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EJC Preview

Multidisciplinary management of stage II-III gastric and gastro-oesophageal junction cancer

Anna D. Wagner [a,*], Florian Lordick [b], Heike I. Grabsch [c,d], Masanori Terashima [e], Mitsumi Terada [m], Takaki Yoshikawa [g], Narikazu Boku [h], Kozo Kataoka [i], Elizabeth C. Smyth [j], Murielle Mauer [f], Karin Haustermans [k], Markus H. Moehler [l]

[a] *Department of Oncology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*
[b] *University Cancer Center Leipzig, University Medicine Leipzig, Leipzig, Germany*
[c] *Department of Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Center, Maastricht, the Netherlands*
[d] *Pathology and Data Analytics, Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK*
[e] *Division of Gastric Surgery, Shizuoka Cancer Center, Japan*
[f] *EORTC Headquarters, Bruxelles, Belgium*
[g] *Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan*
[h] *Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*
[i] *Department of Surgery, Division of Lower GI, Hyogo College of Medicine, Hyogo, Japan*
[j] *Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*
[k] *Department of Radiotherapy and Oncology, University of Leuven, Leuven, Belgium*
[l] *University Medical Center, Johannes Gutenberg University Mainz, Mainz, Germany*
[m] *Japan Clinical Oncology Group, Clinical Research Support Office and National Cancer Center Hospital, Tokyo, Japan*

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Abstract The aim of this manuscript is to discuss the viewpoint of the European Organisation for Research and Treatment of Cancer (EORTC) Gastric Cancer Taskforce and Japan Clinical Oncology Group (JCOG) Gastric Cancer Study Group on the current challenges in the multidisciplinary management of stage II-III gastric and gastro-oesophageal junction (GEJ) cancer. We seek to outline how these challenges are addressed in current trials of both groups. Key elements of future trials of EORTC and JCOG in this indication are described, and a joint vision on how

* *Corresponding author*: Department of Oncology, Lausanne University Hospital and University of Lausanne, Bugnon 46, CHUV, 1011 Lausanne, Switzerland. Fax: +41 21 314 0737.
E-mail address: dorothea.wagner@chuv.ch (A.D. Wagner).

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multidisciplinary research of gastric and GEJ cancer patients should be organised is outlined.

1. Background

The prognosis of patients with gastric cancer (GC) is guarded; while endoscopic or surgical resection is curative in about 90% of patients with early-stage (T1N0) GC, survival decreases dramatically for patients with T2-3 GC or those with regional lymph node involvement [1], especially in Caucasian patients. Interestingly, stage by stage, Asian patients with T2 and T3 GC have a significantly better prognosis than non-Asian patients [2]. The histological phenotype appears to matter for patient's prognosis and patients with diffuse type GC have less favourable outcomes. Although several molecular classifications of gastro-oesophageal junction (GEJ) and GC have been described [3,4], these do not yet contribute to standard patient management decisions (see Fig. 1).

In addition to tumour biology, the quality of surgery and perioperative multidisciplinary management, including perioperative or adjuvant chemotherapy, are major determinants of patients' short-term and long-term outcomes. In Europe, perioperative chemotherapy is standard of care for medically fit patients with clinical stage II-III GC and is recommended in current guidelines [5,6]. In contrast, in Japan, GC patients are usually treated with surgery followed by adjuvant chemotherapy in patients with pathologically confirmed stage II or III GC. Both, European and Japanese Guidelines [5,7] currently agree that surgery should be performed as a D2 resection in high volume centres.

