A Bayesian network meta-analysis comparing concurrent chemoradiotherapy followed by adjuvant chemotherapy, concurrent chemoradiotherapy alone and radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma

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Received 1 August 2014; revised 17 September 2014 and 12 October 2014; accepted 13 October 2014

\textbf{Background:} Given the lack of studies, whether the addition of adjuvant chemotherapy (AC) to concurrent chemoradiotherapy (CCRT) is superior to CCRT alone for locoregionally advanced nasopharyngeal carcinoma (NPC) remains unclear. The main objective of this Bayesian network meta-analysis was to determine the efficacy of CCRT + AC when compared with CCRT alone.

\textbf{Patients and methods:} We systematically searched databases and extracted data from randomized, controlled trials involving NPC patients randomly assigned to receive CCRT + AC, CCRT, or radiotherapy (RT). Overall survival (OS), locoregional recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) with hazard ratios (HRs) were investigated. A Bayesian network for different outcomes was established to incorporate all evidence. Multiple treatment comparisons based on the network integrated the efficacy of CCRT + AC, CCRT, and RT.

\textbf{Results:} Eight studies involving 2144 patients were analyzed. In the network meta-analysis, CCRT + AC and CCRT were both significantly better than RT alone for all outcomes, except that no significant difference was found between

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CCRT and RT for LRFS. Though ranking probabilities showed that CCRT + AC was ranked superior to CCRT for OS, LRFS, and DMFS, no significant differences were found between CCRT + AC and CCRT for all outcomes [OS: HR = 0.86, 95% credible interval (CrI) 0.60–1.16; LRFS: HR = 0.72, 95% CrI 0.43–1.15; DMFS: HR = 0.86, 95% CrI 0.62–1.16].

**Conclusions:** No significant improvement was found following CCRT + AC compared with CCRT alone. Whether the omission of additional AC can reduce toxic effects without adversely affecting survival in patients with locoregionally advanced NPC should be further explored, in addition to the precise patient status that would benefit from AC following CCRT.

**Key words:** concurrent chemoradiotherapy, adjuvant chemotherapy, radiotherapy, nasopharyngeal carcinoma, network meta-analysis

## introduction

Nasopharyngeal carcinoma (NPC) has uneven worldwide distribution and high prevalence in Southeast Asia and North Africa [1]. Radiotherapy (RT) is the primary treatment modality for early-stage patients, but control of locoregionally advanced NPC with RT alone is usually unsatisfactory [2].

Combining chemotherapy and RT is a reasonable strategy for improving the prognosis of locoregionally advanced NPC. A recent meta-analysis [3] showed that concurrent chemoradiotherapy (CCRT) was more beneficial for NPC patients than RT alone, while another meta-analysis showed that neoadjuvant chemotherapy effectively enhanced overall survival (OS) and reduced the distant metastasis rate (DMR), and that adjuvant chemotherapy (AC) aided in improving control of the NPC locoregionally recurrence rate (LRR) [4].

The Intergroup 0099 Study (IGS) was the first randomized, controlled trial (RCT) to achieve a significant improvement in the 3-year OS for stage III–IVB NPC patients by adding concurrent–adjuvant chemotherapy to conventional RT [5]. Since then, the National Comprehensive Cancer Network (NCCN) has recommended RT with concurrent–adjuvant chemotherapy for locoregionally advanced NPC. However, there have been serious concerns regarding the applicability of the IGS results, and the outcomes of several RCTs attempting to verify CCRT + AC efficacy were conflicting [6–13]. Moreover, despite the well-demonstrated efficacy of CCRT for locoregionally advanced NPC, whether adding AC to CCRT is better for locoregionally advanced NPC than CCRT alone has not been confirmed, as we lack trials for direct comparison. To the best of our knowledge, our previous reported study is the first head-to-head trial comparing CCRT + AC with CCRT alone in endemic area, where short-term evaluation found no significant difference between failure-free survival and OS [14]. Therefore, this network meta-analysis is important because it would provide useful information on comparisons of CCRT + AC, CCRT and RT by integrating direct and indirect methods to demonstrate the additional value of AC and to verify its efficacy in treating locoregionally advanced NPC.

