Answer Reviewers

Name of journal: World Journal of Gastrointestinal Oncology

Manuscript NO: 50599

Title: Interpretation of the development of neoadjuvant therapy for gastric cancer based on the vicissitudes of the NCCN guidelines

Reviewer's code: 03017141

I would like to express my gratitude to reviewer 03017141, because he/she has read my manuscript carefully and all the suggestion he/she provided just hit the nail. Here are my replies and revisions.

BRIEF

1. **Authors should review critically and interpret the guideline recommendation in Asian view.**

Answer: The NCCN guidelines was evidence-based and authoritative, but most trials about neoadjuvant chemo-/chemoradiotherapy were based on non-Asian population. In the revision, I declared this situation and the present acceptance of NACT in Japan, South Korea and China, and also added more studies that conducted in Asian countries. In order to provide a more critical view of NACT, and send out Asian voice.

CITE(second paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER): Above all, the validation of NAT in a wider range is necessary. The NCCN guidelines may only reflect a corner of NAT from the western view, and the acceptability of NAT worldwide is still improving, especially in Asia. Chinese GC guidelines recommended patients with advanced resectable gastric cancer (clinical stage III or above) could either receive surgery directly (Grade I recommendations) or receive neoadjuvant chemotherapy (Grade II recommendations). In Japan, preoperative chemotherapy has just been accepted in the latest guidelines for LAGC patients with bulky lymph nodes. And in South Korea, the efficacy of preoperative chemotherapy and chemoradiotherapy for potentially resectable

GC patients remains inconclusive. Meanwhile, numerous trials in Asia, such as JCOG0405, JCOG1002, NCT01515748, NCT01534546, NCT02555358 and NCT00252161 have or will provide more evidence about the best indication of NAT, and physicians should always be critical when adopting the recommendations from foreign guidelines.

PREOPERATIVE NEOADJUVANT CHEMORADIOTHERAPY

1. **Authors describe that 'The French FFCD 9102 study even reported that the efficacy of preoperative chemoradiotherapy could compare favorably with surgery', which sounds inappropriate. The study compared different neoadjuvant regimens and not compare neoadjuvant therapy with other strategy such as surgery alone.**

Answer: I have made my revision to this inappropriate expression. The FFCD 9102 study indicated that, as for chemoradiotherapy-sensitive esophageal cancer patients, the additional surgery after chemoradiotherapy could not provide benefits than additional chemoradiotherapy. I was intend to show the extraordinary effect of chemoradiotherapy in the treatment on esophageal cancer.

CITE (first paragraph of PREOPERATIVE NEOADJUVANT CHEMORADIOTHERAPY): The Fédération Francophone de Cancérologie Digestive 9102 (FFCD 9102) study reported that, for locally advanced thoracic esophageal cancer patients who respond to chemoradiation, the additional surgery could provide no benefit comparing with the continuation of additional chemoradiation.

2. **Authors describe that 'As a result of this evidence, preoperative chemoradiotherapy surpassed perioperative chemotherapy, specifically for esophagogastric junction adenocarcinoma according to the NCCN guidelines', but NCCN guidelines only state 'preferred'. There has not been enough evidence based on randomized trials comparing chemotherapy with chemoradiotherapy.**

Answer: I weigh the accuracy of “preferred” and “surpassed”, and made the revision.

CITE:As a result, preoperative chemoradiotherapy was recommended as the preferred approach for localized EGJ adenocarcinoma (for Siewert type III EGJ cancer, hereinafter the same) according to the NCCN guidelines from 2012 to 2014.

3. **As for EGJ cancer, please clarify that the recommendation preoperative neoadjuvant chemoradiotherapy (category 2B) and re/perioperative chemotherapy (category 1) are for Siewert type III EGJ adenocarcinoma. The NCCN guidelines for esophageal and EGJ cancer, which is applicable in Siewert type I or II EGJ cancer, state that preoperative chemoratidation (category 1) is preferred over preoperative chemotherapy for EGJ (ESOPH-13).**

Answer: thank you for reminding me of this mistake, I made appropriate revision and declared that the EGJ cancers we discussed around NAT were all Siewert type III EGJ cancer.

