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Updated 5-year survival and exploratory T x N subset analyses of ACTS-CC trial: a randomised controlled trial of S-1 versus tegafur-uracil/leucovorin as adjuvant chemotherapy for stage III colon cancer

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ABSTRACT

Objective Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer (ACTS-CC), a randomised phase III trial, demonstrated that adjuvant therapy with S-1 for stage III colon cancer was non-inferior in 3-year disease-free survival (DFS) to that of tegafur-uracil plus leucovorin (UFT/LV). We updated DFS and overall survival (OS) and performed T x N subset analysis

Methods A total of 1518 patients with curatively resected stage III colon cancer were randomly assigned to receive S-1 (80–120 mg/day on days 1–28 every 42 days, four courses) or UFT/LV (UFT: 300–600 mg/day and LV: 75 mg/day on days 1–28 every 35 days, five courses)

Results The 5-year DFS rates of the S-1 and UFT/LV group were 70.2 % and 66.9 %, respectively (HR 0.88; 95% CI 0.74 to 1.06; p=0.177), and non-inferiority of DFS was reconfirmed with a median of 63.5-month follow-up. The similarity of OS was also confirmed (HR 0.92; 95% CI 0.72 to 1.17; p=0.488); 5-year OS rates of the S-1 and UFT/LV group were 86.0 % and 84.4 %, respectively. No significant interactions were identified between the major baseline characteristics and DFS of the S-1 and UFT/LV groups, except for histological type; S-1 was more favourable in patients with poorly differentiated adenocarcinoma. Patient outcomes were well separated by TNM-substages (IIIA/IIIB/IIIC). With the patients divided into 20 subsets by T and N factors, the DFS and OS rates of T3 and N1 subset, which accounted for 62 % of stage IIIB patients and 44 % of all studied subjects, were significantly better than those of the other subsets in stage IIIB and similar to those of stage IIIA.

Conclusions Adjuvant therapy of S-1 for stage III colon cancer was reconfirmed to be non-inferior in DFS to those of UFT/LV after long follow-up. No difference in OS was also demonstrated. T3N1 patients might be considered separately from other patients included in stage IIIB because of its favourable outcome.

Trial registration number NCT00660894.

Key questions

What is already known about this subject?

- Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer (ACTS-CC) trial previously demonstrated the disease-free survival (DFS) non-inferiority of tegafur-gimeracil-oteracil potassium (S-1) compared with tegafur-uracil plus leucovorin (UFT/LV) as adjuvant therapy for stage III colon cancer, with a median of 41-month follow-up.
- S-1 has different profile of toxicity from other oral fluoropyrimidines (FUs): fewer hand-foot syndrome than capecitabine, fewer T-Bil and AST/ALT elevation than UFT/LV and more but mild haematological and mild gastrointestinal toxicities.
- Oxaliplatin-containing regimens (FOLFOX or CapeOX) have been adopted as standard adjuvant chemotherapy in the major Western guidelines, but patients are often suffered by neurotoxicity.

What does this study add?

- Non-inferiority of S-1 compared with UFT/LV in terms of DFS was reconfirmed, with a median of 63.5-month follow-up.
- The similarity of overall survival (OS) was also confirmed; 5-year OS rates were approximately 85% in both S-1 and UFT/LV groups.
- Informative tables of DFS and OS rates divided to 20 T x N subsets were presented, and they disclosed that outcome of T3N1 patients was good to be considered separately from other subsets in stage IIIB and similar to those of stage IIIA.
- DFS and OS of T1-3N1 patients were similar between our study (using 6 months of FU monotherapy) and the International Duration Evaluation of Adjuvant Chemotherapystudy (using 3 or 6 months of FOLFOX or CapeOX).

Key questions

How might this impact on clinical practice?

- Adjuvant therapy of S-1 for stage III colon cancer was confirmed to be non-inferior to those of UFT/LV after long follow-up.
- T3N1 patients might be considered separately from other patients included in stage IIIB because of its favourable outcome.
- FU monotherapy might remain an option, especially for T1-3N1 patients who reject the neurotoxicity and/or intravenous administration.

INTRODUCTION

With the rapid ageing of society and improvement of diagnostics, colorectal cancer has taken the position of most common cancer in Japan, with approximately 150 000 new cases expected in 2017.[1] About 40% of the surgically resected colorectal cancers were accompanied with positive lymph nodes (LNs) and categorised as pathological stage III disease.[2]

Postoperative adjuvant chemotherapy for patients with stage III colon cancer is internationally regarded as a standard care for improving survival. On the basis of their reported superiority in disease-free survival (DFS) with a constant HR of 0.8 compared with 5-FU/leucovorin (LV),[3 4] oxaliplatin-containing regimens (FOLFOX or CAPOX) have been adopted as standard adjuvant chemotherapy in the major Western guidelines since the mid-2000s.[5–7] However, fluoropyrimidine (FU) alone remains one of the options,[5–7] especially for elderly patients and patients who reject the neurotoxicity of oxaliplatin.