## materials and methods

### statistical analysis

The primary end point of our network meta-analysis was OS; the secondary end points were locoregional recurrence-free survival (LRFS) and distant metastasis-free survival (DMFS). The survival end point results are expressed as hazard ratios (HRs). Traditional pairwise meta-analyses were conducted first. Details on end points and direct meta-analysis are described in the supplementary Methods, available at *Annals of Oncology* online. Estimated survival curves for OS, LRFS, and DMFS were plotted using the method detailed by Parmar et al. [15]. To address severe acute toxicities (≥grade 3), we compared toxicity rates between CCRT and RT with the χ² test.

The network meta-analyses were built in WinBUGS. We applied both the fixed- and random-effects model proposed by Woods and co-workers. Treatment effects were estimated by posterior means with corresponding 95% credible intervals (CrIs), which can be interpreted similarly to conventional 95% confidence intervals (CIs). The main difference between the fixed- and random-effects models is that the latter considers between-study variance, thereby producing wider CrIs, and is preferred in the presence of heterogeneity. We used Bayesian deviance information criterion (DIC) statistics to compare the two models. The DIC provides a measure of model fit that penalizes model complexity, with lower values suggesting a simpler model and differences of 2–5 considered important. The probability of each treatment being the best, second best and third best was estimated based on its posterior probabilities. The Bayesian network meta-analyses results were compared with pairwise meta-analyses results to evaluate inconsistency. Also, significant inconsistency was indicated if node-splitting analysis derived P < 0.05. Details on methods of Bayesian network meta-analysis and associated references are described in the supplementary Methods, available at *Annals of Oncology* online.