CITE: (last two paragraphs of PREOPERATIVE NEOADJUVANT CHEMORADIOTHERAPY)As a result, preoperative chemoradiotherapy was recommended as the preferred approach for localized EGJ adenocarcinoma (for Siewert type III EGJ cancer, hereinafter the same) according to the NCCN guidelines from 2012 to 2014.

Since the effects of preoperative chemoradiotherapy in resectable GC were only proposed by small-scale and single-arm studies, the regimens and dosing schedules listed in NCCN guidelines were referred to trials that recruited esophageal and/or EGJ cancers patients. Therefore, the recommendation category of preoperative chemoradiotherapy remains in category 2B according to the latest NCCN guidelines. More than that, since there has not been enough studies compared the effect of pre/perioperative

chemotherapy with chemoradiotherapy, the preferred recommendation of preoperative chemoradiotherapy for localized EGJ (Siewert type III) adenocarcinoma was also deleted in the 2015 NCCN guidelines. In the following sections, we will focus more on the development of neoadjuvant chemotherapy for LAGC.

PRE/PERIOPERATIVE NEOADJUVANT CHEMOTHERAPY

1. **The completion rates of postoperation therapy in MAGIC and FNCLCC/FFCD 9703 are wrong. The rate authors describe are that of commencement of postoperation therapy, not completion rate.**

Answer: I went through the MAGIC, FNCLCC/FFCD 9703 and FLOT4 study again, and corrected my mistake about the rates. In the revision, I re-quote/calculated the commencement and completion rate of postoperative therapy based on the original article.

CITE (the third paragraph of PRE/PERIOPERATIVE NEOADJUVANT CHEMOTHERAPY): However, due to the dissatisfactory commencing rates of postoperative chemotherapy in these studies (137/209 (65.6%), 54/109 (49.5%) and 78/119 (65.5%) for MAGIC, FNCLCC & FFCD 9703 and FLOT4 study, respectively) and even lower completion rates (104/209 (49.8%), 25/109 (22.9%) and 60/119 (55.0%), respectively), the benefits of postoperative chemotherapy were inconclusive.

FLUOROURACIL AND PLATINUM-BASED REGIMENS

1. **In the description of FNCLCC&FFCD 9703 study, authors describe p value of 5-year OS was 0.02. The original report state that the p value was for log rank test not for survival rate at 5 years.**

Answer: Thank you very much for your careful reviewing, I have changed into More importantly, the perioperative FP regimen significantly increased the 5-year OS (38% *vs.* 24%, log-rank P=0.02) and 5-year DFS (34% *vs.* 19%, log-rank P=0.003) of patients.

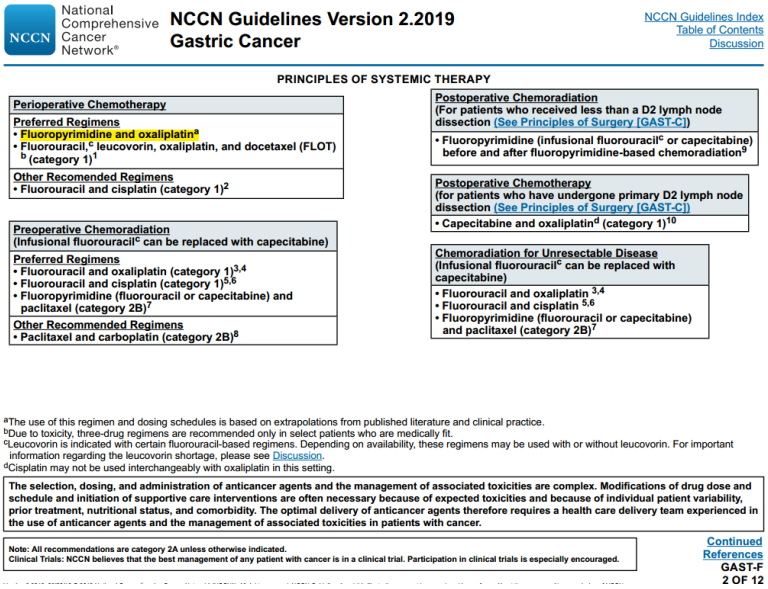
2. **Authors describe 5-year PFS but the original study only report disease free survival (DFS) rate.**

Answer: I have amended this mistake and changed the PFS into DFS.