2. Summary of treatment approaches and challenges in Europe and Japan

The standard of care in Europe has recently changed because of the results of the phase III randomised FLOT4 trial [8], in which perioperative chemotherapy with FLOT (5-fluouracil [5-FU], leucovorin, oxaliplatin and docetaxel) was associated with a significant improvement in overall survival (median survival: 35 versus 50 months; projected 5-year survival: 36 versus 45%) compared with ECF/ECC (epirubicin, cisplatin and 5-FU/capecitabine). Thus, perioperative chemotherapy with FLOT has a clear incremental benefit compared with anthracycline-based perioperative chemotherapy and is now considered European standard of care for patients with locally advanced (resectable) GC. Nevertheless, some clinical challenges remain; for example, more than 40% of patients treated with neoadjuvant FLOT had either a minimal or no histopathological response to neoadjuvant chemotherapy (tumour regression grade [TRG] III according to Becker [9]) or were unable to proceed to surgery, most often because of progressive disease. Furthermore, there are concerns with respect to the suitability of elderly patients or patients with co-morbidities for triplet chemotherapy regimens in general in view of their higher toxicity profile. A final challenge is that there are still patients who have a poor prognosis following perioperative chemotherapy plus surgery, such as patients with incomplete (R1) resections or lymph node metastases [10] indicating an urgent need for further research.

In Japan, the standard of care for patients with stage II or III GC results from the pivotal phase III 'ACTS-GC' study, which demonstrated the efficacy of adjuvant S-1 chemotherapy after D2 surgery in Japanese patients [11,12]. In patients with pathological stage II disease, 5-year survival was over 85% in patients treated with surgery followed by 1 year of S-1 chemotherapy. The question whether the duration of adjuvant S-1 treatment in patients with p-stage II GC can be reduced from 8 to 4 cycles without compromising efficacy was recently investigated in the randomised phase III JCOG1104-trial [13]. However, the non-inferiority (NI) of four versus eight courses of S-1 could not be demonstrated. Thus, 1 year of adjuvant S-1 chemotherapy in patients with p-stage II GC remains the standard of care in Japan. Several years after ACTS-GC, the Korean 'CLASSIC'-trial [14] demonstrated a survival benefit for GC patients treated with surgery followed by adjuvant capecitabine and oxaliplatin (CAPOX) compared with surgery alone and established CAPOX as an alternative to adjuvant S-1 chemotherapy in Korea and Japan.

The more recent randomised phase III JACCRO-07 trial demonstrated that patients treated with S-1 plus docetaxel compared with S-1 alone as adjuvant treatment for curatively resected GC had improved 3-years relapse-free survival (65%) compared with patients treated with S-1 alone (49.6%, hazards ratio [HR] 0.632, 95% confidence interval [CI] 0.400–0.998, $p = 0.0007$) [15]. On this basis, S-1/docetaxel after D2 gastrectomy is expected to become a new standard of care for patients with stage III GC in Japan.

Although the use of neoadjuvant chemotherapy (NAC) is uncommon in Japan, even for locally advanced GC, there has been recent research in this area. JCOG0501 [16] examined the value of neoadjuvant S-1 plus cisplatin followed by surgery + adjuvant S-1 versus surgery + adjuvant S-1 in Borrmann type 4 (diffusely infiltrative) or large (≥8 cm) Borrman type 3 (ulcero-infiltrative) cancers. Interestingly, 3-year overall survival did not appear to be different between the two arms of the trial (60.9% versus 62.4% for patients treated with or without NAC, HR

