pathologically diagnosed with stage IA3 or IB disease according to the 8th edition of the TNM classification (UICC/AJCC) (11). Patients with tumors ≤20 mm in size who were diagnosed as pathological stage IB (pT2a) due to visceral pleural invasion were excluded. Clinical data were collected from electronic medical records.

Data collection and analysis. Eligible patients were stratified into two groups: those aged ≥75 years (older group) and those aged <75 years (younger group). The administration rate of adjuvant UFT therapy was compared between groups. In patients who received UFT, we further compared UFT dose, treatment duration, and incidence of adverse events between groups.

The UFT administration protocol followed the phase III trial cited in the Japanese lung cancer treatment guidelines (3). UFT was administered as 100 mg capsules (tegafur 100 mg plus uracil 224 mg), and the standard administration protocol was 250 mg/m^2/day given orally for 24 months. The dose was rounded up or down to the nearest 100 mg. Because most patients in the reference trial received 400 mg daily, this was defined as the standard-dose group in this study. Patients who started treatment at 300 mg daily or required dose reduction due to adverse events were categorized into the reduced-dose group. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Statistical analyses were performed using the chi-square test, with a significance threshold of $p<0.05$.

Ethical considerations. This study was conducted in accordance with the Declaration of Helsinki (revised in 2017) and was approved by the Ethics Committee of Toyota Kosei Hospital (approval number: 2025-ST10). Given the retrospective nature of this study, individual informed consent was waived, and an opt-out approach was employed.

Results

Patients (Table I). A total of 101 patients met the eligibility criteria. The younger group (<75 years) included 59 patients, and the older group (≥75 years) included 42 patients. Patient characteristics are summarized in Table I. Median ages were 68 years in the younger group and 78 years in the older group. The majority of patients were male, and nearly all had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0 or 1. Lobectomy was the most frequently performed surgical procedure, although some

Table I. *Patient characteristics.*

	No. of patients (%)	
Total (N=101)	Younger group (<75 years) (N=59)	Older group (≥75 years) (N=42)
Age (years; median [range])	68 [46-74]	78 [75-86]
Sex (male)	37 (62.7)	30 (71.4)
ECOG-PS		
0	49 (83.1)	30 (71.4)
1	9 (15.3)	12 (28.6)
2-4	1 (1.7)	0
Surgical procedure		
Wedge resection	7 (11.9)	9 (21.4)
Segmentectomy	2 (3.4)	1 (2.4)
Lobectomy	50 (84.7)	31 (73.8)
Pneumonectomy	0	1 (2.4)
Histology		
Adenocarcinoma	46 (78.0)	30 (71.4)
Squamous cell carcinoma	13 (22.0)	12 (28.6)
p-Stage		
IA3	32 (54.2)	24 (57.1)
IB	27 (45.8)	18 (42.9)

All values are presented as numbers (percentage) or as medians [ranges] where indicated. ECOG-PS: Eastern Cooperative Oncology Group performance status.

Table II. *Patients receiving uracil-tegafur (UFT).*

	No. of patients (%)		*p*-Value
Total (N=101)	Younger group (<75 years) (N=59)	Older group (≥75 years) (N=42)	
UFT-treated patients	37 (62.7)	26 (61.9)	0.934
Non-UFT-treated patients	22 (37.3)	16 (38.1)	

All values are presented as numbers (percentage).

patients underwent limited resections, including segmentectomy or wedge resection. Pathological stage IA3 accounted for 55% of patients, and adenocarcinoma was the most common histological type.

Administration rate of adjuvant UFT therapy (Table II). Administration rate of adjuvant UFT therapy is shown in Table II. Adjuvant UFT therapy was received by 37 patients (63%) in the younger group and 26 patients (62%) in the older group, with no significant difference between groups. Reasons for not receiving UFT are summarized in Table III. The most common reason for physicians not recommending UFT therapy was squamous cell carcinoma histology. Among older patients, physicians judged that UFT therapy should be avoided due to advanced age in only 14.3% of patients. Furthermore, approximately 10% of patients in both groups declined UFT therapy despite physician recommendation.

Table III. *Reasons for not receiving uracil-tegafur (UFT).*

	No. of patients (%)	
Total (N=101)	Younger group (<75 years) (N=59)	Older group (≥75 years) (N=42)
Non-UFT-treated patients	22 (37.3)	16 (38.1)
Physician's decision		
Squamous cell carcinoma	8 (13.6)	7 (16.7)
Interstitial pneumonia	5 (8.5)	0
Impaired pulmonary function	1 (1.7)	4 (9.5)
Impaired renal function	0	4 (9.5)
Other comorbidities	6 (10.2)	3 (7.1)
Unknown	2 (3.4)	0
Advanced age	0	6 (14.3)
Patient declined	7 (11.9)	7 (16.7)

All values are presented as numbers (percentage). Multiple reasons per patient were allowed; percentages may not sum to 100%.