CITE: More importantly, the perioperative FP regimen significantly increased the 5-year OS (38% *vs.* 24%, log-rank P=0.02) and 5-year DFS (34% *vs.* 19%, log-rank P=0.003) of patients.

3. **Please refer that recommendation by the latest NCCN guidelines on the fluorouracil + oxaliplatin regimen is category 1.**

Answer: I checked the latest NCCN guidelines (2019.V2, GAST-F, 2 OF 12), it seems that the regimen of fluoropyrimidine and oxaliplatin was still in category 2A, but was preferred regimen.



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy
Preferred Regimens
- Fluoropyrimidine and oxaliplatin[a]
- Fluorouracil,[c] leucovorin, oxaliplatin, and docetaxel (FLOT)[b] (category 1)[1]

Other Recomended Regimens
- Fluorouracil and cisplatin (category 1)[2]

Preoperative Chemoradiation
(Infusional fluorouracil[c] can be replaced with capecitabine)
Preferred Regimens
- Fluorouracil and oxaliplatin (category 1)[3,4]
- Fluorouracil and cisplatin (category 1)[5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

Other Recommended Regimens
- Paclitaxel and carboplatin (category 2B)[8]

Postoperative Chemoradiation
(For patients who received less than a D2 lymph node dissection (See Principles of Surgery [GAST-C])
- Fluoropyrimidine (infusional fluorouracil[c] or capecitabine) before and after fluoropyrimidine-based chemoradiation[9]

Postoperative Chemotherapy
(for patients who have undergone primary D2 lymph node dissection (See Principles of Surgery [GAST-C])
- Capecitabine and oxaliplatin[d] (category 1)[10]

Chemoradiation for Unresectable Disease
(Infusional fluorouracil[c] can be replaced with capecitabine)
- Fluorouracil and oxaliplatin [3,4]
- Fluorouracil and cisplatin [5,6]
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[7]

[a]The use of this regimen and dosing schedules is based on extrapolations from published literature and clinical practice.
[b]Due to toxicity, three-drug regimens are recommended only in select patients who are medically fit.
[c]Leucovorin is indicated with certain fluorouracil-based regimens. Depending on availability, these regimens may be used with or without leucovorin. For important information regarding the leucovorin shortage, please see Discussion.
[d]Cisplatin may not be used interchangeably with oxaliplatin in this setting.

The selection, dosing, and administration of anticancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and because of individual patient variability, prior treatment, nutritional status, and comorbidity. The optimal delivery of anticancer agents therefore requires a health care delivery team experienced in the use of anticancer agents and the management of associated toxicities in patients with cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
References
GAST-F
2 OF 12

THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER

1. **Authors seem to confuse ACTS-GC and SPIRITS trial. The former was the study on adjuvant S-1 therapy and the latter compared S-1 mono therapy with S-1 plus cisplatin therapy for metastatic disease.**

Answer: We truly mistakenly quoted the ACTS-GC study, and I have replaced it with SPIRITS trial and updated the OS of the two studies. Also explained the intention of this comparison.

CITE(the 4th paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER):The advantages of the S-1 and cisplatin regimens reported by the SPIRITS (S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer) study in Japan were not consistently concluded in the non-Asian trial of the FLAGS (First-Line Advanced Gastric Cancer Study) study (median OS, 13.0 months *vs.* 8.6 months, respectively)

2. **Please refer to ongoing studies other than RESOLVE with their identification numbers.**

Answer: I referred the RESOLVE trial with its NCT number provided by ClinicalTrials.gov, which is NCT01534546. I also changed all other ongoing studies with their NCT numbers.

