Adjuvant chemotherapy for elderly patients with colorectal cancer: a single-center observational study in Japan

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Research Article

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Abstract

**Purpose:** Adjuvant chemotherapy improves the prognosis of patients with colorectal cancer (CRC) following radical resection. The aim of the present study is to review appropriate chemotherapeutic regimens for elderly patients.

**Methods:** We examined 1243 Japanese patients who received adjuvant therapy for high-risk stage II, III, or IV CRC between July 2010 and June 2021 at our hospital. Patients were divided according to an age of 70 years. The efficacy of adjuvant therapy was analyzed in association with age and adjuvant chemotherapeutic regimens.

**Results:** A total of 544 patients (44%) were ≥70 years old. They were less likely to receive adjuvant chemotherapy ($p<0.001$) or palliative chemotherapy after recurrence ($p<0.001$) than patients aged <70 years. Cancer-specific survival (CSS) in stage III CRC patients was longer in the <70 years group than in the ≥70 years group ($p=0.006$); however, CSS by regimens did not significantly differ between these groups. Adjuvant chemotherapy was associated with the longer relapse-free survival of stage III CRC patients in the <70 years group ($p=0.005$). CSS in these patients was prolonged in both the <70 years group ($p=0.019$) and ≥70 years group ($p=0.009$) who received adjuvant chemotherapy.

**Conclusions:** Although adjuvant chemotherapy was associated with a favorable prognosis regardless of age, the implementation rate of adjuvant chemotherapy for elderly CRC patients was low, which may explain shorter CSS in stage III CRC patients the ≥70 years group than in the <70 years group. Further studies are needed to establish an optimal adjuvant regimen for elderly patients.

Introduction

Colorectal cancer (CRC) is the third most deadly and fourth most commonly diagnosed cancer worldwide [1, 2]. Randomized clinical trials (RCTs) previously revealed that 5-fluorouracil (5-FU) effectively prevented the recurrence of CRC after radical resection [3-5]. Another series of RCTs showed better survival with oxaliplatin in combination with 5-FU than with 5-FU alone [6-8]. Therefore, a growing number of CRC patients are receiving oxaliplatin-based adjuvant chemotherapy [9-11].

Regarding the age-dependent efficacy of adjuvant chemotherapy, fluoropyrimidine monotherapy has been shown to effectively improve the prognosis of elderly CRC patients [12, 13]. However, the benefits of adding oxaliplatin to 5-FU for elderly CRC patients remain controversial [13-15]. Moreover, elderly patients are less frequently treated with aggressive adjuvant chemotherapy because of comorbidities, a poor performance status (PS), and concerns regarding toxicity [16, 17]. These factors may contribute to the higher rates of recurrence and mortality in older CRC patients. To establish suitable adjuvant chemotherapy regimens for the elderly, it is important to compare the efficacy of each adjuvant regimen between elderly and younger patients.
Therefore, we herein investigated age-dependent differences in the real-world selection of adjuvant chemotherapy and survival after radical resection.

**Materials And Methods**

**Patients**

We investigated consecutive patients who underwent radical surgery for stage II-IV primary CRC between July 2010 and June 2021 at the University of Tokyo Hospital. Stage II CRC patients were only included when they had high-risk factors, such as T4 tumors, inadequate lymph node sampling, perforation, or a poorly differentiated histology (high-risk stage II) [9, 10, 18]. We included patients with multiple primary synchronous CRC, colitis-associated cancer, and hereditary CRC. Patients who had previously received preoperative chemotherapy and/or radiotherapy were excluded.

The present study was approved by the Ethics Committee of the University of Tokyo (No. 3252-[13]).

**Data extraction**

We retrieved the following data: age, sex, Eastern Cooperative Oncology Group PS, body mass index, the Charlson comorbidity index (CCI) [19], the primary location and histology, the TNM pathological classification of tumors at diagnosis according to the American Joint Committee on Cancer staging manual [20], adjuvant chemotherapeutic regimens, and palliative chemotherapeutic regimens after recurrence. We also reviewed the reasons for no adjuvant chemotherapy in stage III patients from narrative records.