In Japan, oral FU derivatives have been preferred because of their convenience, leading to the development of several oral FU derivatives with different properties, that is, tegafur-uracil (UFT), capecitabine and tegafur-gimeracil-oteracil potassium (S-1). S-1 has been widely used singularly as well as in combination with other cytotoxic agent for several malignancies, both in adjuvant setting and in treatment for metastases.[8 9]

Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer (ACTS-CC) is the first randomised controlled trial (RCT) investigating the efficacy of S-1 as adjuvant chemotherapy for patients with stage III colon cancer, by confirming its non-inferiority to UFT/LV, which is a commonly used regimen in adjuvant chemotherapy for stage III patients in Japan, and for which the non-inferiority to intravenous 5-FU/LV was confirmed by two RCTs, in USA and Japan.[10 11]

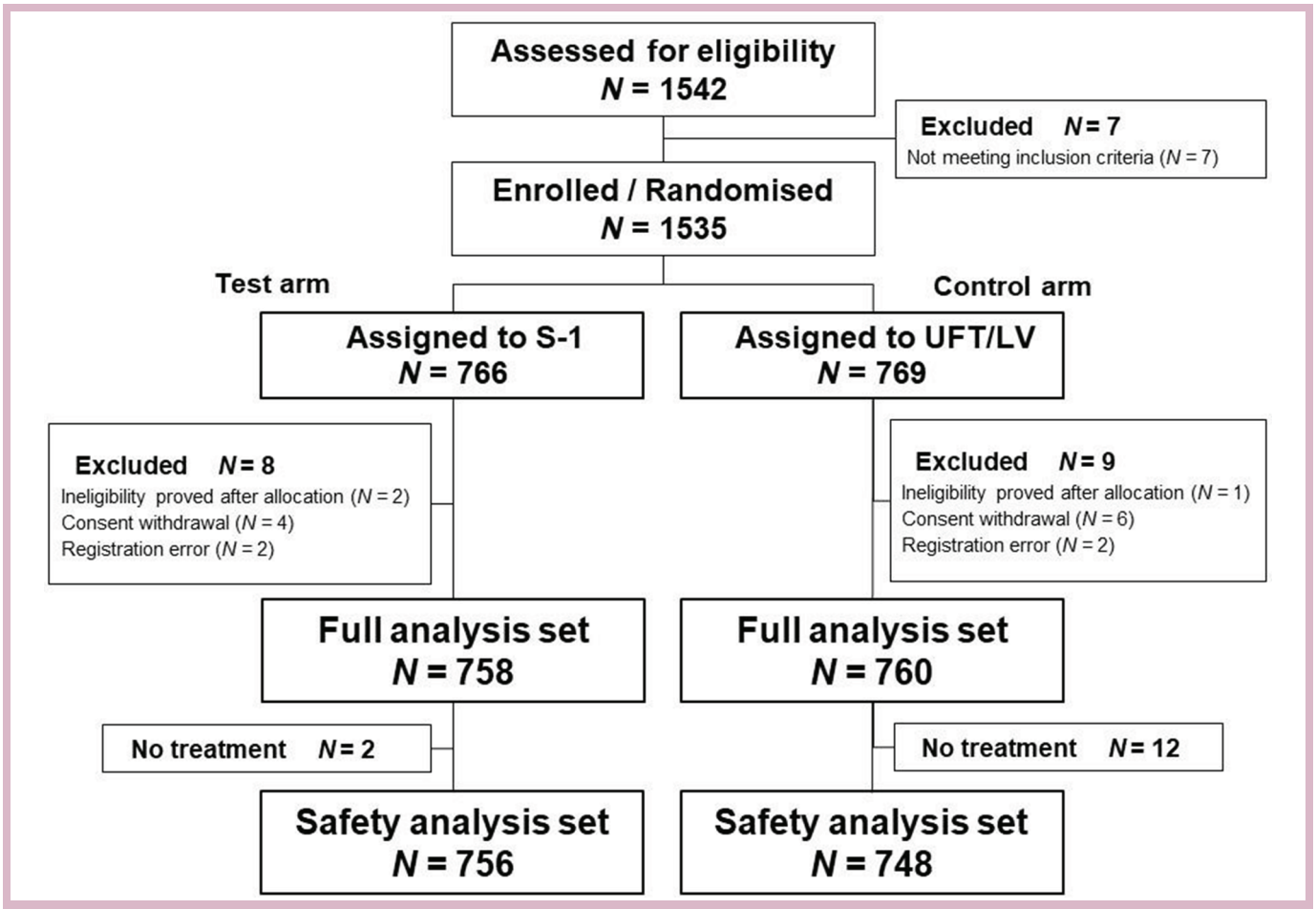

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials; LV, leucovorin; S-1, tegafur-gimeracil-oteracil potassium; UFT, tegafur-uracil.

Through investigation of a total of 1518 patients, we previously demonstrated the non-inferiority of S-1 to UFT/LV in terms of DFS (HR 0.85; 95% CI 0.70 to 1.03) as the primary endpoint of the study, with a median of 41.3-month follow-up.[12]

In this paper, we present updated results of DFS and overall survival (OS) with a median of 63.5-month follow-up and some clinically informative subset analyses.

