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The exact definition of tumour location and extent by white light endoscopy in conjunction with CT scans is the backbone for any treatment decision. Their value is limited with respect to infiltration depth, lymph node involvement and peritoneal involvement. Additional endoscopic ultrasound (EUS) was recommended mainly for tumours of the lower gastrooesophageal junction (i.e. AEG type II and III according to Siewert) and in early cancers before endoscopic resection. Laparoscopy to diagnose peritoneal involvement was thought to be necessary before the start of neoadjuvant treatment in all gastric cancers and in AEG II and III.
In general, perioperative multimodal treatment was suggested for all locally advanced oesophageal tumours and for gastric cancers with a clinical stage above T1N0. There was consensus that the combination of fluorouracil, folinic acid, oxaliplatin and docetaxel is now a new standard chemotherapy regimen for fit patients. In contrast, the optimal choice of perioperative chemotherapy (CTx) versus (neo)adjuvant radiochemotherapy (neoRCTx), especially for AEG, was identified as an open question. Expert treatment recommendations depend on tumour location, biology, the risk of incomplete (R1) resection, response to treatment, local or systemic recurrence risks, the predicted perioperative morbidity and patients' comorbidities.

In summary, any treatment decision requires an interdisciplinary discussion in a comprehensive multidisciplinary setting.

Suggested Reviewers:

***Highlights**

Summary report of the 4th St. Gallen EORTC Gastrointestinal Cancer Conference, a moderated expert consensus discussion and vote, which focused on the primary treatment of gastric and gastrooesophageal adenocarcinoma.

4th St. Gallen EORTC Gastrointestinal Cancer Conference: Controversial Issues in the Multimodal Primary Treatment of Gastric, Junctional and Oesophageal Adenocarcinoma

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Abstract (max 250 words)

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The exact definition of tumour location and extent by white light endoscopy in conjunction with CT scans is the backbone for any treatment decision. Their value is limited with respect to infiltration depth, lymph node involvement and peritoneal involvement. Additional endoscopic ultrasound (EUS) was recommended mainly for tumours of the lower gastrooesophageal junction (i.e. AEG type II and III according to Siewert) and in early cancers before endoscopic resection. Laparoscopy to diagnose peritoneal involvement was thought to be necessary before the start of neoadjuvant treatment in all gastric cancers and in AEG II and III.

In general, perioperative multimodal treatment was suggested for all locally advanced oesophageal tumours and for gastric cancers with a clinical stage above T1N0. There was consensus that the combination of fluorouracil, folinic acid, oxaliplatin and docetaxel is now a new standard chemotherapy regimen for fit patients. In contrast, the optimal choice of perioperative chemotherapy (CTx) versus (neo)adjuvant radiochemotherapy (neoRCTx), especially for AEG, was identified as an open question. Expert treatment recommendations depend on tumour location, biology, the risk of incomplete (R1) resection, response to treatment, local or systemic recurrence risks, the predicted perioperative morbidity and patients' comorbidities.

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Introduction

The topic of the 4th St. Gallen EORTC Gastrointestinal Cancer Conference 2018 was the primary approach to patients with potentially curable adenocarcinoma of the stomach, the gastrooesophageal junction or the oesophagus, three anatomically defined tumour locations with distinct, although overlapping molecular features and treatment strategies (1). Differences in histopathology can be used to distinguish between intestinal type gastric cancer and diffuse type according to the Lauren classification. The pathogenesis of intestinal type gastric cancer and oesophageal adenocarcinoma is thought to follow a metaplasia-dysplasia-carcinoma sequence with identifiable premalignant conditions, namely atrophy in the stomach and Barrett's metaplasia in the distal oesophagus (2).

More recently, comprehensive genomic characterisation has identified four molecular subtypes of gastric cancer: i) tumours positive for Epstein-Barr virus, ii) microsatellite unstable tumours, iii) genomically stable tumours and iv) tumours with chromosomal instability (CIN) (3). Oesophageal adenocarcinoma commonly exhibits chromosomal instability which makes its molecular background mechanism comparable to CIN-type gastric cancer (4).

About 2% of gastric cancers are associated with familial cancer syndromes: i) hereditary diffuse gastric cancer (HDGC), ii) gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), iii) familial intestinal gastric cancer (FIGC) (5, 6) and also the Lynch Syndrome. These may need more extensive surgical approaches than those recommended for sporadic cancers (7).