CITE(in CONCLUSION section): We are looking forward to more high-quality studies such as the NCT01534546, NCT02555358, NCT00252161 and so on, which will help to establish a characteristic neoadjuvant therapy strategy that is more appropriate for Asian populations.

(the 2nd paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER)Meanwhile, numerous trials in Asia, such as JCOG0405, JCOG1002, NCT01515748, NCT01534546, NCT02555358 and NCT00252161 have or will provide more evidence about the best indication of NAT, and physicians should always be critical when adopting the recommendations from foreign guidelines.

OTHERS

1. **Please cite relevant manuscript on the description of Gompertzian model.**

Answer: The proper citation of Gompertzian model has been added.

CITE(reference 36): Norton L. A Gompertzian model of human breast cancer growth. Cancer Res 1988; 48(24 Pt 1): 7067-7071 [PMID: 3191483]

2. In the FLOT section, please clarify that V325 was the study for metastatic disease.

Answer: The appropriate clarification was added to the V325 study.

CITE(the 2nd paragraph of FLOT): The V325 study published in 2006 was the first large clinical trial that applied docetaxel in gastric cancer. Although the DCF regimen (docetaxel, cisplatin and fluorouracil) used in this study improved the response rate of chemotherapy and prolonged the OS and PFS of patients with metastatic or locally recurrent disease, severe side effects have prevented this regimen from being widely accepted.

Reviewer's code: 00505755

1. **The appropriate citation for the RESOLVE study in conclusion may be added.**

Answer: I referred the RESOLVE trial with its NCT number provided by ClinicalTrials.gov, which is NCT01534546. I also changed all other ongoing studies with their NCT numbers.

CITE(in CONCLUSION section): We are looking forward to more high-quality studies such as the NCT01534546, NCT02555358, NCT00252161 and so on, which will help to establish a characteristic neoadjuvant therapy strategy that is more appropriate for Asian populations.

(the 2nd paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER)Meanwhile, numerous trials in Asia, such as JCOG0405, JCOG1002, NCT01515748, NCT01534546, NCT02555358 and NCT00252161 have or will provide more evidence about the best indication of NAT, and physicians should always be critical when adopting the recommendations from foreign guidelines.

2. **Categories based on NCCN guidelines for perioperative chemotherapy and preoperative chemoradiotherapy may be described more in detailed in the text and Table 2 with citations or references.**

Answer: The recommendation made by NCCN was based on high-quality trials. In the guideline, NCCN referred to certain studies/trials for every recommendation, and I quoted the references accordingly in table 2. In the last paragraph of PRE/PERIOPERATIVE NEOADJUVANT CHEMOTHERAPY and PREOPERATIVE NEOADJUVANT CHEMORADIOTHERAPY, I discussed about the recommendations and also declare that to which references certain regimens and dosing schedules were referred.

CITE: (please see Table 2 in the revision)

(the last paragraph of PRE/PERIOPERATIVE NEOADJUVANT CHEMOTHERAPY) Although undisputed benefits of perioperative chemotherapy have been presented by many clinical trials (see Table 1), the category 1 recommendation made by NCCN guidelines was mainly derived from the above three landmark studies (the MAGIC, FNCLCC & FFCD 9703, and FLOT4 study). Sequentially, the dosing schedules of recommended regimens were also based on these three or their relevant studies (except for fluorouracil and oxaliplatin regimen, see Table 2).

(the last paragraph of PREOPERATIVE NEOADJUVANT CHEMORADIOTHERAPY) Since the effects of preoperative chemoradiotherapy in resectable GC were only proposed by small-scale and single-arm studies, the regimens and dosing schedules listed in NCCN guidelines were referred to trials that recruited esophageal and/or EGJ cancers patients. Therefore, the recommendation category of preoperative chemoradiotherapy remains in category 2B according to the latest NCCN guidelines. More than that, since there has not been enough studies compared the effect of pre/perioperative chemotherapy with chemoradiotherapy, the preferred recommendation of preoperative chemoradiotherapy for localized EGJ (Siewert type III) adenocarcinoma was also deleted in the 2015 NCCN guidelines. In the following sections, we will focus more on the development of neoadjuvant chemotherapy for LAGC.