PATIENTS AND METHODS

Patients

This study was conducted in accordance with the Declaration of Helsinki and comparable Japanese ethical standards and was approved by the Institutional Review Boards of each participating institute. Written informed consent was obtained from all patients before enrolment.

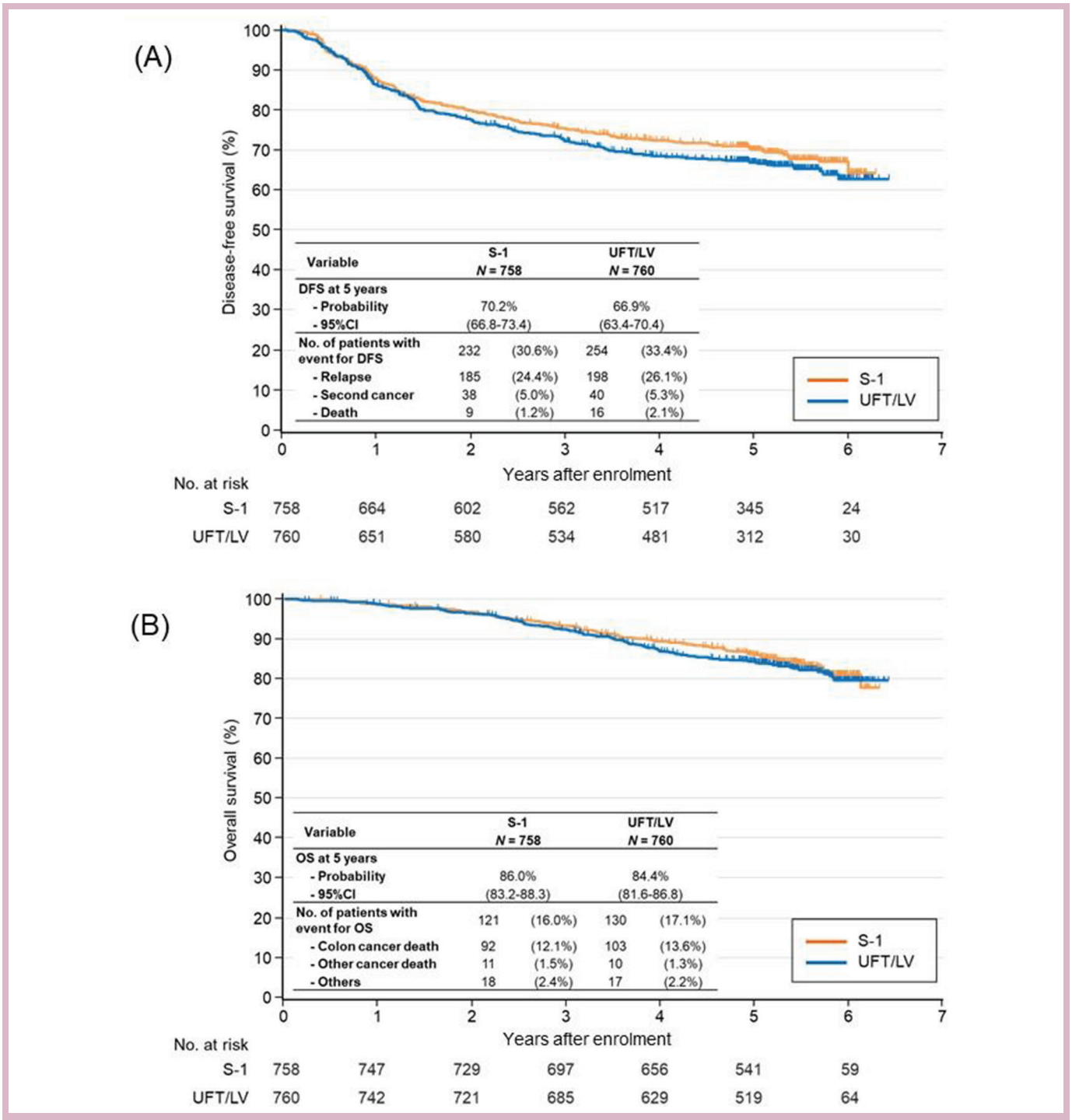

Figure 2 Survival curves. (A) Disease-free survival (DFS). (B) Overall survival (OS). LV, leucovorin; No., number; S-1, tegafur-gimeracil-oteracil potassium; UFT, tegafur-uracil.