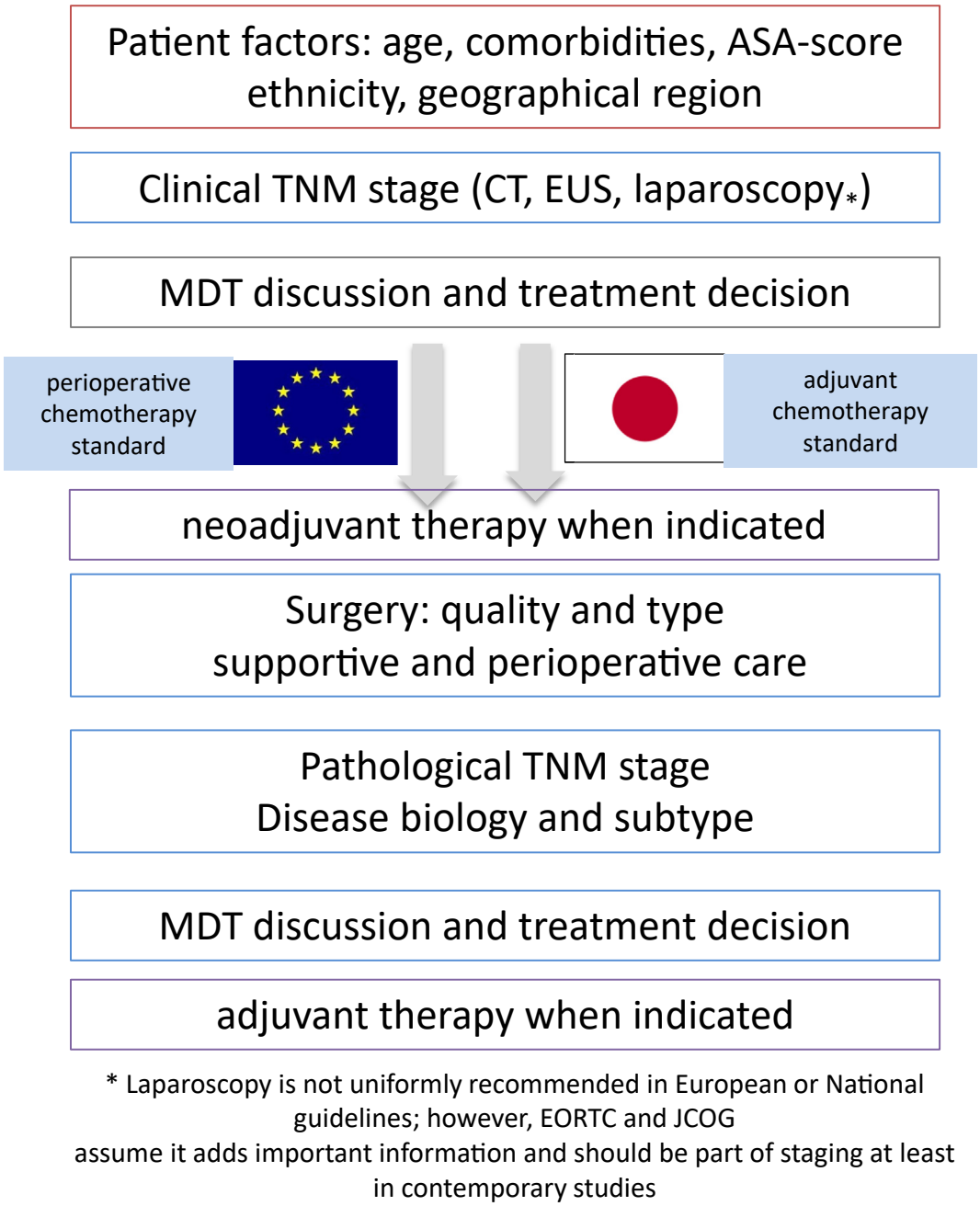

Fig. 1. Summary of patient flow and factors influencing treatment outcomes in stage II and III GC.

0.91; 95% CI 0.679–1.236, p = 0.284). Both, the selection of cases and the NAC regimen used might be reasons for the lack of success of this approach. According to a subgroup analysis of this trial [17], NAC might be beneficial for cancers with non-poorly cohesive type GC.

Based on the results of a recent observational study in Japan, which examined the accuracy of computed tomography (CT) and oesophageal ultrasonography for preoperative staging, there are concerns that patients with early disease might be overtreated with NAC: The positive and negative predictive value of an endoscopic or CT diagnosis of cT3-4 disease to detect pT3-4 GC were 79.2% (95% CI 76.2–81.9) and 59.2% (95% CI 54.3–63.9) in this trial. Additional imaging options such as endoscopic ultrasound or 1 mm slice CT could not improve these results (JCOG1302A) [18]. Considering the incidence of p-stage I and the magnitude of the potential benefit of NAC for p-stage III, JCOG decided to include patients with cT3-4, cN1-3 GC (corresponding to clinical stage III and IVA in the 8th edition of the UICC TNM classification) in the ongoing phase III JCOG1509-trial investigating the superiority of NAC with S-1 plus oxaliplatin followed by surgery and adjuvant S-1 over surgery followed by adjuvant S-1.