A multidisciplinary faculty of specialized surgeons, medical and radiation oncologists, pathologists, radiologists and gastroenterologists reviewed the current treatment recommendations in a panel session based on a moderated consensus process. The main focus was on controversial issues that could not be easily resolved through the study of published evidence and guidelines. As in the St. Gallen Breast Cancer Conferences, the panel was asked to discuss the scientific evidence, contribute their personal and center experiences and finally vote on recommendations developed from a pre-circulated set of questions. As an introductory question, the panel was asked if it is still appropriate to differentiate between patients with gastric and gastrooesophageal cancer with respect to multimodal treatment decisions. The vast majority (89 % or 16/18 including one abstention) of the panel members voted 'Yes' on this issue. Hence, we have summarised the key discussion points of the panel members for gastric

cancer and adenocarcinoma of the gastro-oesophageal junction or the oesophagus (AEG according to Siewert) (8) separately.

Methods

In preparation for the panel session held on March 17, 2018, existing guidelines were used to identify areas of uncertainty in order to define the topics for debate (9-15). Topics and the resulting questions were circulated amongst panel members three weeks before the meeting. Seventy-seven questions were retained for the panel discussion. During the session, which was moderated by JZ and ML, the panel members were asked to assess and comment on optimal care based on existing data and to recommend treatment strategies from the perspective of experts in the field. Panel members were given the opportunity to comment on the issues raised by the questions before and after an electronic vote. Here, we summarise the discussion and extent of agreement or disagreement of the panel members on specific topics. Even though care was taken to invite a representative spectrum of panellists from relevant disciplines, the general applicability of their conclusions may be limited by an unequal distribution of disciplines and/or underrepresentation of some regions of the world (all panellists are co-authors). In general, the ensuing statements are meant for reasonably fit patients without severe comorbidities. In clinical practice, patients may not fit within this category and treatment decisions will need to be adapted on an individual basis by multidisciplinary boards accordingly.

Gastric cancer

Staging

Routine staging of **gastric cancer** includes white light endoscopy with biopsies taken for histopathological diagnosis and cross-sectional radiologic imaging of the thorax and abdomen.

The minimum number of biopsies needed for optimal evaluation was recommended by the panel to be at least 6 (72% of the panellists) or 8 (17%), mainly because gastric cancers display a highly variable growth pattern with intratumoural heterogeneity and because diagnosis may be missed (16, 17). At least five biopsies containing tumour are required to reliably determine the HER2 receptor expression profile (18) and for the accurate diagnosis in case of infiltrative growth as compared to ulcerated or polypoid growth patterns (19, 20).

Even though computed tomography (CT) is routinely used as the backbone imaging method, it was thought by 56% of the experts that CT scanning alone was not sufficient as the sole imaging method for clinical T staging. All panellists considered information from additional EUS helpful and 82% regarded EUS as part of the routine staging procedure. Questions arose as to the impact of EUS on the therapeutic strategy. Staging by EUS may be most useful to distinguish T2 from T3/4 tumours and hence may help to decide whether staging laparoscopy is needed, whereas CT scans may be most relevant to image the extent of T4 tumours. In contrast, N staging was considered to be more accurate with CT scans (63%) than EUS (50%), with some comments on the notoriously unreliable evaluation of lymph node involvement by any staging method.

Additional PET-CT scan with the aim to exclude locally unresectable tumours or distant metastases was recommended by half of the panellists, a vote that was debated heavily. Arguments in favour of PET-CT cited a 15% rate of avoided surgery without benefit for the patient (21). Others stated that high-quality CT scans or diffusion-weight magnetic resonance imaging (MRI) might yield similar results at lower costs. In summary, the cost-effectiveness of PET-CT is debatable especially in diffuse type cancers which tend to be PET-negative when fluorodeoxyglucose is used as a radiotracer (22). The question remains open for intestinal type cancers.

The vast majority (83%) considered diagnostic laparoscopy necessary before the start of preoperative therapy, with somewhat less common recommendations for peritoneal washings (59%). The consequences are discussed below.

