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Review

The 4th St. Gallen EORTC Gastrointestinal Cancer Conference: Controversial issues in the multimodal primary treatment of gastric, junctional and oesophageal adenocarcinoma

Manfred P. Lutz [a,*], John R. Zalcberg [b], Michel Ducreux [c], Antoine Adenis [d], William Allum [e,u], Daniela Aust [f], Fatima Carneiro [g], Heike I. Grabsch [h,i], Pierre Laurent-Puig [j], Florian Lordick [k], Markus Möhler [l], Stefan Mönig [m], Radka Obermannova [n], Guillaume Piessen [o], Angela Riddell [p], Christoph Röcken [q], Franco Roviello [r], Paul Magnus Schneider [s], Stefan Seewald [t], Elizabeth Smyth [u], Eric van Cutsem [v], Marcel Verheij [w], Anna Dorothea Wagner [x], Florian Otto [y]

[a] *CaritasKlinikum St. Theresia, Saarbrücken, Germany*
[b] *Department of Epidemiology and Preventive Medicine, School of Public Health, Monash University, The Alfred Centre, Melbourne, Australia*
[c] *Institut Gustave Roussy, Villejuif, France*
[d] *Département d'Oncologie Médicale, Institut du Cancer de Montpellier, Montpellier, France*
[e] *Royal Marsden NHS Foundation Trust, London, United Kingdom*
[f] *Institut für Pathologie, Universitätsklinikum Carl Gustav Carus, Dresden, Germany*
[g] *Department of Pathology, Faculdade de Medicina, Universidade do Porto, Porto, Portugal*
[h] *Department of Pathology and GROW-School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands*
[i] *Division of Pathology and Data Analytics, Leeds Institute of Medical Research at St James's, School of Medicine, University of Leeds, Leeds, UK*
[j] *Université René Descartes, UFR Biomédicale des Saints-Pères, Paris, France*
[k] *University Cancer Center Leipzig (UCCL) and Department of Hematology and Oncology, University Medicine Leipzig, Germany*
[l] *Medizinische Klinik und Poliklinik, Universitätsmedizin Mainz, Mainz, Germany*
[m] *Hôpitaux Universitaires de Genève, Service de Chirurgie Viscéral, Geneva, Switzerland*
[n] *Department of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic*
[o] *Université de Lille, Department of Digestive and Oncological Surgery, Claude Huriez University Hospital, 59000 Lille, France*
[p] *Department of Diagnostic Radiology, The Royal Marsden, London, United Kingdom*

* *Corresponding author*: Caritasklinikum Saarbrücken – St. Theresia, Medizinische Klinik, Rheinstrasse 2, 66113, Saarbrücken Germany. Fax: +49 681 406 1003.
E-mail address: m.lutz@caritasklinikum.de (S. Ogino).

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[q] Department of Pathology, Christian-Albrechts-University, Kiel, Germany
[r] Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy
[s] Centre for Visceral, Thoracic and Specialized Tumor Surgery, Klinik Hirslanden, Zurich, Switzerland
[t] Gastroenterology Centre, Klinik Hirslanden, Zurich, Switzerland
[u] Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom
[v] University Hospital Gasthuisberg, Leuven, Belgium
[w] Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands
[x] Department of Oncology, Lausanne University Hospital, Lausanne, Switzerland
[y] Tumor- und Brustzentrum ZeTuP, St. Gallen, Switzerland

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Abstract Multimodal primary treatment of localised adenocarcinoma of the stomach, the oesophagus and the oesophagogastric junction (AEG) was reviewed by a multidisciplinary expert panel in a moderated consensus session. Here, we report the key points of the discussion and the resulting recommendations. The exact definition of the tumour location and extent by white light endoscopy in conjunction with computed tomography scans is the backbone for any treatment decision. Their value is limited with respect to the infiltration depth, lymph node involvement and peritoneal involvement. Additional endoscopic ultrasound was recommended mainly for tumours of the lower oesophagogastric 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 type 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 (CTx) regimen for fit patients. In contrast, the optimal choice of perioperative CTx versus neoadjuvant radiochemotherapy (neoRCTx), especially for AEG, was identified as an open question. Expert treatment recommendations depend on the 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.