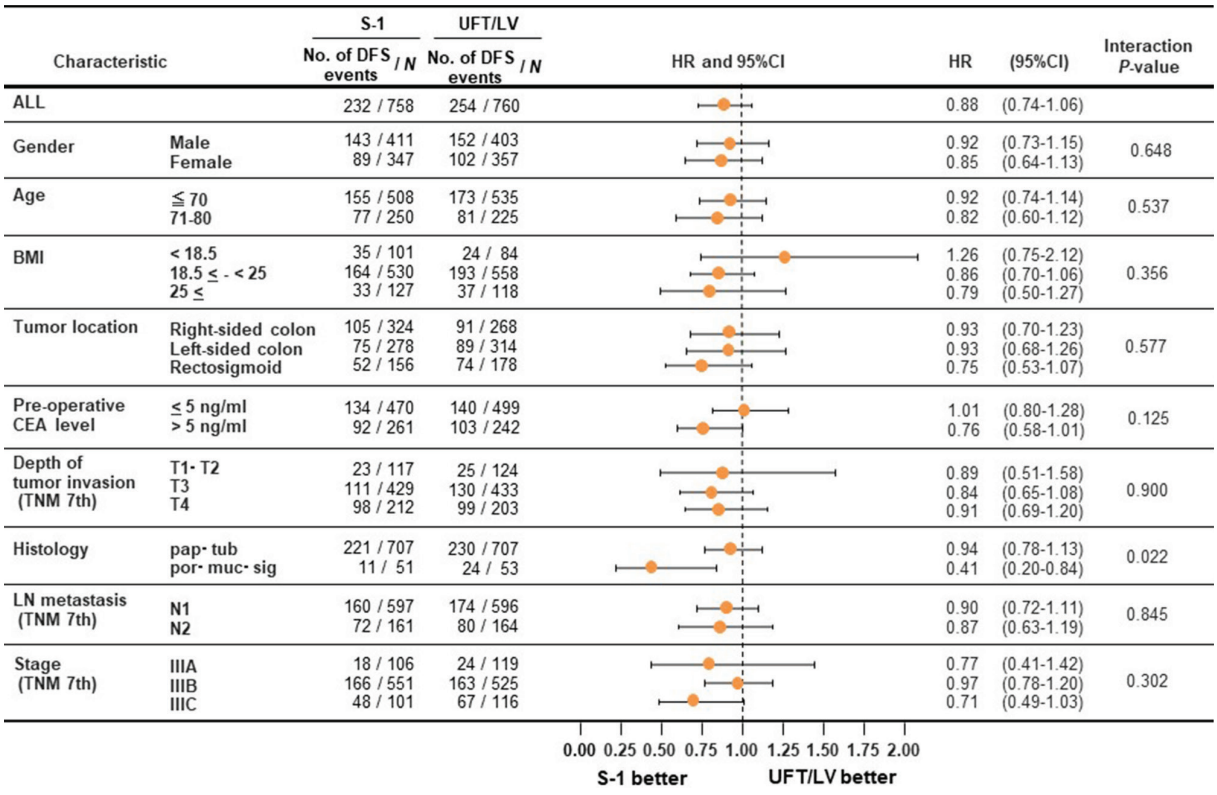

Figure 3 Subgroup analysis of disease-free survival in the S-1 group compared with the UFT/LV group. Annotation: right-sided colon includes caecum, ascending and transverse colon. Left-sided colon includes descending and sigmoid colon. BMI, body mass index; CEA, carcinoembryonic antigen; DFS, disease-free survival; LN, lymph node; LV, leucovorin; muc, mucinous adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; S-1, tegafur-gimeracil-oteracil potassium; tub, tubular adenocarcinoma; UFT, tegafur-uracil.

Patients aged 20–80 years with curatively resected stage III (T1-4, N1-2, M0) colon cancer were randomly assigned in a 1:1 ratio to an UFT/LV group or S-1 group, using a minimisation algorithm with stratification for LN metastasis (N1 vs N2 in UICC-TNM seventh classification) and institution. The study was open label.

Protocol treatment

In the S-1 group, S-1 was orally administered at a dose corresponding to the body surface area (BSA) (40 mg with BSA <1.25 m²; 50 mg with BSA 1.25–1.50 m²; 60 mg with BSA >1.50 m²) twice daily after meals for 28 consecutive days, followed by a 14-day rest. A total of four courses (24 weeks) were administered.

In the UFT/LV group, UFT (300 mg with BSA <1.17 m^2, 400 mg with BSA 1.17–1.49 m^2, 500 mg with BSA 1.50–1.83 m^2, 600 mg with BSA >1.83 m^2) and LV (75 mg/body) were administered orally in three divided doses (every 8 hours) more than 1 hour before or after meals for 28 consecutive days, followed by a 7-day rest. A total of five courses (25 weeks) were administered.

Assigned treatment was started within 8 weeks after surgery. After completion of the protocol treatment, patients were followed up according to a predefined surveillance schedule. Additional details were provided previously.[12 13]

Statistical methods

DFS was defined as the time from randomisation to recurrence, second cancers, or death, whichever occurred first. 'Second cancers' included metachronous cancers developed in both colorectum and other organs. OS was calculated from randomisation to death from any cause. DFS and OS curves were estimated using the Kaplan-Meier method, and Log-rank tests were used to test for treatment differences overall. Comparisons were based on the intention-to-treat principle, with data of the full analysis set. The HR for DFS, OS and its CI were calculated using a stratified Cox proportional hazards model with LN metastasis (N1/N2) as stratification factor. Cox models were used to estimate HRs and their CIs to examine the effect of other potentially prognostic covariates and to test for treatment–covariate interaction. All reported p values were two sided, and SAS V.9.3 was used for statistical analyses.