## results

### eligible studies

During selection (supplementary Figure S1, available at *Annals of Oncology* online), we excluded the study by Chen et al. [16] as it involved stage II NPC patients, and excluded the study by Lin et al. [17] for not meeting the eligibility criterion of unpredictable treatment assignment [18]. As Kwong et al. [6] used uracil + tegafur instead of platinum in CCRT, it was excluded from this network meta-analysis, but was included in an additional meta-analysis that did not restrict the agents used, and the results are described in the supplementary Results, available at *Annals of Oncology* online. Thus, eight studies were considered eligible [5, 7–14, 19–22]. The study by Lee et al. was first published in 2005 [8] and updated in 2010 with the 5-year OS data [9]. The same updates were made to the studies of Lee et al. [10, 11], Chen et al. [12, 13], Chan et al. [19, 20], and Zhang et al. and Wu et al. [21, 22]. In the study by Lee et al. [10, 11], patients were divided into four treatment groups: conventional fractionation (CF); CF with concurrent–adjuvant chemotherapy; accelerated fractionation (AF); and AF with concurrent–adjuvant...
<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Inclusion period</th>
<th>Median follow-up (months)</th>
<th>Stage</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Adjuvant</th>
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<td>CCRT + AC versus RT</td>
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<tr>
<td>Al-Sarraf et al. [5]</td>
<td>193</td>
<td>1989–1995</td>
<td>32.4</td>
<td>AJCC III–IV</td>
<td>1.8–2.0 Gy/fx/day, 5 fx/wk, to 66–70 Gy</td>
<td>3* DDP 100 mg/m² (days 1, 22 and 43)</td>
<td>4* DDP 80 mg/m² (day 1) + FU 1000 mg/m² (days 1–4 civ)</td>
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<td>Wee et al. [7]</td>
<td>221</td>
<td>1997–2003</td>
<td>38.4</td>
<td>AJCC II–IV, any T, any N</td>
<td>70 Gy (2 Gy/fx/day, 5 fx/wk for 7 weeks)</td>
<td>DDP 25 mg/m²/day for 4 days, alternatively 30/30/40 mg/m²/day for 3 days</td>
<td>DDP 20 mg/m²/day for 4 days, +FU 1000 mg/m²/day for 4 days</td>
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<td>Lee et al. [8, 9]</td>
<td>348</td>
<td>1999–2004</td>
<td>70.8</td>
<td>AJCC III–IV, any T, N2 or N3, M0</td>
<td>≥66 Gy (2 Gy/fx/day, 5 fx/wk), + additional boosts for parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy</td>
<td>3* DDP 100 mg/m² (days 1, 22 and 43)</td>
<td>q4 wk DDP 80 mg/m² +FU 1000 mg/m²/day (days 71, 99 and 127)</td>
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<td>Lee et al. [10, 11]</td>
<td>93</td>
<td>1999–2004</td>
<td>75.6</td>
<td>AJCC III–IV, T3–4, N0–1, M0</td>
<td>≥66 Gy (2 Gy/fx/day, 5 fx/wk), + additional boosts for parapharyngeal space, primary or nodal sites when indicated not exceeding 20 Gy</td>
<td>3* DDP 100 mg/m² (days 1, 22 and 43)</td>
<td>q4 wk DDP 80 mg/m² +FU 1000 mg/m²/day (days 71, 99 and 127)</td>
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<td>Chen et al. [12, 13]</td>
<td>316</td>
<td>2002–2005</td>
<td>70</td>
<td>AJCC III–IV, T1–4, N0–3, M0</td>
<td>≥68 Gy (2 Gy/fx/day, 5 fx/wk for 7 weeks), + additional boost in case of parapharyngeal extension, residual neck nodes and residual nasopharyngeal disease</td>
<td>3* DDP 100 mg/m² (days 1, 22 and 43)</td>
<td>3* q4 wk DDP 80 mg/m² (day 1) + FU 800 mg/m²/day (days 1–5)</td>
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<td>CCRT versus RT</td>
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<td>Chan et al. [19, 20]</td>
<td>350</td>
<td>1994–1997</td>
<td>66</td>
<td>AJCC II–IV, any T, any N, M0</td>
<td>66 Gy, + additional boost in case of parapharyngeal extension, residual neck nodes and/or residual nasopharyngeal disease (brachytherapy)</td>
<td>8* DDP 40 mg/m² (day 1) weekly</td>
<td>None</td>
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<td>Zhang et al. [21]</td>
<td>115</td>
<td>2001–2003</td>
<td>114</td>
<td>AJCC III–IV, any T, N2 or N3, M0</td>
<td>70–74 Gy (2 Gy/fx/day, 5 fx/wk) + additional boost in case of parapharyngeal extension, residual neck nodes and/or residual nasopharyngeal disease</td>
<td>6* Oxaliplatin 70 mg/m² weekly</td>
<td>None</td>
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<td>CCRT + AC versus CCRT</td>
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<tr>
<td>Chen et al. [14]</td>
<td>508</td>
<td>2006–2010</td>
<td>38</td>
<td>AJCC III–IV, any T, any N, M0, except T3–4N0</td>
<td>2.0–2.27 Gy/fx/day, 5 fx/wk, to 60–66 Gy, irradiation to 50 Gy for potential sites*</td>
<td>7* DDP 40 mg/m² (day 1) weekly</td>
<td>3* q4 wk DDP 80 mg/m² (day 1) + FU 800 mg/m²/day (days 1–5)</td>
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CCRT, concurrent chemoradiotherapy; AC, adjuvant chemotherapy; RT, radiotherapy; AJCC, American Joint Committee on Cancer; fx, fraction; DDP, cisplatin; FU, fluorouracil; civ, continuous i.v.; q4 wk, every 4 weeks.
*Intensity-modulated radiotherapy and 3D conformal radiotherapy were adopted for partial patients.
Chemotherapy. The benefit of AF has not yet been confirmed [11], and the two groups that were treated with AF were excluded as they did not meet our inclusion criterion for the use of CE. Table 1 lists the baseline characteristics of all included studies. These pooled 8 studies involved 2144 randomly assigned patients: 840 received CCRT + AC, 490 received CCRT, and 814 received RT alone. The OS was available for all trials (to include all 193 available patients in the study by Al-Sarraf et al. [5], we obtained the corresponding observed minus expected number of deaths [O–E] and variance from a previous meta-analysis based on individual patient data [18]). The LRFS and DMFS were available for only seven studies [7, 14, 19–22] (for the study by Chan et al. [19, 20], we could obtain corresponding O–E and variance from the individual patient data meta-analysis [18]). Al-Sarraf et al. reported only the absolute number of locoregional and distant failures of 147 patients [5]; information on the time to event was not available. Supplementary Table S1, available at Annals of Oncology online, describes the assessment of the quality of all eligible RCTs.