1. 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 gastro-oesophageal 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 CIN, 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, (ii) gastric adenocarcinoma and proximal polyposis of the stomach and (iii) familial intestinal gastric cancer [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 specialised 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 centre experiences and finally vote on recommendations developed from a precirculated set of questions. As an introductory question, the panel was asked if it is still appropriate to differentiate between patients with gastric and gastro-oesophageal 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.

2. Methods

In preparation for the panel session held on March 17, 2018, existing guidelines were used to identify areas of uncertainty to define the topics for debate [9–15]. Topics and the resulting questions were circulated among panel members 3 weeks before the meeting. Seventy-seven questions were retained for the panel discussion. During the session, which was moderated by J.Z. and M.L., 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 coauthors). 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.

3. Gastric cancer

3.1. 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 six (72% of the panellists) or eight (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 human epidermal growth factor receptor 2 (HER2) receptor expression profile [18] and for the accurate diagnosis in case of infiltrative growth compared with 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 endoscopic ultrasound (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 positron-emission tomography (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-weighted magnetic resonance imaging 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 in the following section.

3.2. 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 CTx followed by postoperative radiochemotherapy (RCTx; 11%) or even planned primary surgery followed by adjuvant postoperative RCTx alone (0%) [23].

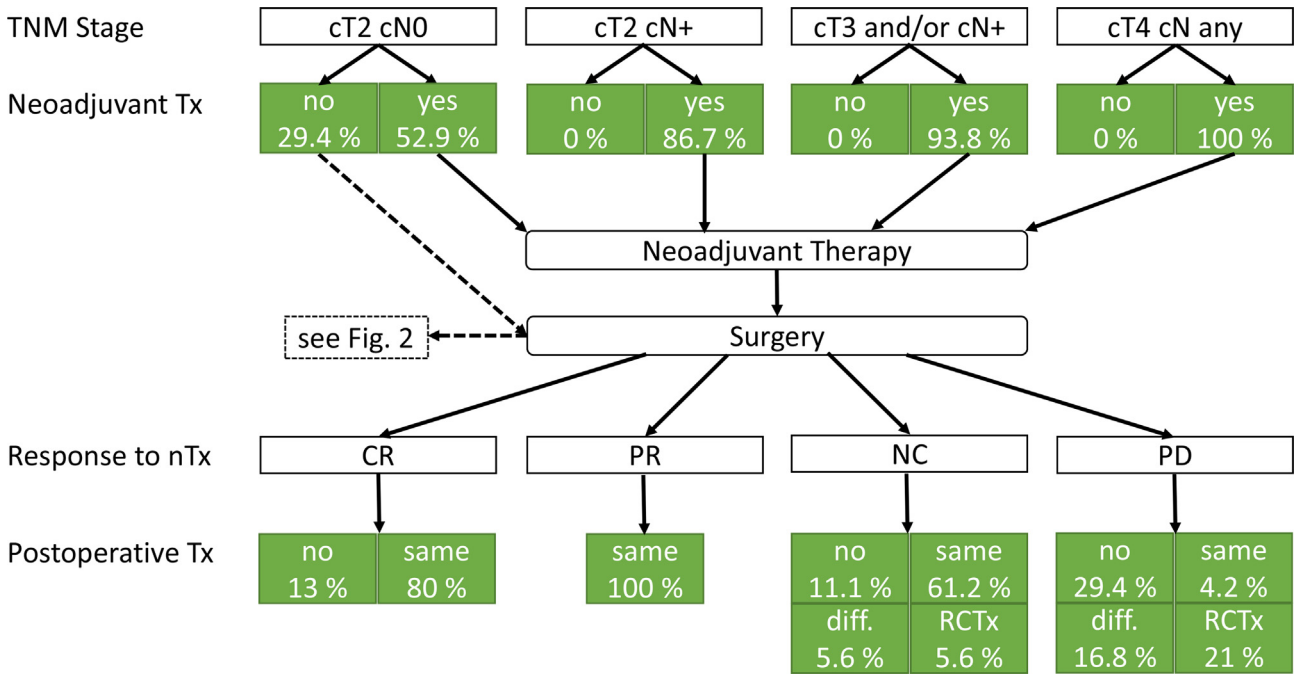

Fig. 1. Panel votes on perioperative therapy in gastric cancer. RCTx, radiochemotherapy; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

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

The clinical stage was considered to be the major determinant of the choice of multimodal treatment. Preoperative systemic therapy was strongly recommended for patients with cT4 gastric cancer (100%), cT3 (any N) (94%), cT2 N+ tumours (87%) and somewhat less commonly for patients with cT2 N0 tumours (53% for, 29% against and 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]. (Fig. 1)

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

If limited peritoneal carcinomatosis is detected during laparoscopic staging, perioperative 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.