Indication for multimodal treatment of gastric cancer

When asked for the preferred sequence and type of multimodal treatment – if this was indicated as detailed below- most panellists were in favour of perioperative chemotherapy (CTx) (83 %) as opposed to preoperative chemotherapy followed by postoperative radiochemotherapy (11 %) or even planned primary surgery followed by adjuvant postoperative radiochemotherapy (RCTx) alone (0 %) (23).

The choice of multimodal therapy did not depend on Lauren's classification (88% of panellists agreed) nor on the presence of signet ring cells (88%), the proliferation index (100%), the HER-2 status (77%), the molecular subtype (84%), microsatellite status or mismatch repair deficiency (100%), or the thymidylate synthase genotype (100%) (24).

Clinical stage was considered to be the major determinant of the choice of multimodal treatment. Pre-operative systemic therapy was strongly recommended for patients with cT4

gastric cancer (100%), cT3 (any N) (94%), for cT2 N+ tumours (87%), and somewhat less commonly for cT2 N0 tumours (53% for, 29 % against, 18 % abstain). For patients with cT2 N0 tumours, some experts commented that good patient performance status and diffuse-type histology could be considered as a positive selection criterion in favour of perioperative treatment (25).

The consequence of positive peritoneal cytology was far less clear. 56% of the panel would consider this as the basis of the treatment decision. One suggestion was to re-perform lavage cytology after the preoperative treatment and to proceed to surgery only if the lavage became negative. However, most of the participants would recommend surgical exploration independently from lavage results (no formal vote).

If limited peritoneal carcinomatosis is detected during laparoscopic staging, peri-operative CTx would still be favoured by most (79%), with repeat laparoscopy before resection (80%). If – after CTx - carcinomatosis is still present, the vote was evenly split: some experts opted for a purely palliative approach without resection because of the risk of progress, whereas others were in favour of a combined primary tumour and peritoneal resection.

Restaging after preoperative treatment was deemed necessary by 92% and should at least include a CT scan. Some panel members perform additional standard endoscopy (17%) and/or EUS (8%). In addition, there may be a need for repeat laparoscopy in lavage-positive patients.

Type and sequence of multimodal treatment in gastric cancer

If pre-operative CTx was clinically indicated, 86% of the panel members would choose the FLOT regimen (infusional 5-FU, leucovorin, oxaliplatin and docetaxel) with some exceptions for elderly patients because of the associated toxicity (suggestion: reduced doses or FOLFOX (5-FU, leucovorin, oxaliplatin)) (26). Of note, experience with this regimen in elderly patients is limited: the median age in the trial establishing the FLOT regimen was 62 years, with less than 24% of the patients older than 70 years (25). A minority (7%) voted for ECF/ECX or EOF/EOX (epirubicin, cis- or oxaliplatin and 5-FU or capecitabine, respectively) (27). The preferred interval between CTx and surgery – given complete recovery from side-effects – varies from 2 weeks (19%) to 4 and 6 weeks (38% and 31%, respectively).

In tumours with no response at restaging, most experts would proceed to immediate surgery (79%) rather than switch to an alternative CTx regimen (14%). Similarly, if clinical follow-up or restaging revealed local progression, most would try to proceed to immediate

surgery (64%), with some comments on the vote suggesting that this is a high risk patient group which might potentially benefit from a switch to an alternative CTx regimen (9%) or to RCTx (9%).

After surgery - and at least stable disease - postoperative continuation of CTx was recommended by the majority of the panel members. This recommendation did not depend on the remission status (complete remission: 80% pro; partial remission: 100% pro; no change: 89% pro), considering it 'standard' to suggest CTx if the patient was able to tolerate it.

If patients had experienced disease progression during preoperative treatment, some form of post-operative therapy was still favoured by 59% of the panel members, albeit with a change in CTx protocol (29%) or a switch to RCTx (36%).

In the case of R1 resection, RCTx was favoured by most (79%), if re-resection had prior been judged as unreasonable by an expert surgeon.