3. Special populations

Special populations, such as elderly patients, are usually inadequately represented in clinical trials.

For example, the ACTS-GC trial excluded patients aged over 80 years, and thus, it is unclear whether the evidence from this trial can be generalised to this patient group.

Moreover, several studies showed that renal dysfunction and sarcopenia, frequently observed in elderly patients, are risk factors for early termination of S-1 treatment because of adverse events. Both, EORTC and the International Society of Geriatric Oncology [19,20] have suggested that trials specifically recruiting elderly or frail patients should be conducted. The recently presented phase III GO2 trial [21] was designed to find the optimum doses of capecitabine/oxaliplatin (CAPOX) in patients with advanced gastroesophageal adenocarcinoma not suitable for standard full dose 3-drug chemotherapy, mostly because of age or frailty. This trial demonstrated NI in terms progression-free survival (PFS) for 60% of the full dose of cap/ox (oxaliplatin 130 mg/m^2 and capecitabine 625 mg/m^2 twice daily from day 1–21 every 3 weeks). Furthermore, the overall treatment utility, a composite end-point including clinical benefit, tolerability, quality of life and patient value, was better using this reduced dose level compared with full dose cap/ox. Both results confirm the importance of specific trials for the elderly population, as well as their potential to improve treatment outcomes for this population.

A survey conducted by JCOG among 58 participating institutions revealed that only a minority of elderly patients are able to receive the full dose of S-1 adjuvant chemotherapy and that surgery alone is considered standard of care for elderly patients by the community [22]. On this basis, the ongoing JCOG1507 trial is designed to confirm the superiority of adjuvant treatment with a reduced dose of S-1 for vulnerable elderly patients (80 years old or older) treated with D1+/D2 gastrectomy compared with surgery alone. A detailed description of the inclusion criteria including definitions for vulnerability and frailty has been published [22].

4. The EORTC and JCOG collaboration: shared challenges and goals

EORTC and JCOG believe in international, multidisciplinary collaboration [23,24] including surgery, medical oncology, pathology, gastroenterology, endoscopy, radiology, nuclear medicine, radiotherapy and biostatistics to further improve treatment outcomes for patients with GEJ and GC.

Current key challenges: the perspective of EORTC and JCOG.

1. The limited precision of clinical staging, especially for lymph node staging, including the impossibility to exclude peritoneal carcinomatosis without invasive laparoscopy.
2. The heterogeneity of GC with respect to molecular and histopathological subtypes and development of appropriate treatment strategies according to subtype.
3. The development and validation of biomarkers, including liquid biopsies.
4. The toxicity of standard of care perioperative/adjuvant chemotherapy.
5. The development of evidence-based treatment strategies for special populations, such as elderly and frail patients.
6. The improvement of surgical quality assurance, as well as standardisation and quality assurance of multidisciplinary perioperative management and supportive care
7. The development of validated surrogate end-points for clinical trials.

The JCOG and EORTC trials are designed to address these major clinical and translational research challenges and are expected to have a significant impact on future GC patient management. The identification of molecularly, histopathologically and/or clinically defined subtypes, the integration of targeted-therapies and immunotherapies, with or without neoadjuvant radiotherapy into state-of-the-art perioperative chemotherapy, and the development of rational and specific treatment strategies is in our view the best way to move the field forward and improve patient outcomes.