3.3. Type and sequence of multimodal treatment in gastric cancer

If preoperative CTx was clinically indicated, 86% of the panel members would choose the infusional 5-fluorouracil (5-FU), leucovorin, oxaliplatin and docetaxel (FLOT) regimen, with some exceptions for elderly patients because of the associated toxicity (suggestion: reduced doses or 5-FU, leucovorin and oxaliplatin [FOLFOX]) [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, cisplatin 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

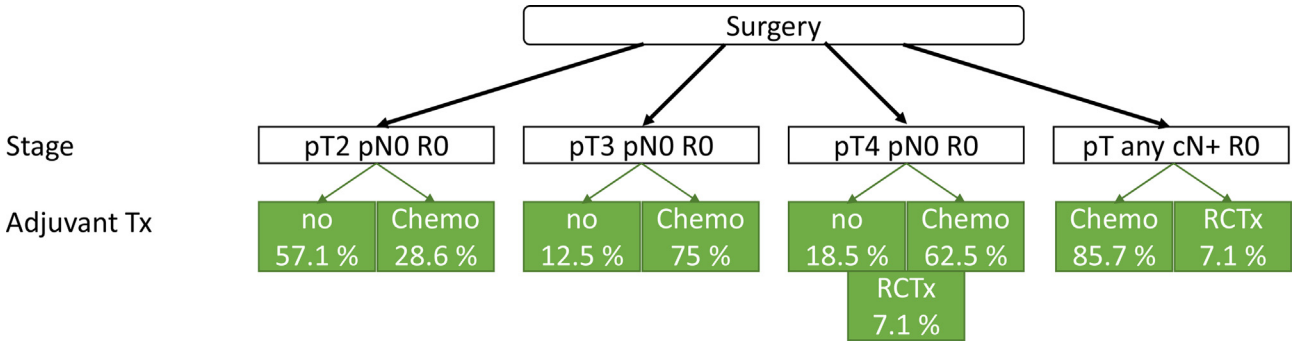

Fig. 2. Panel votes on adjuvant therapy in gastric cancer (nonstandard approach!). RCTx, radiochemotherapy.

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 that 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 CTx; partial remission: 100% pro; no change: 89% pro), considering it 'standard' to suggest CTx if the patient was able to tolerate it. (Fig 1)

If patients had experienced disease progression during preoperative treatment, some form of postoperative therapy was still favoured by 59% of the panel members, albeit with a change in the 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 earlier been judged as unreasonable by an expert surgeon.

For the patients exceptionally 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) Fig. 2. 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 SRC 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 SRCs used to define a tumour as SRC tumour, which varies widely between studies. This question has recently been addressed by a European consensus of experts that distinguishes three categories: (i) 'pure' SRC cancers (90% of tumour cells or more having the signet ring morphology); (ii) poorly cohesive (PC) carcinoma with SRC component (<90% but >10% of SRCs) and (iii) PC carcinoma not otherwise specified (10% of SRCs or less). Future studies are requested to fully evaluate the prognostic significance of SRC categories [28].

4. Adenocarcinoma of the oesophagus and the gastro-oesophageal junction

4.1. Staging

Routine staging of **AEG** includes white light endoscopy and 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 gastro-oesophageal 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 type I tumours.

Staging laparoscopy as part of the staging routine was recommended for AEG type II tumours by 73% and for AEG type 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 the primary treatment option. They do not address the approach to early mucosal cancers (i.e. T1a), where initial endoscopic resection by endoscopic submucosal dissection or endoscopic mucosal resection is preferred to define the infiltration depth and thus can be used both as a staging and as a therapeutic intervention.

4.2. 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 randomised trials is still missing. Results from ongoing trials addressing this question are not expected before 2021 (Neo-AEGIS NCT01726452, ESOPEC NCT02509286).