To analyze age-dependent differences in adjuvant chemotherapy, we divided patients into the following groups: ≥70 years and <70 years. The cancer-specific survival (CSS) and relapse-free survival (RFS) of CRC patients for each staging in the two groups were reviewed to evaluate the efficacy of adjuvant chemotherapy for the elderly. We also investigated the prognosis of CRC patients according to adjuvant chemotherapeutic regimens: oral 5-FU analogues (capecitabine, tegafur-uracil, and S-1), oxaliplatin-including regimens (oxaliplatin plus leucovorin/5-FU [FOLFOX] or capecitabine [CAPOX]), and no adjuvant chemotherapy.

**Statistical analysis**

Statistical analyses were performed using JMP Pro 16.0.0 (SAS institute, Cary, NC, USA). All variables were summarized as medians (range), means ± standard deviations, or numbers (percentages). Quantitative variables were compared using the Mann-Whitney U test. Qualitative variables were compared using Fisher’s exact test or the chi-squared test with Yates’ correction. CSS and RFS were estimated by the Kaplan–Meier method, and compared using the Log-rank test. All reported p-values were two-sided, and results were considered to be significant at a p-value <0.05.
Results

Patient characteristics

A total of 1243 patients who underwent radical resection for CRC were included in the present study. Among them, 544 patients (44%) were aged ≥70 years (Fig. 1).

Table 1 summarizes the characteristics of patients divided according to an age of 70 years. Body mass index was higher in the <70 years group than in the ≥70 years group (p=0.004). More patients with a poor PS were included in the ≥70 years group (19% vs. 3%, p<0.001), while more patients had CCI ≥2 in the ≥70 years group (36% vs. 15%, p<0.001). In the ≥70 years group, there were more patients with colon cancer (70% vs. 57%, p<0.001), poorly differentiated tumor (11% vs. 7%, p=0.011), an advanced T stage (p<0.001), and an early N stage (p<0.001). High-risk stage II cancer was more frequent in the ≥70 years group (45% vs. 32%, p<0.001). Overall, 63% of the ≥70 years group did not receive adjuvant chemotherapy, whereas 35% and 34% of the <70 years group received adjuvant monotherapy or doublet therapy, respectively. The ≥70 years group also received fewer lines of palliative chemotherapy after recurrence than the <70 years group (0.81 vs. 1.46, p<0.001).

Patient prognosis

We compared the prognosis of CRC patients between the ≥70 years and <70 years in each stage. As shown in Fig. 2, there was no intergroup difference in RFS (5-year RFS rates: 77% vs. 82% in high-risk stage II, p=0.25, 62% vs. 67% in stage III, p=0.20, and 26% vs. 31% in stage IV, p=0.41).

We also reviewed the impact of adjuvant chemotherapy on RFS. In the <70 years group (Supp. Fig. 1), adjuvant chemotherapy was associated with improved RFS in stage III CRC patients (5-year RFS rates: 69% and 55%, p=0.005), but not in stage II (5-year RFS rates: 80% and 83%, p=0.77) or stage IV CRC patients (5-year RFS rates: 33% and 22%, p=0.22).

In the ≥70 years group (Supp. Fig. 2), the impact of adjuvant chemotherapy on RFS in stage III CRC patients was limited (5-year RFS rates: 64% and 60%, p=0.12). Similar to the <70 years group, adjuvant chemotherapy did not improve RFS in stage II (5-year RFS rates: 71% vs. 78%, p=0.44) or stage IV CRC patients (5-year RFS rates: 33% vs. 12%, p=0.15).