4.1. Integrating immunotherapy into EORTC/JCOG gastric cancer trials

Immunotherapy has been transformative in diseases such as metastatic melanoma [25] and is one of the key themes in our groups' work [26]. Several trials of anti-PD1 therapy have demonstrated modest efficacy in GC [27] and raised hope that immune checkpoint blockade alone or in combination with chemotherapy or other immune modifying agents may improve outcomes of selected patients with GC [28–30]. Keynote-62 (NCT02494583) [31] presented at ASCO 2019 randomised 763 patients with a PD-L1 combined positive score ≥ 1 [32] to either first-line palliative chemotherapy with cisplatin and 5-FU or capecitabine alone versus the same chemotherapy combined with pembrolizumab or pembrolizumab alone. Within a NI limit of 1.2, pembrolizumab alone was not inferior compared with cisplatin/5-FU for the primary end-point overall survival (OS) and improved survival in patients with combined positive score (CPS) $\geq$ 10. However, the combination of chemotherapy plus pembrolizumab compared with chemotherapy alone was not superior for

OS or PFS in patients with a CPS score of >1. Whether these results will result in an approval for pembrolizumab as first-line treatment in any subgroup of patients is currently under discussion. Of note, while chemotherapy with cisplatin/5-FU, which was used as the comparator and backbone in this trial, has been an internationally accepted standard for more than a decade, in 2019 it is neither the most effective nor the best tolerated chemotherapy regimen for advanced GC.

Thus, at this moment in time, chemotherapy will remain standard of care for the majority of patients with GC and the identification of predictive biomarkers remains one of the biggest challenges: While DNA mismatch repair deficiency, resulting in microsatellite instability (MSI-high), predicts the response to immunotherapy in multiple solid tumours including GC [33], Epstein-Barr-Virus (EBV) infection may further predict response to immune checkpoint inhibition [34]. However, the percentage of patients with these GC subtypes is relatively low, response to immune checkpoint inhibition may not be limited to these patients and not all patients with MSI-high or EBV positive tumours respond to immunotherapy. Especially the role of tumour mutation burden and extent of tumour infiltrating lymphocytes needs further investigation in this context. Patients treated according to the European standard with platinum-fluoropyrimidine–based perioperative chemotherapy plus surgery [5,6], who have lymph node metastases after neoadjuvant chemotherapy have a very poor prognosis [10]. For these patients, EORTC is currently initiating a trial (EORTC-1707 VESTIGE; NCT03443856) investigating adjuvant anti-PD1 plus anti-CTLA4 therapy. Patients with MSI-high GC appear to have consistent response rates of >50% to anti-PD1 therapy but do not appear to benefit from standard perioperative chemotherapy [35], while patients with microsatellite stable GC might benefit from a combination of immunotherapy and chemotherapy. To this end, another EORTC trial investigating immunotherapy for resectable MSI-high GC is in preparation.

4.2. Integrating targeted therapies

Several recent attempts to integrate targeted therapies (e.g. bevacizumab [36], panitumumab [37]) into perioperative treatment of GC patients have not been able to demonstrate survival benefits in unselected patient populations.

At present, the only validated predictive biomarker in GC is the HER2 status [38,39]. For patients with HER2-positive, locally advanced, unresectable or metastatic disease [39], the addition of trastuzumab to fluoropyrimidine/cisplatin chemotherapy [38] is an international standard-of-care treatment. However, the clinical impact of HER2 targeting therapies in *early* GC is unknown. Both, EORTC and JCOG are convinced that introducing molecular targeting agents in patients selected on the basis of a predictive biomarker is a promising strategy for tailored adjuvant or neoadjuvant therapy and consider the investigation of the role of HER2 targeting treatments in early GC as a major challenge. EORTC 1203, the INNOVATION-trial (NCT02205047) [40], an intergroup collaboration of EORTC with the Dutch Upper GI group, Korean Cancer Study Group and surgical quality assurance done by JCOG, addresses the question whether the integration of trastuzumab, with or without pertuzumab, into perioperative chemotherapy improves histopathologic response rate (primary end-point), PFS and OS in locally advanced resectable (clinical stage Ib-III) HER2 positive GC. The 'TRIGGER' study (JCOG 1301C) [41], a randomised phase II trial evaluating the efficacy of neoadjuvant trastuzumab for patients with HER2-positive GEJ or GC with extensive lymph node metastases, addresses a complementary question to the EORTC-1203 'INNOVATION'-trial. A collaboration between JCOG and EORTC on the histopathological reporting of the resection specimen after neoadjuvant treatment is ongoing.