### direct meta-analysis

Supplementary Figure S2, available at Annals of Oncology online, presents all direct meta-analyses. Compared with RT alone, CCRT + AC (P < 0.0001, HR = 0.64, 95% CI 0.53–0.76), and CCRT (P = 0.005, HR = 0.66, 95% CI 0.49–0.88) benefited OS significantly; there was no significant difference between CCRT + AC and CCRT. CCRT + AC was associated with lower locoregional recurrence risk when compared with RT alone (P = 0.01, HR = 0.59, 95% CI 0.40–0.89); there was no significant difference between CCRT + AC and CCRT, and CCRT and RT alone. There was significantly reduced distant failure in patients who received CCRT + AC (P = 0.002, HR = 0.67, 95% CI 0.52–0.87) and CCRT (P = 0.02, HR = 0.68, 95% CI 0.50–0.95) when compared with RT alone. No significant difference in DMFS was found between CCRT + AC and CCRT. There was no between-study effect size heterogeneity in all comparisons for all end points. To determine whether excluding the trial by Al-Sarraf et al. [5] would affect our conclusions on locoregional and distant failures, we carried out direct meta-analyses of LRR and DMR for CCRT + AC versus RT that included that study. The results are summarized in the supplemen-
tary Results, Tables S3 and S4, and Figures S6, S7, and S8, available at Annals of Oncology online. The conclusions remained valid after including the abovementioned study, but there was effect size heterogeneity in the direct comparisons of CCRT + AC versus CCRT for DMFS.

### network meta-analysis of efficacy

We established a network to compare CCRT + AC, CCRT, and RT alone (Supplementary Figure S4, available at Annals of Oncology online). Figure 1 summarizes the multiple treatment meta-analyses results for OS, LRFS, and DMFS. The respective sets of HRs and corresponding 95% CIs from the fixed- and random-effects models had good consistency despite the relatively wider CIs of the latter (Figure 1A, C, and E). Moreover, we confirmed good coherence between direct and indirect comparisons for all end points; node-splitting analysis indicated no significant inconsistency (all P > 0.05).

Based on the DIC (Figure 1A, C, and E), the fixed-effects model fit the data better than the random-effects model, with relatively lower DIC values for all end points (though the differences were all between 1 and 2), indicating that heterogeneity might not be obvious. Furthermore, as both models yielded consistent conclusions, we applied the fixed-effects model for the rest of the study. Except the CCRT and RT LRFS, CCRT + AC, and CCRT outcomes were both significantly better than RT alone. However, CCRT + AC and CCRT shared equivalent efficacy, and there were no significant differences for all treatment outcomes (OS, LRFS, DMFS) (Figure 1A, C, and E).

Figure 1B, D, and F shows the probability of each treatment being ranked the best, second best, and third best, and the cumulative probabilities for the most efficacious treatments were as follows (OS, LRFS, DMFS): CCRT + AC (84%, 90%, 85%), CCRT (16%, 10%, 15%), RT (0%, 0%, 0%). Supplementary Figure S5, available at Annals of Oncology online, depicts the estimated survival curves for all end points.

### severe acute toxicities

Supplementary Table S2, available at Annals of Oncology online, summarizes the severe acute toxicities (≥ grade 3) of the studies included in this network meta-analysis. In the initial phase, severe adverse events occurred more often following CCRT compared with RT alone. No significant differences existed between the CCRT + AC and CCRT arms in the initial phase of the study by Chen et al. [14]. In the adjuvant phase, the commonly recorded severe acute toxicities were neutropenia (14.1%), nausea/vomiting (13.4%), leukopenia (13.3%), and mucositis (12.0%).