We then analyzed CSS in CRC patients in each stage according to an age of 70 years (Fig. 3). CSS was independent of age in stage II (5-year CSS rates: 94% vs. 97%, p=0.15) and stage IV CRC patients (5-year CSS rates: 72% vs. 70%, p=0.82). In contrast, the CSS in stage III CRC patients was better in the <70 years group than in the ≥70 years group (5-year CSS rates: 91% and 82%, p=0.006). However, CSS in stage III CRC patients by regimens did not significantly differ between the two groups (Fig. 4). RFS in stage III CRC patients by regimens was similar between the two groups (Supp. Fig. 3).

We investigated the impact of adjuvant chemotherapy on CSS. In the <70 years group (Supp. Fig. 4), CSS in stage III CRC patients was improved by adjuvant chemotherapy (5-year CSS rates: 92% and 84%,
However, no clinical benefit of adjuvant chemotherapy on CSS was evident in stage II (5-year CSS rates: 96% vs. 97%, \(p=0.56\)) or stage IV CRC patients (5-year CSS rates: 74% vs. 67%, \(p=0.61\)). Similar results were also observed in the \(\geq 70\) years group (Supp. Fig. 5); adjuvant chemotherapy was associated with prolonged CSS in stage III CRC patients (5-year CSS rates: 87% and 76%, \(p=0.009\)), but not in stage II (5-year CSS rates: 95% and 94%, \(p=0.69\)) or stage IV CRC patients (5-year CSS rates: 78% and 53%, \(p=0.20\)).

**Reasons for no adjuvant chemotherapy**

Table 2 shows the reasons for not receiving adjuvant chemotherapy in stage III CRC patients. In the \(\geq 70\) years group, 24 patients (21%) avoided adjuvant chemotherapy due to their age.

**Discussion**

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines listed FOLFOX and CAPOX as adjuvant chemotherapy options in 2010, but revised these oxaliplatin-including doublets as preferred regimens for patients who undergo radical resection for high-risk stage II and stage III CRC in 2019 [21]. On the other hand, the National Comprehensive Cancer Network and European Society of Medical Oncology guidelines had already recommended doublet regimens in 2012 [22-24]. Therefore, few studies have been reported on the long-term outcomes of adjuvant doublet therapy in Japanese patients, particularly the elderly population. To the best of our knowledge, this is the first study to investigate and compare the efficacy of adjuvant chemotherapy including oxaliplatin-based regimens in a Japanese population of elderly and younger stage II-IV CRC patients.

Regarding the outcomes of adjuvant therapy for elderly Japanese CRC patients, Yamano et al. reported that adjuvant monotherapy prolonged overall survival in stage III CRC patients aged \(>75\) years [25]. On the other hand, Kawamura et al. showed that the effectiveness of adjuvant therapy including oxaliplatin-based regimens for all-cause mortality was limited in stage III colon cancer patients aged \(\geq 75\) years after adjustments for clinical parameters [26]. In the present study, we demonstrated that adjuvant chemotherapy improved CSS in stage III CRC patients aged \(\geq 70\) years. RFS in these patients was also improved by adjuvant chemotherapy. The benefits of adjuvant chemotherapy were only observed in CSS, partly due to the small number of palliative chemotherapeutic regimens administered to elderly patients after recurrence. Since palliative treatments for the elderly were limited, adjuvant chemotherapy needs to be proactively administered to this population.

The latest JSCCR guidelines recommend that stage III CRC patients aged \(\geq 70\) years with a good PS and few comorbidities receive adjuvant chemotherapy [21]. However, previous studies reported that the implementation rate of adjuvant chemotherapy for Japanese patients aged \(\geq 75\) years was <40% [25, 26]. Similarly, in the present study, only 37% of patients aged \(\geq 70\) years received adjuvant chemotherapy. Yamano et al. indicated that elderly patients were likely to avoid adjuvant chemotherapy due to their advanced age, regardless of the severity of their comorbidities [25]. In our cohort, 21% of elderly stage III patients did not receive adjuvant chemotherapy because of old age. Moreover, the socioeconomic status...
of elderly patients, such as a low income, poor access to hospitals, and a low level of education, was associated with a low implementation rate of adjuvant chemotherapy in previous reports [27-29]. These factors may contribute to a poor prognosis after radical resection in elderly CRC patients.