RESULTS

Patient characteristics

From April 2008 to June 2009, 1535 patients were enrolled from 358 hospitals in Japan (see online supplementary appendix 1). After excluding 17 ineligible patients, 1518

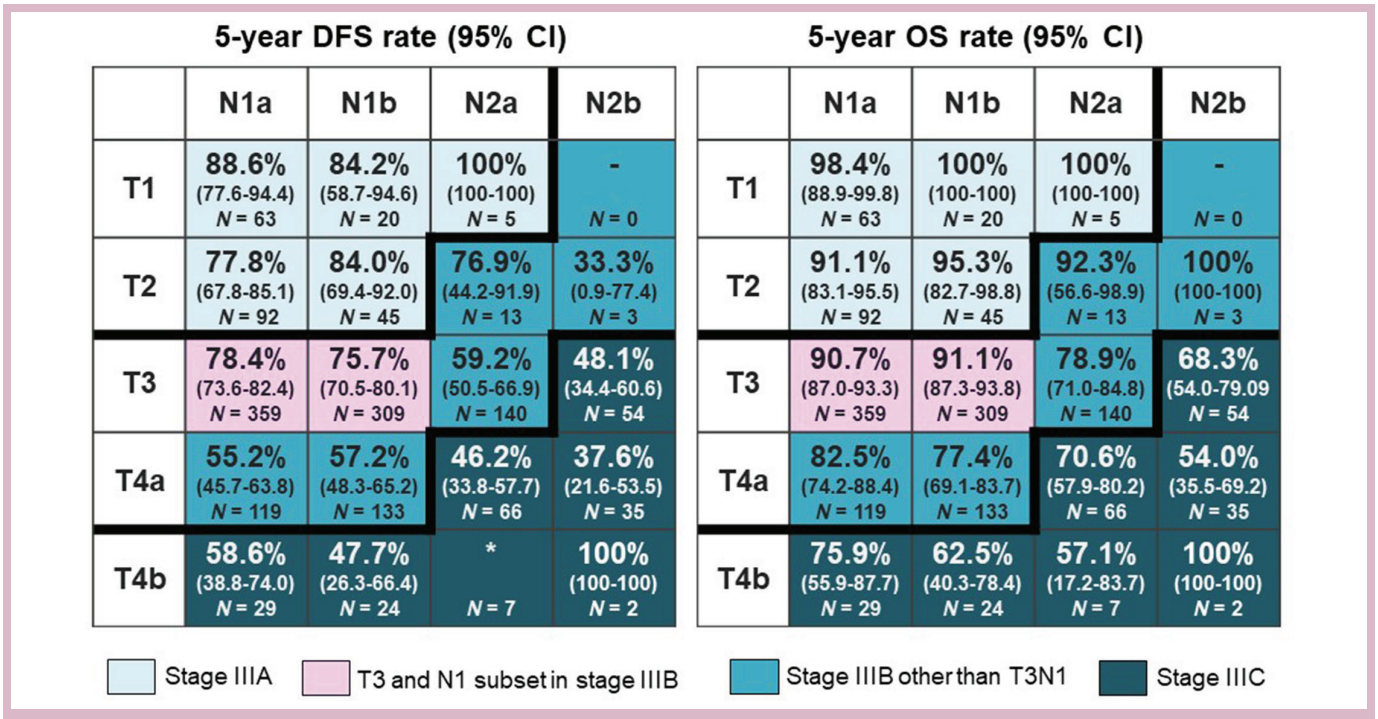

Figure 4 Five-year DFS and OS rates of T x N subsets. *: DFS rate at 5 years could not be estimated (not reached). DFS, disease-free survival; OS, overall survival.

were included in the full analysis set (758 and 760 in the S-1 and UFT/LV group, respectively) (figure 1).

The median age at enrolment was 66 years, and wide LN dissection (D3 in the Japanese Classification[14]) was performed in 79.8% patients. The TNM-stage distribution was similar in the two groups; stages IIIA/IIIB/IIIC were 15%/71%/14%, respectively. The planned 6-month treatments were completed in 76.5% and 73.4% of patients in the S-1 and UFT/LV group, respectively. Details of the treatment delivery and adverse events were reported previously.[13] Median follow-up was 63.5 months (data cut-off date: 11 November 2014).

Disease-free survival

The DFS curves and correspondent event status for both groups are shown in figure 2A. The DFS rate at 5 years of the S-1 group and UFT/LV group was 70.2% (95% CI 66.8 to 73.4) and 66.9% (95% CI 63.4 to 70.4), respectively. The stratified HR for DFS of S-1 versus UFT/LV was 0.88 (95% CI 0.74 to 1.06; p=0.177); non-inferiority of S-1 to UFT/LV was reconfirmed in this updated analysis.

Approximately 5% of patients in both groups experienced second cancers, comprising approximately 16% of DFS events. Among them, the most common was lung cancer, followed by breast and gastric cancers.