4.3. Neoadjuvant treatment of AEG

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

The tumour location has a direct effect on treatment decisions for many experts. In AEG type 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 type II tumours, there was a split vote (43% for neoRCTx), albeit with a relevant number of abstentions (29%). In AEG type III tumours (which were not included in the CROSS trial), a large majority (91% of those voting) would opt for neoCTx.

In addition, the 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 on 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 on 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 RCTx 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 RCTx.

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 (≥T3).

In summary, multimodal treatment options include both neoCTx and neoRCTx. A clear preference for either treatment is not yet available from present studies. Expert preferences vary considerably depending on the 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.

Conflict of interest statement

Manfred Lutz received grants or research support from Celgene and Shire and honoraria or consultation fees from Eli Lilly and Falk Foundation. John Zalcberg received grants or research supports from Specialized Therapeutics and Shire and honoraria or consultation fees from Pfizer, Amgen and MSD. Arnaud Roth received honoraria or consultation fees from Roche, Bayer, BMS, Celgene, Amgen and Merck. William Allum received honoraria or consultation fees from Eli Lilly, Nestle and Taiho and is a member of speakers’ bureau for Lilly, Nestle and Taiho. Michel Ducreux received grants or research supports from Roche, Chugai and Pfizer and honoraria or consultation fees from Roche, Celgene, Merck Serono, Amgen, Novartis, Sanofi, Pfizer, Lilly and Servier, and his spouse is the head of BU, Sandoz. Pierre Laurent-Puig received honoraria or consultation fees from Amgen, Boehringer Ingelheim, AstraZeneca, BMS, Merck, Roche and Lilly. Florian Lordick received grants or research support from BMS and Fresenius Biotech and honoraria or consultation fees from Amgen, Astellas, Biontech, BMS Boston Biomedical, Ganymed, Lilly, MSD, Nordic, Roche and Taiho. Markus Möhler received grants or research support from Merck, Amgen, BMS, Taiho, Roche, AIO, MSD and honoraria or consultation fees from Falk, Nordic, Amgen, MCI, AstraZeneca, Lilly, MSD, Merck, Pfizer and BMS. Radka Obermannová received grants or research supports from Merck and honoraria or consultation fees from BMS and is a member of speakers’ bureau for Eli Lilly, Servier, Roche and BMS. Guillaume Piessen received honoraria or consultation fees from Amgen. Christoph Röcken is a member of advisory boards for BMS, MSD and Roche. Stefan Seewald received grants or research supports from WATS and honoraria or consultation fees from