Indications for adjuvant chemotherapy in elderly patients are not fully described in the published guidelines [9, 10, 21, 30]. Along with PS and comorbidity, frailty, such as malnutrition, and dementia in elderly colon cancer patients were associated with a lower tolerance of adjuvant chemotherapy [31-33]. The utility of classifying elderly patients with geriatric assessment methods has been suggested to identify those who may benefit from adjuvant chemotherapy [34, 35]. Antonio et al. reported that a comprehensive geriatric assessment may be an aid for selecting elderly patients suitable for adjuvant chemotherapy as well as the dose intensity of chemotherapeutic drugs [34].

Regarding adjuvant regimens for the elderly, we previously reported that CAPOX therapy was tolerable in a selected subpopulation of elderly patients, and its clinical outcome was similar to that in younger patients [36]. However, studies in Western countries showed that the addition of oxaliplatin to fluoropyrimidine was associated with severe toxicities in elderly patients, and, thus, capecitabine monotherapy appeared to be preferable as an adjuvant regimen [37, 38]. The guidelines do not recommend the uniform administration of doublet therapy to elderly patients [9, 10, 21]. On the other hand, RCTs revealed racial discrepancies in the tolerability profiles of regimens including oxaliplatin; Asian patients showed less toxicities than patients of other races [39, 40]. Therefore, oxaliplatin-including regimens may be implemented for elderly Japanese patients with a low risk of adverse events. Further studies are needed to identify the optimal regimen for elderly CRC patients.

There are several limitations that need to be addressed. This was a retrospective study that was conducted at a single hospital. Moreover, the present study may have included a selection bias; adjuvant chemotherapy may not have been selected for elderly patients with a poor PS or for those with severe background comorbidities. In addition, reasons for not receiving adjuvant chemotherapy were retrieved from narrative records, and, thus, may not be precise.

**Conclusions**

In a Japanese population, adjuvant chemotherapy was associated with a better prognosis in elderly CRC patients. However, the implementation rate of adjuvant chemotherapy was low in the elderly partly due to their advanced age, and the prognosis of elderly patients with stage III CRC was worse than that of their younger counterparts. Further studies with a larger patient cohort are needed to select the treatment strategies of adjuvant chemotherapy for elderly CRC patients.

**Declarations**

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from Japan Society for the promotion of Science.

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Ethics approval:** This study was approved by the Ethics Committees of the University of Tokyo (No. 3252-[15]).

**Consent:** All patients were given informed consent before enrollment.

**Data availability:** The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

**Author contributions:** Kazuaki Okamoto, Hiroaki Nozawa and Soichiro Ishihara developed the study design and concept, retrieved the data of patients and carried out the analysis. Kazuaki Okamoto, Hiroaki Nozawa, Shigenobu Emoto, Koji Murono, Kazuhito Sasaki and Soichiro Ishihara participated in writing and revising the manuscript critically. All authors read and approved the final manuscript.