In the subgroup analysis for DFS, no significant interactions were identified between the major baseline characteristics and the therapeutic effects of S-1 or UFT/LV, except for histological type; S-1 was more favourable in patients with poorly differentiated adenocarcinoma, although the subgroup was very small (103 patients) (figure 3).

Overall survival

The OS rate at 5 years of the S-1 group and the UFT/LV group was 86.0% (95% CI 83.2 to 88.3) and 84.4% (95% CI 81.6 to 86.8), respectively (figure 2B). The stratified HR for OS of S-1 to UFT/LV was 0.92 (95% CI 0.72 to 1.17; p=0.488); there was no difference in OS between the two groups. Among OS events, deaths caused by second cancers consisted of 9.1% and 7.7% in the S-1 and UFT/LV group, respectively.

Exploratory analysis of T x N subsets

To achieve additional information that might contribute to clinical practice, we performed an exploratory subset analysis focusing on prognostic stratification by T and N factors. The patients were divided into 20 subsets by T and N factors. The 5-year DFS and OS rates of each cluster are shown in figure 4. While the survival outcomes were well divided by TNM substage (IIIA/IIIB/IIIC), the DFS and OS rates of T3 and N1 (T3N1) subset were better than those of the other subsets in stage IIIB. Notably, T3N1 patients (668 patients) accounted for 62.1% of stage IIIB and 44.0% of all 1518 patients. T2 and N2a subset showed similar DFS and OS to T3N1, but its population was very small (13 patients).

Survival curves of the four groups, stage IIIA, IIIB-1 (T3N1), IIIB-2 (stage IIIB other than T3N1) and IIIC (figure 5A,B) revealed the DFS and OS of IIIB-1 disease were significantly divided from those of IIIB-2 (p<0.001 and p<0.001, respectively) but did not differ from those of IIIA (p=0.135 and p=0.190, respectively). For reference, 3-year DFS rates of T x N subsets are shown in figure 6.