### additional network meta-analysis

The additional network meta-analysis results, which included the study by Kwong et al. [6], are described in the supplementary Results, Tables S3 and S4, and Figures S6, S7, and S8, available at Annals of Oncology online. The conclusions remained valid after including the abovementioned study, but there was effect size heterogeneity in the direct comparisons of CCRT + AC versus CCRT for DMFS.

### discussion

Multiple treatment comparison is a powerful method for investigating RCT networks, and has been used for head and neck squamous cell carcinoma [23]. Our Bayesian network meta-analysis is the first study to compare CCRT + AC, CCRT, and RT efficacy for locoregionally advanced NPC through direct and indirect statistical comparisons based on all available information from the included RCTs. As HR was the only summary statistic allowing for both censoring and time to an event, we assessed OS, LRFS, and DMFS with HR and its 95% CI or CrI, confirming good consistency between direct and network meta-analyses of these end points.

Compared with RT alone, CCRT + AC had a significant treatment effect on OS, LRFS, and DMFS; CCRT had a significant treatment effect on OS and DMFS, but did not improve locoregional control significantly. However, there was no significant difference between CCRT + AC and CCRT for all end points, indicating that AC following CCRT did not improve treatment outcome remarkably. All included studies involving AC used the IGS regimen for the adjuvant phase, adopting cisplatin and
fluorouracil (PF regimen) as recommended [5]. A phase III study [24] showed that this combination improved the response rate but not the survival rate when compared with either agent individually, indicating that the adjuvant PF regimen may be insufficiently effective for eradicating micrometastases and improving OS in head and neck cancers and NPC. The well-recognized favorable results for CCRT may also have diluted any potential benefit of AC for controlling locoregional recurrence and distant metastases. Moreover, given the acute toxic effects during CCRT, adjuvant therapy compliance was similar (52%–61%) and relatively poor in the CCRT + AC RCT [14], which may have affected the efficacy of AC. The actual magnitude of the AC survival benefit may also have been reduced due to the toxicities of chemotherapy, possibly successful salvage after relapse, and increased noncancer deaths [8, 10, 12].

As expected, RT ranked worst for OS, LRFS, and DMFS. As for CCRT + AC and CCRT, the former ranked superior to the latter for all treatment outcomes. However, in network meta-analysis, even if the effect size differences among treatments were small and nonsignificant, a probability of treatment ranking would have been produced without a clear statistical meaning. It would be misleading if clinical decisions regarding the therapeutic regimens selected were mainly dependent on it. In fact, CCRT + AC and CCRT did not differ significantly for all outcomes in our study. Also, it was noteworthy that the survival curves for CCRT + AC and CCRT were gradually separated by a slight difference in approximately the first 2–3 years, but later became

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\begin{align*}
\text{Fluorouracil (PF regimen) as recommended [5]. A phase III study [24] showed that this combination improved the response rate but not the survival rate when compared with either agent individually, indicating that the adjuvant PF regimen may be insufficiently effective for eradicating micrometastases and improving OS in head and neck cancers and NPC. The well-recognized favorable results for CCRT may also have diluted any potential benefit of AC for controlling locoregional recurrence and distant metastases. Moreover, given the acute toxic effects during CCRT, adjuvant therapy compliance was similar (52%–61%) and relatively poor in the CCRT + AC RCT [14], which may have affected the efficacy of AC. The actual magnitude of the AC survival benefit may also have been reduced due to the toxicities of chemotherapy, possibly successful salvage after relapse, and increased noncancer deaths [8, 10, 12].}
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relatively smoother and closer, with slightly smaller absolute differences at 5 years than at 3 years (supplementary Figure S5, available at Annals of Oncology online). This trend may have been due to the more common occurrence of locoregional recurrence and distant metastasis in the early years after RT [12], and it has been hypothesized that AC may only prolong the latency of locoregional recurrence and distant metastasis occurrence instead of improving their long-term control effectively [13]. Overall, a dialectical and comprehensive view on the choice between CCRT + AC and CCRT in the clinic is required.