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References

[1] Allum W, Lordick F, Alsina M, Andritsch E, Ba-Ssalamah A, Beishon M, et al. ECCO essential requirements for quality cancer care: Oesophageal and gastric cancer. Crit Rev Oncol Hematol 2018;122:179–93.
[2] Ajani JA, Lee J, Sano T, Janjigian YY, Fan D, Song S. Gastric adenocarcinoma. Nat Rev Dis Primers 2017;3:17036.
[3] Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014; 513(7517):202–9.
[4] Cancer Genome Atlas Research N, Analysis Working Group: Asan U, Agency BCC, Brigham, Women's H, Broad I, et al. Integrated genomic characterization of oesophageal carcinoma. Nature 2017;541(7636):169–75.
[5] Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol 2015;16(2):e60–70.
[6] Li J, Woods SL, Healey S, Beesley J, Chen X, Lee JS, et al. Point mutations in Exon 1B of APC reveal gastric adenocarcinoma and proximal polyposis of the stomach as a familial adenomatous polyposis variant. Am J Hum Genet 2016;98(5):830–42.
[7] van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet 2015;52(6):361–74.
[8] Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998;85(11):1457–9.
[9] Lordick F, Mariette C, Haustermans K, Obermannova R, Arnold D, Committee EG. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(suppl 5):v50–7.
[10] NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer [Version 5.2017]. 2017.
[11] NCCN Clinical Practice Guidelines: Esophageal and Esophagogastric Junction Cancers [version 4.2017]. 2017.
[12] Moehler M, Al-Batran SE, Andus T, Anthuber M, Arends J, Arnold D, et al. German S3-guideline "Diagnosis and treatment of esophagogastric cancer". Z Gastroenterol 2011;49(4):461–531.
[13] Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Eur J Surg Oncol 2014;40(5):584–91.
[14] Lutz MP, Zalcberg JR, Ducreux M, Ajani JA, Allum W, Aust D, et al. Highlights of the EORTC St. Gallen International Expert Consensus on the primary therapy of gastric, gastroesophageal and oesophageal cancer - differential treatment strategies for subtypes of early gastroesophageal cancer. Eur J Cancer 2012; 48(16):2941–53.
[15] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016; 27(suppl 5):v38–49.
[16] Lordick F, Janjigian YY. Clinical impact of tumour biology in the management of gastroesophageal cancer. Nat Rev Clin Oncol 2016;13(6):348–60.
[17] Vradelis S, Maynard N, Warren BF, Keshav S, Travis SP. Quality control in upper gastrointestinal endoscopy: detection rates of gastric cancer in Oxford 2005–2008. Postgrad Med J 2011; 87(1027):335–9.
[18] Tominaga N, Gotoda T, Hara M, Hale MD, Tsuchiya T, Matsubayashi J, et al. Five biopsy specimens from the proximal part of the tumor reliably determine HER2 protein expression status in gastric cancer. Gastric Cancer 2016;19(2):553–60.
[19] Bartley AN, Washington MK, Colasacco C, Ventura CB, Ismaila N, Benson 3rd AB, et al. HER2 testing and clinical decision making in gastroesophageal adenocarcinoma: guideline from the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology. J Clin Oncol 2017;35(4):446–64.
[20] Kwack WG, Ho WJ, Kim JH, Lee JH, Kim EJ, Kang HW, et al. Understanding the diagnostic yield of current endoscopic biopsy for gastric neoplasm: A prospective single-center analysis based on tumor characteristics stratified by biopsy number and site. Medicine (Baltimore) 2016;95(30):e4196.
[21] Purandare NC, Pramesh CS, Karimundackal G, Jiwnani S, Agrawal A, Shah S, et al. Incremental value of 18F-FDG PET/CT in therapeutic decision-making of potentially curable esophageal adenocarcinoma. Nucl Med Commun 2014;35(8):864–9.
[22] Lehmann K, Eshmuminov D, Bauerfeind P, Gubler C, Veit-Haibach P, Weber A, et al. 18)FDG-PET-CT improves specificity of preoperative lymph-node staging in patients with intestinal but not diffuse-type esophagogastric adenocarcinoma. Eur J Surg Oncol 2017;43(1):196–202.
[23] Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):616–28.
[24] Smyth EC, Wotherspoon A, Peckitt C, Gonzalez D, Hulkki-Wilson S, Eltahir Z, et al. Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the medical research council adjuvant gastric infusional chemotherapy (MAGIC) trial. JAMA Oncol 2017;3(9):1197–203.
[25] Al-Batran SE, Pauligk C, Homann N, Schmalenberg H, Kopp HG, Haag GM, et al. LBA-008Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) as perioperative treatment of resectable gastric or gastro-esophageal junction adenocarcinoma: The multicenter, randomized phase 3 FLOT4 trial (German Gastric Group at AIO). Ann Oncol 2017; 28(suppl_3).
[26] Al-Batran SE, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, et al. Effect of neoadjuvant chemotherapy followed by surgical resection on survival in patients with limited metastatic gastric or gastroesophageal junction cancer: the AIO-FLOT3 trial. JAMA Oncol 2017;3(9):1237–44.

[27] Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355(1):11–20.

[28] Mariette C, Carneiro F, Grabsch HI, van der Post RS, Allum W, de Manzoni G, et al. Consensus on the pathological definition and classification of poorly cohesive gastric carcinoma. Gastric Cancer 2019; 22(1):1–9.

[29] Markar SR, Noordman BJ, Mackenzie H, Findlay JM, Boshier PR, Ni M, et al. Multimodality treatment for esophageal adenocarcinoma: multi-center propensity-score matched study. Ann Oncol 2017;28(3):519–27.

[30] Mariette C. What is the optimal neoadjuvant treatment for locally advanced oesophageal adenocarcinoma? Ann Oncol 2017;28(3): 447–50.

[31] Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011;29(13): 1715–21.

[32] Shapiro J, van Lanschot JJB, Hulshof M, van Hagen P, van Berge Henegouwen MI, Wijnhoven BPL, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 2015;16(9):1090–8.

[33] van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366(22):2074–84.