For the rare patients treated by initial surgery, panel members suggested adjuvant CTx in all pN+ tumours (86%), in pT4 N0 tumours (63% with some additional votes for RCTx), in pT3 N0 tumours (75%), and much less commonly for those staged pT2 N0 (57% against, 29% pro). There was no agreement whether histological or molecular features (split vote) should influence the decision for adjuvant CTx. It was commented, that even though there is some evidence that signet ring cell cancers might benefit more from primary surgery (possibly followed by adjuvant therapy) than from perioperative treatment, the available literature is conflicting and does not allow a clear recommendation (25, 28). One of the reasons is the definition of diffuse type cancer and the threshold of signet ring cells used to define a tumour as signet ring cell tumour which varies widely between studies. This question has recently been addressed by a European Consensus of experts that distinguishes 3 categories: i) "pure" Signet Ring Cell cancers (SRC) (90% of tumour cells or more having the signet ring morphology); ii) Poorly Cohesive (PC) carcinoma with SRC component (PC-SRCc) (<90% but >10% of signet ring cells); iii) Poorly Cohesive Carcinoma Not Otherwise Specified (PC-NOS) (10% of signet ring cells or less). Future studies to fully evaluate the prognostic significance of SRC categories are requested (28).

Adenocarcinoma of the oesophagus and the gastrooesophageal junction (AEG)

Staging

Routine staging of **AEG** includes white light endoscopy as well as cross-sectional radiologic imaging of the thorax and abdomen. In selected cases chromoendoscopy can help to define the longitudinal extent of the tumours with the aim to classify them as AEG type I (in the distal oesophagus), Type II (cardia or gastrooesophageal junction) or type III (subcardial gastric cancer) according to Siewert (8, 14).

EUS in addition to thoracic CT was recommended for all patients by most experts (75%), the others (19%) opting for EUS only if evaluation of resectability by CT is inconclusive. There was a discussion, however, that the impact of EUS on the decision process is usually rather limited in AEG I tumours.

Staging laparoscopy as part of the staging routine was recommended for AEG II tumours by 73% and for AEG III tumours by 80% of the panellists, similar to gastric cancers.

Of note, these statements are only valid for penetrating tumours (i.e. T1b or more as judged by EUS), where multimodal treatment with surgical resection is considered as primary treatment option. They do not address the approach to early mucosal cancers (i.e. T1a), where initial endoscopic resection by ESD (endoscopic submucosal dissection) or EMR (endoscopic mucosal resection) is preferred to define the infiltration depth and thus can be used both as a staging and as a therapeutic intervention.

Type and sequence of multimodal treatment in AEG

Combined modality treatment of AEG has become the standard of care in western countries, although surgery remains the primary modality for cure (29). Starting with neoadjuvant treatment – either with CTx or RCTx – is considered more effective than adjuvant treatment alone (30). The recent European Society of Medical Oncology guidelines recommend both strategies with an equal level of evidence/grade of recommendation (9). Results from pivotal trials have shown an increase of 5-year survival rates of up to 14% for neoadjuvant chemotherapy (neoCTx) (27, 31) or neoadjuvant radiochemotherapy (neoRCTx) (32). In a recent retrospective propensity-score matched analysis of patients with stage II and III AEG, pathologically complete remissions and R0 resections were more frequent in the neoRCTx group at the cost of increased anastomotic postoperative morbidity (leak in 23.1% vs. 6.8%, p|0.001) and somewhat increased 90-day postoperative mortality (5.9% vs. 2.3%; p=0.09) (29). However, formal comparison of neoRCTx or neoCTx from randomized trials is still missing. Results from ongoing trials addressing this question are not expected before 2021 (Neo-AEGIS NCT01726452, ESOPEC NCT02509286)

Neoadjuvant treatment of AEG

A comparison of neoadjuvant chemotherapy (neoCTx) with neoadjuvant radiochemotherapy (neoRCTx) does not generally favour either approach over the other. The choice of treatment thus mainly depends on confounding factor and expert opinion (30). This is different in patients with squamous cell carcinoma, where the role of RCTx is well established (9).

Tumour location has a direct effect on treatment decisions for many experts. In AEG I tumours, neoRCTx with carboplatin/paclitaxel/41.4Gy (the CROSS trial regimen (33)) was preferred over neoCTx by the majority (71%) of the panellists. In AEG II tumours, there was a split vote (43% for neoRCTx), albeit with a relevant number of abstentions (29%). In AEG III tumours (ed: which were not included in the CROSS trial) a large majority (91% of those voting) would opt for neoCTx.