Currently, the 2014 NCCN recommends CCRT followed by AC for locoregionally advanced NPC (Category 2A); CCRT alone is also an option (Category 2B) (http://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf). The National Cancer Institute also recommends CCRT + AC for locoregionally advanced NPC (http://www.cancer.gov/cancertopics/pdq/treatment/nasopharyngeal/HealthProfessional). However, the European Society for Medical Oncology recommends CCRT alone for locoregionally advanced NPC, and indicates that the benefit of three cycles of adjuvant cisplatin-fluorouracil is uncertain and that it has a substantial toxic effect [25]. Compared with CCRT + AC, CCRT alone has the following advantages: (i) relatively fewer toxic effects without additional adjuvant therapy; (ii) more satisfactory compliance; (iii) relatively lower expense. Although the CCRT and RT LRFS were not significantly different in our study, improved radiation techniques such as intensity-modulated RT may have compensated for it.

Regardless, a trend toward a higher rate of efficacy for CCRT + AC compared with CCRT alone was observed. Certain patient statuses might therefore benefit most from additional AC following CCRT. The subgroup analysis by Lee et al. [9] showed that among NPC patients with T1–4N2–3M0 disease, CCRT + AC mainly benefited patients with T1–2N2–3 disease. A retrospective study [26] showed that CCRT + AC mainly benefited intermediate-risk patients (T2b–3N0–2M0), with significant benefit in 5-year OS when compared with RT or CCRT alone. Recently, it was reported that unfavorable Epstein–Barr virus DNA response midpoint of RT was an adverse prognosticator for treatment outcome in advanced-stage NPC [27], and may serve as an indicator for the addition of adjuvant therapy to initial treatment. Overall, CCRT + AC appears to benefit patients who meet certain selection criteria, and further studies are required to define this patient population.

The study limitations also should be acknowledged: extracted all information from published data other than individual patient data, which may have resulted in publication and reporting bias. Some of this unreported individual patient information may have aided better evaluation of the quality of an RCT. Moreover, without access to individual patient data, missing information on certain prognostic factors and end points could have affected our analysis, e.g. LRFS and DMFS were not available in the study by Al-Sarraf et al. [5]. To minimize the risk of bias, we restricted inclusion criteria, searched and reviewed the publications comprehensively, and two independent investigators extracted the data and assessed RCT quality. Excluding the study by Al-Sarraf et al. [5] from the LRFS and DMFS analysis might have affected the validity of our findings, although our conclusions remained valid following additional direct meta-analyses of LRR and DMR that included that trial.

In conclusion, our network meta-analysis shows that there was no significant survival improvement following CCRT + AC when compared with CCRT alone. The long-term follow-up results of our trial [14], which would be instructive, is awaiting to be reported. Whether the omission of additional AC can reduce toxic effects without adversely affecting survival outcomes for patients with locoregionally advanced NPC should be further explored. In addition, the specific patient statuses that would benefit from AC following CCRT deserve further investigation.

acknowledgements

We thank the anonymous reviewers for their insightful comments and great efforts to improve this manuscript.

disclosure

The authors have declared no conflicts of interest.

references

Acceptance of surrogate end points in clinical trials supporting approval of drugs for cancer treatment by the Japanese regulatory agency

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Received 3 July 2014; revised 24 August 2014 and 12 September 2014; accepted 15 October 2014

Background: This study investigated the historic use of different end points to support approval of drugs for cancer treatment in Japan.

Patients and methods: Anticancer drugs approved between April 2001 and April 2014 were comprehensively investigated using publicly available information.

Results: Before the revision of the guideline for oncology drugs in April 2006 in Japan, >80% of end points supporting approval were response rate and overall survival (OS) was not frequent. After the revision of the guideline in Japan, using OS in pivotal clinical trials applied for approval increased to more than approximately one-third of oncology drugs, although trials with an end point of response rate decreased. Regarding drugs for major cancers including non-small-cell lung cancer, gastric cancer, colorectal cancer, and breast cancer, survival was used as an end point in 44.0%, whereas surrogate end points were used in 56.0%. Exploration of potential factors for using surrogate end points other than survival carried out through determinations of

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