Reviewer's code: 03478911

Also, I would like to thank reviewer 03478911 for his/her constructive suggestion. I made careful revisions to my manuscript according to this reviewer's advices, which definitely improve the quality of the article.

1. **Neoadjuvant therapy refers to preoperative chemotherapy. Don't have to use two words in the same line.**

Answer: I made my revision based on your recommendation and further polished the language.

2. **Before using abbreviations such as EORTC or MAGIC, it is necessary to provide official names.**

Answer: The official names of these studies have been added at the first time they appeared, and the abbreviations were used after.

CITE:

the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) study;

the European Organisation for Research and Treatment of Cancer Randomized Trial 40954 (EORTC 40954) study;

The Fédération Nationale des Centres de Lutte contre le Cancer and Fédération Francophone de Cancérologie Digestive 9703 (FNCLCC&FFCD 9703) study;

The FLOT4 (Fluorouracil, leucovorin, oxaliplatin, docetaxel) study;

the Intergroup-0116 (INT-0116) study;

the Radiation Therapy Oncology Group 9904 (RTOG 9904) study;

Cancer and Leukemia Group B 9781 study, CALGB 9781 study;

Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study, CROSS study;

the PreOperative therapy in Esophagogastric adenocarcinoma Trial (POET);

the Randomized ECF for Advanced and Locally Advanced

Esophagogastric Cancer 2 (REAL-2) study;

the S-1 Plus cisplatin versus S-1 In RCT In the Treatment for Stomach cancer (SPIRITS) study;

the First-Line Advanced Gastric Cancer Study (FLAGS);

the Trastuzumab for Gastric Cancer (ToGA) study.

3. **There are many types of neoadjuvant chemotherapy and chemoradiotherapy for the treatment of LAGC, and treatment efficiencies, such as survival or recurrence rate, varies according to incidence region, TNM stage, sex, age, or etc. However, the author only provided small scale of the therapeutic option and their simple contents of the effectiveness. This reviewer considers that it has to be the most focused part of this mini-review. Therefore, a detailed chapter or table must be provided.**

Answer: Since NCCN GC guidelines were one of the most authoritative evidence-base guidelines at present, we intended to review the development and practice of neoadjuvant therapy (mainly chemotherapy) via it vicissitudes according to NCCN guideline.

The preferences and effects of different regimens varies according to regions and disease status. I review the effects of the four regimens (ECF related, Fluorouracil+cisplatin, Fluorouracil+oxaliplatin, and FLOT) in clinical practices based on your recommendation, which were extracted and demonstrated in the table 3.

During the review, I amended some data provided by the original article and re-calculated surgical rate, R0 rate and so on, in order to improve the comparability. The table 3 was carefully organized and summarize, and I thought the content may be appropriate for revealing the short-term and long-term effects of different regimens. Honestly, table 3 alone may be insufficient to make comprehensive comparison of different regimens. And the different dosing schedules, completion rates, surgical and R0 rates,

pathological regression standards may disturb the accuracy of comparison. I tried to provide integrated information and increase the comparability of these data in Table 3, and also provided representative results in the manuscript.

CITE(please see Table 3 in the revision)