**References**


Tables

Table 1 Clinicopathological parameters of patients according to age.
<table>
<thead>
<tr>
<th>Variable</th>
<th>≥70 years (n = 544)</th>
<th>&lt;70 years (n = 699)</th>
<th>p-value</th>
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<tr>
<td>Demographic data</td>
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<td></td>
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<tr>
<td>Age, years</td>
<td>77 (70-95)</td>
<td>60 (21-69)</td>
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<tr>
<td>Sex, male</td>
<td>301 (55%)</td>
<td>401 (57%)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>22 (13-33)</td>
<td>23 (14-45)</td>
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<td>ECOG PS</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0</td>
<td>440 (81%)</td>
<td>680 (97%)</td>
<td></td>
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<tr>
<td>≥1</td>
<td>104 (19%)</td>
<td>19 (3%)</td>
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<tr>
<td>Charlson comorbidity index</td>
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<td>&lt;0.001</td>
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<tr>
<td>≤1</td>
<td>345 (66%)</td>
<td>594 (85%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>198 (36%)</td>
<td>105 (15%)</td>
<td></td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colon</td>
<td>379 (70%)</td>
<td>400 (57%)</td>
<td></td>
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<tr>
<td>Rectum</td>
<td>165 (30%)</td>
<td>299 (43%)</td>
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<tr>
<td>Tumor histology</td>
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<td>Well- to moderately differentiated</td>
<td>485 (89%)</td>
<td>652 (93%)</td>
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</tr>
<tr>
<td>Poorly differentiated</td>
<td>59 (11%)</td>
<td>47 (7%)</td>
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<tr>
<td>Pathological TNM classification</td>
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<td>T stage</td>
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<tr>
<td>T1</td>
<td>18 (3%)</td>
<td>43 (6%)</td>
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</tr>
<tr>
<td>T2</td>
<td>26 (5%)</td>
<td>50 (7%)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>340 (63%)</td>
<td>371 (53%)</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>160 (29%)</td>
<td>235 (34%)</td>
<td></td>
</tr>
<tr>
<td>N stage</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>N0</td>
<td>251 (46%)</td>
<td>242 (35%)</td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td>231 (42%)</td>
<td>298 (43%)</td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td>62 (11%)</td>
<td>159 (23%)</td>
<td></td>
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<tr>
<td>Pathological stage</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage</td>
<td>≥70 years (n = 117)</td>
<td>&lt;70 years (n = 53)</td>
<td>p-value</td>
</tr>
<tr>
<td>-------</td>
<td>---------------------</td>
<td>--------------------</td>
<td>---------</td>
</tr>
<tr>
<td>II (high-risk)</td>
<td>243 (45%)</td>
<td>225 (32%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>264 (49%)</td>
<td>406 (58%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>37 (7%)</td>
<td>68 (10%)</td>
<td></td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>344 (63%)</td>
<td>216 (31%)</td>
<td></td>
</tr>
<tr>
<td>Oral 5-fluorouracil analogue</td>
<td>154 (28%)</td>
<td>248 (35%)</td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin-including regimen</td>
<td>46 (8%)</td>
<td>235 (34%)</td>
<td></td>
</tr>
<tr>
<td>Number of palliative chemotherapy lines after recurrence *</td>
<td>0.81 ± 1.12</td>
<td>1.46 ± 1.44</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as the number of patients (%) or the mean ± standard deviation.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; N/E: not evaluated.

* Only patients with recurrence were included.

Table 2 Reasons for no adjuvant chemotherapy in stage III CRC patients according to age.
Values are presented as the number of patients (%).

PS: Performance Status; AC: adjuvant chemotherapy.

**Figures**

**Figure 1**

Primary high-risk stage II and stage III/IV CRC patients between July 2010 and June 2021 (n = 1395)

Preoperative chemoradiotherapy (n = 152)

Patients included in this study (n = 1243)

Patients ≥70 years (n = 544)
  - High-risk stage II (n = 243)
  - Stage III (n = 264)
  - Stage IV (n = 37)

Patients <70 years (n = 699)
  - High-risk stage II (n = 225)
  - Stage III (n = 406)
  - Stage IV (n = 68)

**Figure 1**

Study flow diagram for analyses.

**Figure 2**

A. High-risk stage II

B. Stage III

C. Stage IV
Figure 2

Kaplan-Meier relapse-free survival curves of colorectal cancer patients according to age. (A) High-risk stage II. (B) Stage III. (C) Stage IV.

Figure 3

Cancer-specific survival curves of colorectal cancer patients according to age. (A) High-risk stage II. (B) Stage III. (C) Stage IV.

Figure 4

Cancer-specific survival curves of stage III colorectal cancer patients according to age. (A) No adjuvant chemotherapy. (B) Oral 5-fluorouracil analogues. (C) Oxaliplatin-including regimens.

Supplementary Files
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