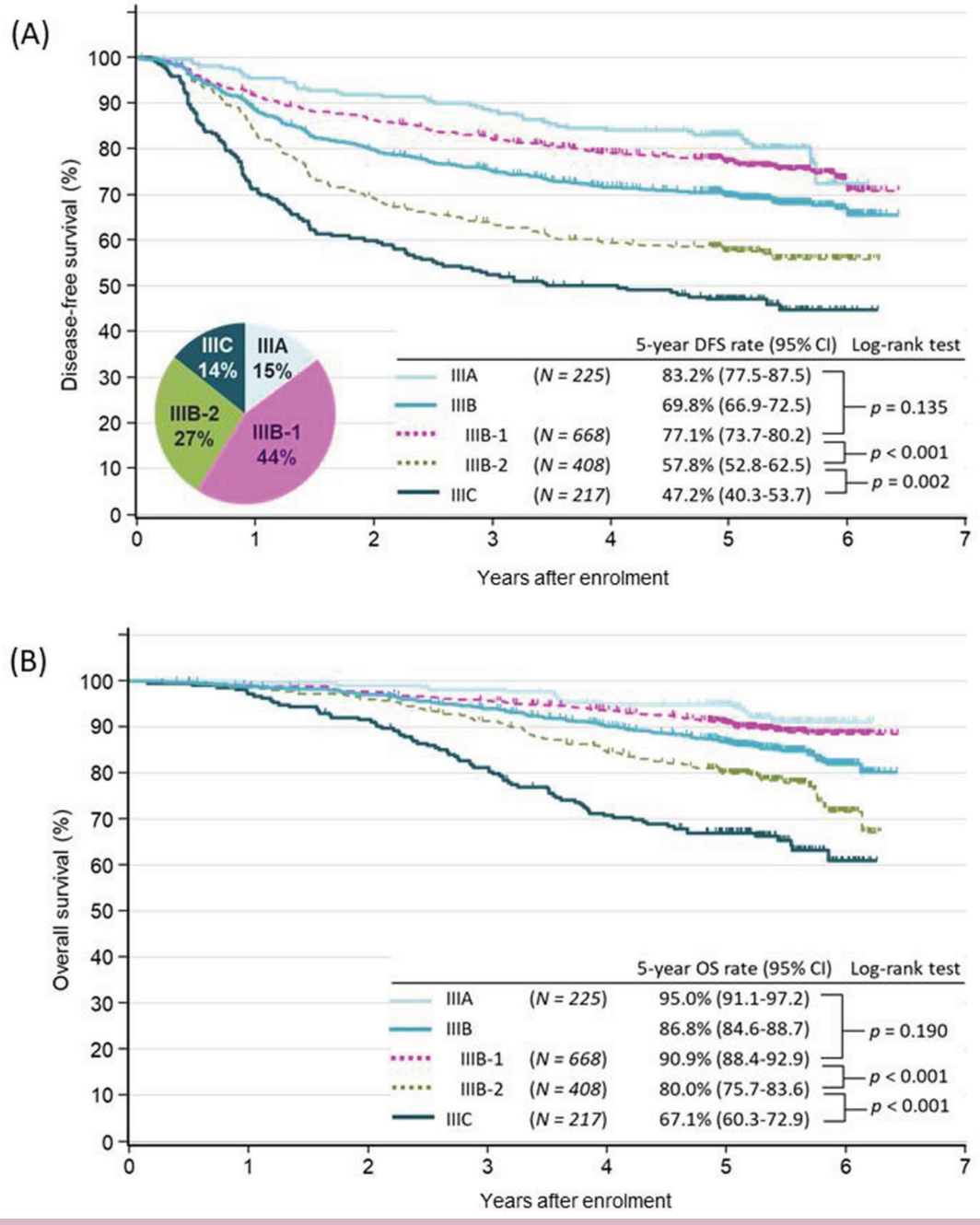

Figure 5 Survival curves of the modified four TNM substages. (A) Disease-free survival (DFS). (B) Overall survival (OS). Annotation: IIIB-1: T3N1, IIIB-2: stage IIIB other than T3N1.

DISCUSSION

In our updated results, non-inferiority of S-1 to UFT/LV in terms of DFS was reconfirmed, and no difference in OS was also demonstrated. The OS at 5 years was favourable, approximately 85% in both the S-1 and UFT/LV group (figure 2B). This was similar to 5-year OS rates reported in the recent Japanese RCTs studying FU monotherapy for stage III patients[11 15] but quantitatively better than in other western RCTs, with fluoropyrimidines only[10 16] or even in some of the pivotal oxalipatin trials.[3 4] The greatest reason for this OS improvement in the last decade could be the progress of chemotherapy for metastatic colorectal cancer, for example, the rise of molecular-targeting agents. However, improvements in toxicity control and the prevalence of adequate surgical technique such as D3 LN dissection and complete mesocolic excision[14 17] might also have had impact on the outcome improvement of patients with colon.

Notably, our T x N subset analysis provided clinically informative findings. As already known, prognoses of patients with stage III colon cancer are well divided by TNM substage. However, the number of patients included in each substage varied substantially; while stage IIIA and IIIC comprised approximately 15% of patients, stage IIIB