4.3. Biobanking and translational research

The multiple histological and molecular classifications described reflect the intertumoural heterogeneity of GC. However, significant intratumour heterogeneity of biomarkers also exists, which is a challenge for development of novel therapies (for review see Refs. [42,43]). With the exception of microsatellite instability [44] and HER2 [38] in advanced GC and the histological subtype in early GC to assess the suitability for endoscopic resection [45], none of the published classifiers are currently used in routine clinical practice. We consider the collection of high-quality biospecimens including but not limited to tissue, blood ('liquid biopsies'), body fluids, images (CT, magnetic resonance imaging, positron-emission tomography), linked to high quality clinical and pathological data from all trials mandatory for advancing personalised treatment using next generation 'omic' technologies (genomic and/or transcriptomic sequencing, proteomics, metabolomics, etc.), morphology-based methodology (multiplex immunohistochemistry, *in situ* hybridisation), as well as deep learning approaches ('Histiomics and Radiomics'). As nearly all contemporary high-throughput investigations on tissue samples involving DNA or RNA can be performed using routine formalin-fixed paraffin embedded (FFPE) material from endoscopic biopsy or resection specimens, we mandate FFPE tissue collection in all prospectively developed trials. We already provide detailed guidance on specimen workup and material collection to the local pathologists in the EORTC 1203 trial. In addition, central pathology review of pretreatment biopsies and resected specimens by experienced

gastro-intestinal pathologists ensures high-quality pathology data of our groups' trials. Being faced with substantial heterogeneity of GC and neoadjuvant therapy being standard of care in Europe, investigating endoscopic biopsies poses a significant challenge with respect to the question whether the sample is representative of the tumour as a whole. Existing guidelines on where and how often to biopsy are currently limited to HER2 testing [46–49]. Liquid biopsies sampling circulating tumour cells or DNA or other compartments of tumour cells are far less invasive than tissue biopsies and can relatively easily be performed at various different time points during treatment or at disease progression. Whether investigations using liquid biopsies are able to improve the selection of patients for targeted or other treatments is an open question at this moment in time. EORTC strives to collect liquid biopsies within current and future trials to explore their potential clinical utility. Investment in infrastructure and a central EORTC biobanking facility (https://www.ibbl.lu), quality accredited according to ISO 9001, compliant with the principles of NF S96-900 certification and robust governing principles will ensure appropriate acquisition, storage and annotation of biospecimens and facilitate their optimal use. JCOG has also initiated a biobank project for clinical trials, which started with the collection of blood samples but recommends tissue biobanking as well. Of note, validation of biomarkers across different populations (e.g. East versus West or male versus female gender) will be crucial for designing and understanding the results of international trials. As a first step, the central histopathology review in the EORTC 1203 and the JCOG TRIGGER [41] trial will be performed in a standardised manner between Japanese and European pathologists to facilitate a pooled analysis of both trials. Both are excellent examples of the collaboration between JCOG and EORTC.