Analysis of patients receiving UFT (Table IV). Analysis of patients receiving UFT are summarized in Table IV. Treatment duration was stratified into 0-3, 4-23, and 24 months. In the younger group, six (16%), nine (24%), and 22 (60%) patients were classified into each category, respectively; in the older group, nine (35%), five (19%), and 12 (46%) patients were classified into each category. Although no statistically significant differences were observed between groups, early discontinuation within three months was more frequent in the older group, while completion of 24 months of therapy was more common in the younger group.

Stratification by UFT dose showed that in the younger group, 21 patients (57%) received the standard dose and 16 (43%) received a reduced dose, whereas in the older

group, 13 patients (50%) received the standard dose and 13 (50%) received a reduced dose. No significant differences in the proportion of patients receiving the standard dose were observed between groups.

No UFT-related deaths occurred during the study period. Adverse events of any grade were observed in 19 patients (51%) in the younger group and 15 (58%) in the older group, with no significant difference. Grade 3 adverse events occurred in three younger patients (8.1%) and two older patients (7.7%). These events included hepatic dysfunction at one and three months and acute exacerbation of interstitial pneumonia at 12 months in the younger group, and hepatic dysfunction at two and three months in the older group.

Detailed analysis by UFT dose (Table V). Table V presents a detailed analysis by UFT dose, focusing on treatment completion and adverse events. In the standard-dose group, 14 younger patients (67%) completed therapy, and seven (33%) experienced adverse events, whereas in the older group, five patients (39%) completed therapy and eight (62%) experienced adverse events. No statistically significant differences were observed between groups, although the older group tended to have lower completion rates and higher incidence of adverse events.

In the reduced-dose group, eight younger patients (50%) completed therapy and seven (75%) experienced adverse events, whereas in the older group, seven patients (54%) completed therapy and seven (54%) experienced adverse events, with no significant differences between groups.

Table IV. *Analysis of patients receiving uracil-tegafur (UFT).*

	No. of patients (%)		*p*-Value
	Younger group (<75 years) (N=37)	Older group (≥75 years) (N=26)	
Treatment duration			0.240
0-3 months	6 (16.2)	9 (34.6)	
4-23 months	9 (24.3)	5 (19.2)	
24 months (complete)	22 (59.5)	12 (46.2)	
UFT dose			0.596
Standard dose (400 mg/day)	21 (56.8)	13 (50)	
Reduced dose	16 (43.2)	13 (50)	
Adverse events			0.619
All grades	19 (51.4)	15 (57.7)	
Grade ≥3	3 (8.1)	2 (7.7)	

All values are presented as numbers (percentage). No treatment-related deaths were observed. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Table V. *Detailed analysis by uracil-tegafur (UFT) dose (standard vs. reduced) treatment completion and adverse events.*

	No. of patients (%)		*p*-Value
	Younger group (<75 years) (N=37)	Older group (≥75 years) (N=26)	
Standard dose	21	13	
24 months (complete)	14 (66.7)	5 (38.5)	0.107
Adverse events	7 (33.3)	8 (61.5)	0.107
Reduced dose	16	13	
24 months (complete)	8 (50)	7 (53.8)	0.837
Adverse events	12 (75)	7 (53.8)	0.233

All values are presented as numbers (percentage).

Discussion

In this study, we investigated the safety of oral uracil-tegafur (UFT) ACT in older patients (≥75 years) with completely resected early-stage NSCLC. As a result, no statistically significant differences were observed between the older and younger groups in terms of the administration rate, completion rate of 24 months, incidence of adverse events, or UFT dose. However, in the standard-dose group (400 mg daily), the older group tended to have a lower completion rate and a higher incidence of adverse events, whereas in the reduced-dose group, no significant differences were observed between age groups. These results suggest that adjuvant UFT therapy may be safely administered to older patients, provided that appropriate dose adjustments are made. The efficacy of UFT has been demonstrated in previous large randomized controlled trials, establishing its role as ACT (3-5). In the JCOG 0707 trial, UFT was compared with

S-1, and although S-1 was shown to be non-inferior in terms of efficacy, the incidence of adverse events was higher in the S-1 group, thereby reaffirming the favorable safety profile of UFT (6). Moreover, despite the widespread use of molecular targeted therapies and immune checkpoint inhibitors, real-world data continue to support the clinical benefit of adjuvant UFT therapy (7), underscoring its ongoing clinical relevance. Furthermore, a meta-analysis of patients who received UFT as maintenance therapy after definitive treatment for nasopharyngeal carcinoma demonstrated that UFT maintenance therapy improved both progression-free survival and overall survival (12). In that report, the economic advantage of UFT and its low incidence of adverse events were highlighted, particularly in the context of many low- and middle-income countries where the high cost and limited availability of molecular targeted therapies and immune checkpoint inhibitors restrict treatment options. These findings support the notion that UFT is a relatively low-invasive and clinically feasible oral anticancer drug that can be safely administered to a wide range of patients, including older patients.