In addition, lymph node location and number of positive lymph nodes had a major impact for most panel members (82%). Neoadjuvant CTx was favoured for its systemic effect in tumours with increased number or size of involved lymph nodes because of the elevated risk of systemic spread and because of the need for a relatively large radiation volume with associated toxicities. In contrast, neoRCTx was preferred for its downsizing effect in bulky tumours because of their high risk for R1 resections.

In contrast to the optional wait and watch approach in oesophageal squamous cell cancer, there is currently no routine role for definitive radiochemotherapy in patients with oesophageal adenocarcinoma even after complete clinical remission after neoadjuvant RCTx (79%), with some discussion on the occasional situation that patients are unfit for surgery but fit for radiochemotherapy.

In patients treated by primary surgery without neoadjuvant treatment, most panellists see a role for adjuvant RCTx (67%), even though the level of evidence was judged rather limited. Potential selection criteria could be the same as in gastric cancer, e.g. lymph node metastases, positive margins or possibly also bulky tumours (ed: ≥T3)

In summary, multimodal treatment options include both neoCTx and neoRCTx. A clear preference for either treatment is not yet available from current studies. Expert preferences vary considerably depending on tumour location, extent, histological subtype and comorbidities. There is no simple ‘one size fits all’ approach (1) and any treatment decision requires an interdisciplinary discussion in a comprehensive multidisciplinary setting.

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Conflict of interest statement

Will be provided separately

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Figure legends

Figure 1:
Distribution of panel votes on perioperative therapy in gastric cancer.
Percentages do not necessarily add up to 100%, since "abstain" was a possible vote.
Abbreviations: Tx, therapy; neoTx, neoadjuvant therapy; same, same chemotherapy protocol as used pre-operatively; diff., different chemotherapy protocol from the one used pre-operatively; RCTx, radiochemotherapy.

Figure 2:
Distribution of panel votes on adjuvant therapy in gastric cancer.
Please note that primary surgery was considered a non-standard approach by the panel.
Abbreviations: see legend to figure 1.