4.4. Integrating radiotherapy into future EORTC GC trials

In contrast to JCOG, where radiotherapy is not considered for gastrointestinal cancers (except patients with oesophageal squamous cancer), EORTC as a multidisciplinary academic group sees the development of combined modality treatment regimens, which integrate radiotherapy into systemic treatment across diseases as major challenge and strategic axis. Especially in gastrointestinal cancers, pivotal EORTC trials in rectal [50] and anal [51] cancers defined international standards of care for the last decades. Two recent trials demonstrated disappointing results for postoperative chemoradiation in patients with GC:

1. 'CRITICS' [52], which showed no benefit for postoperative chemoradiotherapy, as compared with postoperative chemotherapy after preoperative chemotherapy with ECF.
2. ARTIST-2 [53], conducted in Korea, which randomised stage II/III, node-positive, D2-resected GC to receive 1 year of adjuvant S-1 versus SOX (S-1/oxaliplatin) for 6 months or SOX plus radiotherapy (45 Gy) and did not show any difference in disease-free survival between SOX and SOX/radiotherapy.

Nevertheless, the EORTC GC task force considers several major questions regarding the use of radiotherapy in the perioperative management of GEJ and GC still open:

First, is there a role for the integration of radiotherapy in the neoadjuvant component of perioperative chemotherapy? This question is being investigated in the EORTC supported 'TOPGEAR'–trial (NCT01924819) [54].

Second, which patients benefit from radiotherapy? As a consequence of differences in anatomy and disease biology, the rationale to integrate radiotherapy may be stronger in GE junction cancers compared with GC. Owing to their reduced anatomic mobility, radiation volumes can be smaller, which improves the tolerance and decreases off-target side effects. Further important questions regarding radiotherapy include the evaluation of technical progress in radiotherapy, such as high precision, high field, MRI-guided radiotherapy, to allow a fully adaptive treatment, which takes organ filling and motion into account.

The third major question, and perhaps the most interesting one for the future, concerns the immune stimulatory effect [55] of radiotherapy and whether it is possible to integrate radiotherapy in current multimodal treatment regimens to fully exploit its potential to enhance the benefit of immunotherapy.

5. Surgical quality assurance

In contrast to drug treatment, which may easily be standardised, surgery is an individually manufactured intervention, highly variable according to expertise and technique, and has therefore not been considered as suitable for randomised controlled trials (RCTs) for a long time. Only at the end of the 20th century and decades after their development in medicine, RCTs have been introduced in surgery. Since then, they allowed for significant progress and permitted to establish high-level evidence in many surgical fields. The quality of surgery, especially regarding key elements, such as lymph node dissection, has a major impact on the individual patients and trial outcome. To standardise and improve the quality of surgery in surgical and multimodal trials, surgical quality assurance (QA) is of major importance [56]. Surgical QA has many issues to be discussed: In clinical trials, credentialing of surgeons before enrolment, standardisation of surgical techniques and monitoring of surgical performance all have a positive effect on the quality of a RCT. Surgeons participating in

Table 1
Current EORTC and JCOG trials on perioperative treatment of gastric cancer.

EORTC	
22114	EORTC-22114-4011-GITCG-ROG-TOPGEAR: Trial of preoperative therapy for gastric and oesophagogastric junction adenocarcinoma. A randomised phase II/III-trial of preoperative chemoradiotherapy for resectable gastric cancer https://clinicaltrials.gov/ct2/show/NCT01924819
1203	EORTC-1203-GITCG-INNOVATION: INtegration of trastuzumab, with or without pertuzumab, into periOperatiVe chemoTherapy of HER2 posiTive stOmach caNcer: The INNOVATION-trial https://clinicaltrials.gov/ct2/show/NCT02205047
1707	EORTC-1707-GITCG-VESTIGE: Adjuvant immunotherapy in patients with resected gastric cancer following preoperative chemotherapy and high risk for recurrence (N+ and/or R1)—an open-label randomised controlled phase II-study (not yet recruiting) https://clinicaltrials.gov/ct2/show/NCT03443856
JCOG	
1104	JCOG 1104: Optimal period of adjuvant S-1 chemotherapy for pathological stage II gastric cancer patients who underwent D2 gastrectomy: OPAS-1 phase III https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000008210&language=J
0501	JCOG 0501: Randomised phase III trial of surgery plus neoadjuvant TS-1 and cisplatin compared with surgery alone for type 4 and large type 3 gastric cancer https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&recptno=R000000356&type=summary&language=J
1301C	JCOG 1301C: A randomised phase II study of systemic chemotherapy with and without trastuzumab followed by surgery in HER2 positive advanced gastric or oesophago-gastric junction adenocarcinoma with extensive lymph node metastasis: Trigger study https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000018667&language=J
1507	JCOG 1507: A phase III trial to confirm S-1 adjuvant chemotherapy for pathological stage II/III vulnerable elderly gastric cancer patients who underwent gastric resection: BIRDIE https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000029398
1509	JCOG 1509: Phase III trial to evaluate the efficacy of neoadjuvant chemotherapy with S-1 plus oxaliplatin followed by D2 gastrectomy with adjuvant S-1 in locally advanced gastric cancer: NAGISA trial https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000027564