As mentioned above, when limiting the analysis to the standard-dose group (400 mg daily), the completion rate of 24 months was lower, and the incidence of adverse events was higher in the older group compared with the younger group. Considering that some patients were started at a reduced dose of 300 mg daily due to advanced age, it can be inferred that those who received 400 mg daily were relatively fit and judged capable of continuing treatment by their physicians. Nevertheless, the safety of standard-dose UFT appeared to be lower in the older group. One possible explanation is the age-related decline in drug metabolism and organ function. Tegafur, the active component of UFT, is metabolized to 5-fluorouracil (5-FU) by the hepatic enzyme CYP2A6, which is known to exhibit substantial interindividual variability (13). Moreover, aging is associated with decreased activity of the CYP enzyme family overall (14), and CYP2A6 is unlikely to be an exception. In addition, older patients are more prone to decreased renal and hepatic functional reserve, which may delay drug clearance, increase systemic drug exposure, and elevate the risk of adverse events (15). Furthermore, recent pharmacokinetic studies have quantitatively demonstrated considerable interindividual variability in plasma concentrations of UFT. Kobuchi *et al.* analyzed fluctuations in plasma and intratumoral 5-FU concentrations following repeated oral administration of UFT in a colorectal cancer rat model and developed a pharmacokinetic-pharmacodynamic (PK-PD) model. As a result, substantial variation in intratumoral 5-FU levels (coefficient of variation approximately 30-120%) was observed. These findings support that the pharmacokinetics of UFT are strongly influenced by age-related and organ-function-related factors, underscoring the need for individualized dosing strategies to ensure safety in older patients (16). According to current guidelines, the standard UFT dose is 250 mg/m^2/day, which corresponds to 400 mg daily for most patients. However, in this study, some older patients were started on a reduced dose of 300 mg daily from the outset. This reflects real-world clinical practice, where flexible dose adjustments are made according to patient age and comorbidities. Moving forward, pharmacokinetic studies specifically targeting patients aged ≥75 years will be essential for establishing safer and more effective individualized treatment strategies.

A recent large-scale retrospective research by Adachi *et al.* suggested that ACT, including UFT, for patients aged ≥75 years with stage IA (tumor >2 cm) or IB NSCLC did not improve overall survival, and considering the risk of adverse events, they concluded that ACT "is not recommended" for older patients (17). However, that study did not evaluate recurrence-free survival, which is directly relevant to primary tumor control. Moreover, no details on administered doses or treatment duration were provided, raising the possibility that the inclusion of low-dose or short-duration UFT cases may have contributed to the lack of demonstrated survival benefit. Therefore, this single study alone does not provide sufficient evidence to uniformly deny adjuvant UFT therapy to patients aged ≥75 years. Indeed, current guidelines issued by the Japanese Lung Cancer Society do not specify an

upper age limit for adjuvant UFT therapy (18). Meanwhile, ACT has been shown to be effective in patients with stage II-IIIA NSCLC aged ≥75 years, and when considering the balance between efficacy and toxicity, UFT may represent a more suitable option for older patients compared with platinum-based ACT (19). Since the present study focused on safety and did not directly assess efficacy, prospective studies comprehensively evaluating both efficacy and safety of UFT in older patients are warranted.

Limitations of this study include its retrospective single-center design, the limited number of cases, which restricts the statistical power of subgroup analyses, and the lack of efficacy evaluation (*e.g.*, recurrence or survival outcomes). The significance of this study lies in the direct comparison of the safety of adjuvant UFT therapy between older and younger patients in real-world clinical practice. The outcomes in the older group appeared not to be inferior in terms of safety across the examined parameters, and in particular, the incidence of adverse events was not significantly higher. These findings underscore the importance of considering overall patient condition, comorbidities, and patient preferences rather than imposing a strict age-based restriction when making decisions regarding adjuvant UFT therapy. In the context of a super-aging society, these results provide a basis for optimizing future treatment selection and dose planning.

Conclusion

In this study, we investigated the safety of adjuvant UFT therapy in patients with completely resected early-stage NSCLC, with a particular focus on older patients. Compared with patients aged <75 years, those aged ≥75 years showed outcomes that appeared not to be inferior in terms of treatment administration rate, completion rate of 24 months, or incidence of adverse events, suggesting that UFT may be safely administered, provided that appropriate dose adjustments are made. However, in the standard-dose group (400 mg daily), older patients tended to have a lower completion rate and a higher incidence of adverse events, possibly influenced by age-related declines in drug metabolism and organ function. Moving forward, efforts to establish safer and more effective individualized treatment strategies will be important. These findings underscore that, in a super-aging society, decisions regarding adjuvant UFT therapy should consider not only chronological age but also each patient's overall condition.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

All Authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization, Y.A. and T.O.; Investigation, Y.A. and Y.I.; Methodology, Y.A. and T.O.; Project Administration, Y.A. and T.O.; Supervision, T.O.; Visualization, Y.A., T.Ichino, and T.Ito; Roles/Writing – Original Draft, Y.A. and T.O.; Writing – Review & Editing, Y.A., Y.I., T.Ichino, T.Ito, and T.O.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (GPT-5, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were

produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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