(last paragraph of the THE EVOLUTION OF NEOADJUVANT CHEMOTHERAPY REGIMENS chapter) The efficacy of these regimens was further verified in many studies (see Table 3). However, the absolute advantages of different regimens can hardly be concluded, because of the different regions, dosing schedules, completion rates, surgery/R0 resection rates and so on. Generally, the fluorouracil plus platinum regimens are more popular in Asia, while the ECF/ECF modifications and the FLOT are widely accepted in Europe. An excellent 4-year OS was achieved by Li *et al.* with perioperative FOLFOX regimen. In this prospective non-randomized study, LAGC patients received a total of 6 cycles FOLFOX chemotherapy perioperatively or postoperatively. The clinical and pathological response rate of FOLFOX was 69.7% and 39.4%, and the 4-year OS, as well as the 4-year DFS, of the neoadjuvant arm was 78%. Meanwhile, the highest pathological response rate was achieved by Favi *et al.* with preoperative FLOT regimen. Patients with advanced distal esophageal and EGJ cancer in this study received 3-6 cycles of FLOT chemotherapy before surgery, the tumor regression rate of Cologne regression grade 1-3 was 52% and the 3-year OS was 37%. Nevertheless, the disease recurrences were still common among all the studies and regimens, with the recurrence rates ranged from 32% to 62.5% (see Table 3).

4. **In the paragraph "THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER", introduction is missing for newly developed anticancer drug candidates. It would be better to briefly describe the potential possibility for utilizing neoadjuvant chemotherapy targeting**

LAGC, from 3rd generation immunotherapy to 4th generation cancer-specific metabolism-regulating drugs.

Answer: The development of targeted therapy, immunotherapy and cancer-specific metabolism-regulating therapy was briefly introduced in THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER chapter. Considering the length and theme of the manuscript, I didn't added new table to this topic, but referred published reviews instead.

CITE:(the 3rd paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER) Besides traditional cytotoxic regimens, the development of targeted therapy, immunotherapy and metabolism based anticancer therapy may help us usher in a new era of LAGC treatment. Targeted drugs such as trastuzumab (anti-HER2) and ramucirumab (anti-VEGF2) have shown potential in improving clinical outcomes for late staged patients. The immunotherapy, such as anti-PD-1/PD-L1 and anti-CTLA-4 drugs (nivolumab, pembrolizumab, avelumab, Tremelimumab, *etc*.), the adoptive cell therapy, as well as the VEGF related cancer vaccine, have also been evaluated in gastric cancer and have shown promising effects. Researches about cancer metabolomics also provided new insights in cancer treatment. Drugs targeting at hexokinase II may intervene the glycolysis of tumor cells, and others that altered the metabolism of lipid, amino acid, *etc*. also presented exciting prospects in treating gastric cancer in vitro.

Reviewer's code: 03806663

1. **The authors handle topic of gastric cancer as a one disease issue regardless of the type of histopathology i.e is there a difference between neoadjuvant for well and undifferentiated adenocarcinoma, signet ring adenocarcinoma.**

Answer：There are many classification standard for gastric cancer from pathologic (Borrmann, Lauren, WHO classification) and molecular (TCGA, ACRG classification) view, and the histopathologic regression and/or absolute benefit after neoadjuvant chemotherapy and chemoradiotherapy varies according to plenty of clinical trials (such as the FLOT4 study, the SPIRITS and FLAGS study, the pharmacogenetic analyses published by Goekkurt E, etc.). I fully agree that gastric cancer is not a one kind disease, unfortunately, the neoadjuvant therapy strategy of NCCN (or gastric cancer guidelines of ESMO) didn't provided physicians with certain regimens for different pathological patterns. It is partially because of the lacking of clinical studies, and we have seen that there are more and more studies focused on the effect prediction on preoperative treatment. To make up the defect of the manuscript base on your suggestion, I put more detailed description on the heterogeneity of gastric cancer, and also added more review in the chapter of *THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER*.

CITE(the 4th paragraph of THE FUTURE OF NEOADJUVANT THERAPY FOR GASTRIC CANCER): The heterogeneity of histopathology in GC also results in different response rate to the same regimen. Although the latest NCCN guidelines of GC (2019.V2) didn't recommend the best regimen for each pathological type, clinical trials such as the FLOT study have proposed the different histopathological regression rate among different histology types. We should never handle gastric cancer as a one kind of disease, and preoperative treatment will eventually be recommended based on the histopathology types (Lauren, JGCA, WHO classification, *etc.*) and/or the molecular types (TCGA, ACRG classification, *etc.*).