JCOG trials must have been credentialed with a certain number of interventions, depending on the procedure. Furthermore, surgical techniques have been standardised in detail based on the discussion of videos from experts, and operative pictures are monitored on a regular basis. EORTC is facing this challenge by collaborating with JCOG and the European Society of Surgical Oncology (ESSO) in the surgical research QA platform named SURCARE [56] (http://www.eortc.org/quality-assurance/surgery/). The main purpose of SURCARE is to develop better surgical oncology trials and establish an integrated approach to ensuring high QA standards in surgical clinical research in Europe and globally. SURCARE advocates the development of a standard surgical QA process, which includes credentialing, standardisation of technique and assessment, as well as central monitoring. Furthermore, SURCARE aims to facilitate engagement of young surgeons in international and multidisciplinary clinical research through research fellowships. SURCARE has been adopted for the surgical QA of the EORTC-1203 'INNOVATION' trial: Independent surgeons and pathologists from JCOG and EORTC will conduct a central review of intraoperative photographs and macroscopic pictures of the resected specimens to assess the completeness of the surgical treatment. Furthermore, data from surgical and pathology case report forms and 30-day and 90-day surgical complications graded by Clavien-Dindo classification [57] will be documented and analysed.

6. Challenges in trial design

To increase the efficacy of drug development, 'platform' and adaptive randomisation designs such as e.g. I-SPY 2 in breast cancer [58] or non-Bayesian alternatives (MAMS platform trials) [59] as e.g. NCI-MATCH (https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match) or FOCUS4 (http://www.focus4trial.org/) in colorectal cancer have been developed. Furthermore, moving towards seamless phase II/III trials with best treatment arm or target population selection and sample size re-estimation based on early observed treatment difference [59,60] helps to shorten the development. In addition, it uses resources more efficiently by avoiding restarting the accrual for the phase III trial. Finally, with modern perioperative treatment of GC, at least half of all patients will be long-term survivors. While our trials aim at increasing this percentage, the EORTC survivorship research protocol YOU-(**Y**our-**O**utcome-**U**pdate) [61] presents a unique opportunity to assess the causal relationship between treatment and long-term outcomes because of the high quality registration of treatment details in the EORTC clinical database. In addition to physical issues, YOU also collects data on the psychological and socio-economic well-being among long-term survivors (http://www.eortc.org/other-research-initiatives/survivorship-outcome/). Whenever possible, patients will be included in this protocol. Apart from the ongoing interventional

trials listed below, an update and validation of the GC-specific EORTC-QLQ-STO 22 quality-of-life questionnaire module [62], which includes interviews with both GC patients and healthcare professionals, is ongoing in collaboration between JCOG and EORTC.

EORTC, European Organisation for Research and Treatment of Cancer; JOCG, Japan Clinical Oncology Group.

In conclusion, despite different standards and outcomes for patients with GC between Europe and Japan, EORTC and JCOG share their view of challenges, goals and a vision for future clinical trial design and questions. Both collaborative and complementary projects between both groups are ongoing, and future activities of both groups are coordinated in regular meetings (See Table 1).

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Declaration of competing interest

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