Figure 1

Figure 1: Panel Votes on Perioperative Therapy in Gastric Cancer

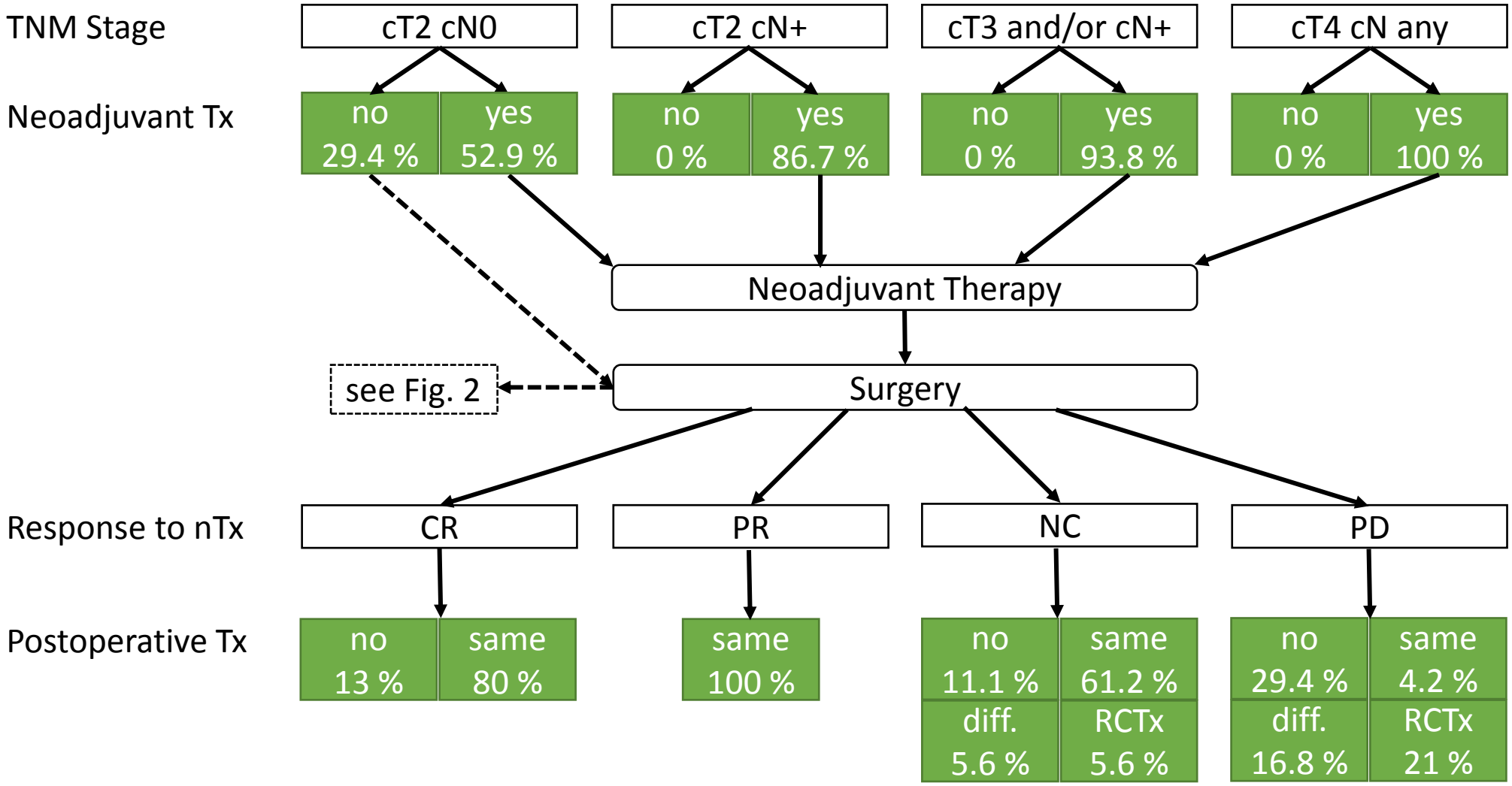
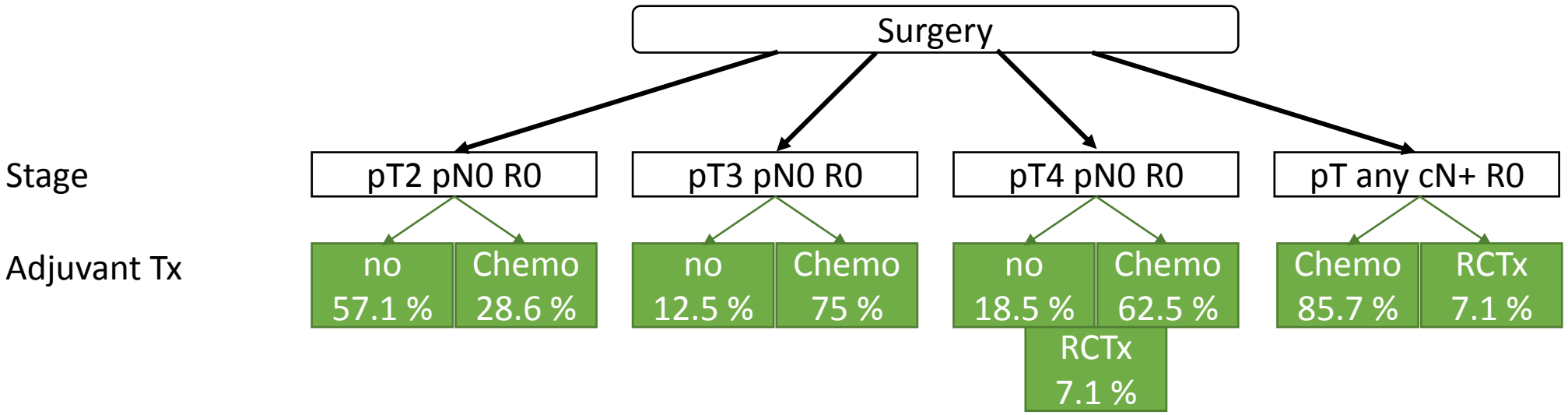


Figure 2

Figure 2: Panel Votes on Adjuvant Therapy in Gastric Cancer (Non-Standard Approach!)



***Conflict of Interest statement**

Conflict of interest statements

Have been collected from all co-authors before the conference

Comprehensive list of statements will be provided separately