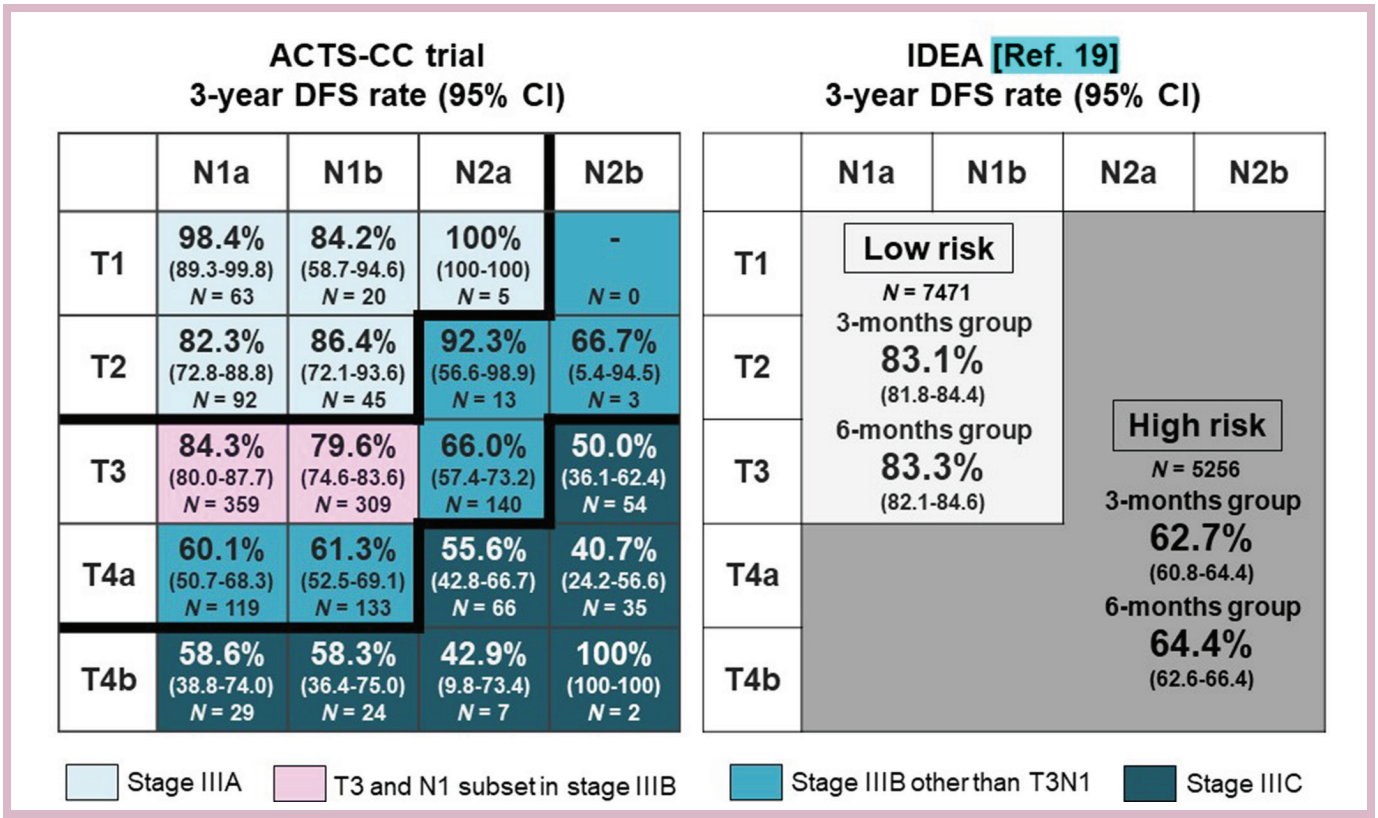

Figure 6 Three-year DFS rates of T x N subsets of the ACTS-CC trial and IDEA study.[19] Annotation: definitions of DFS in ACTS-CC and IDEA were different. In the ACTS-CC trial, DFS was defined as the time from randomisation to recurrence, second cancers or death, whichever occurred first. 'Second cancers' included metachronous cancers developed in both colorectum and the other organs. In the IDEA study, DFS was defined as the time from randomisation to the date of a first relapse, the diagnosis of a secondary colorectal cancer after the initial diagnosis or death from any cause, whichever occurred first. Malignancies developed in the other organs, that is, breast, head and neck, were not included. ACTS-CC, Adjuvant Chemotherapy Trial of TS-1 for Colon Cancer; DFS, disease-free survival; IDEA, International Duration Evaluation of Adjuvant Chemotherapy.

patients consistently accounted for approximately 70% of stage III population in Japanese RCTs studying adjuvant chemotherapy.[11 15 18] This might mean that stage IIIB subgroup contained subpopulations of patients with different prognosis because of its largeness. Our T x N subset analysis disclosed that T3N1 subset was a large population (62% of stage IIIB and 44% of all studied patients), and its prognosis was significantly better than other subsets in stage IIIB and rather similar to that of stage IIIA patients (figures 4, 5A,B).

In the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration, a non-inferiority study of 3 months of FOLFOX or CAPOX compared with 6 months to reduce the medical costs and toxicities of oxaliplatin,[19] non-inferiority of 3 months of therapy to 6 months was not confirmed, while 3 months of therapy reduced adverse events as expected and showed similar 3-year DFS rate as 6 months in patients treated with CAPOX, particularly in those with T1, T2 or T3 and N1 (T1-3N1) disease, which was categorised as 'low-risk' group in the study. The study group therefore proposed 3 months CAPOX as a promising option for adjuvant chemotherapy for this 'low-risk' colon cancer patients.

Our results of T x N subset analysis (figures 4, 5A,B) strongly support that it is reasonable to divide stage III colon cancer into T1-3N1 and others. The prospect of '3 months oxaliplatin' treatment is encouraging news for T1-3N1 patients, who account for approximately 60% of stage III patients. However, although it was a cross-trial comparison and the definition of DFS was slightly different between IDEA and our study, the 3-year DFS rate of T1-3N1 patients in our study was similar to that in the IDEA study[19] (figure 6). Based on this finding, FU monotherapy might remain an option, especially for patients who reject the neurotoxicity and/or intravenous administration.

However, there was limitation that our T x N subset analysis was an exploratory, unplanned and retrospective multiple subset analysis. The question should be answered by only hypothesis-generating and required RCT focusing on T1-3N1 disease for concluding that which therapeutic approach would be the best for these patients.

A means for choosing the most suitable oral FU for each patient, outside of the profile of toxicity, has been sought. A recent Japanese RCT, JCOG0910,[18] failed to demonstrate the non-inferiority of DFS of S-1 to that of

capecitabine as adjuvant chemotherapy for stage III colon cancer. However, OS of the two groups was quite similar, and in the subgroup analysis, S-1 showed better DFS than capecitabine in the patient subgroup having tumours with poorly differentiated histology,[18] as shown in our study (figure 3). It was reported that poorly differentiated colon and gastric cancer tissues contained higher level of dihydropyrimidine dehydrogenase (DPD), a catabolic enzyme of 5-FU, than in well-differentiated tumour.[20] On the basis of these findings, it was theoretically comprehensible that the DPD inhibitory fluoropyrimidine S-1 affected poorly differentiated tumour, although the populations were small. We have focused on the relation between the differences in the mechanism of action and efficacy among oral FUs. Associated translational studies in ACTS-CC trial investigating the tumour mRNA expressions and DNA copy numbers of 5-FU-related enzymes are being conducted.

In conclusion, non-inferiority of adjuvant chemotherapy for stage III colon cancer using S-1 compared with UFT/LV was reconfirmed in the updated analysis. T3N1 patients might be considered separately from the other patients in stage IIIB because of its favourable outcome.

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Contributors MI and KS contributed to the conception and design of the study. TK, MI, EN and KS contributed to data analysis and interpretation. TK, MY, TI, YN, AS, AT, ES, HS, YT, AM, HO, HH, MM, TY, MN and YM contributed to collection and assembly of data. All authors contributed to manuscript writing and final approval if the manuscript.

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Patient consent Not required.

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