Updates in Surgery (2018) 70:173–179
https://doi.org/10.1007/s13304-018-0539-z

REVIEW ARTICLE

Multimodal treatment in locally advanced gastric cancer

Oliver Thorsten Goetze[1] · Salah-Eddin Al-Batran[1] · Mickael Chevallay[2] · Stefan Paul Mönig[2]

Received: 13 March 2018 / Accepted: 13 May 2018 / Published online: 26 June 2018

Abstract
According to the data of the GLOBOCAN-network of the World Health Organization, there were 952,000 (6.8% of the total) new cases of gastric cancer in 2012, making it the fifth most common malignancy in the world. It represents a substantive change since the very first estimates in 1975 when stomach cancer was the most common neoplasm. More than 70% of cases (677,000 cases) occur in developing countries, and half the world total occurs in Eastern Asia, mainly in China. Gastric cancer is the third leading cause of cancer death in both sexes worldwide (Globocan, Estimated cancer incidence, mortality and prevalence worldwide in 2012, http://globocan.iarc.fr, 2012). Annually, worldwide 723,000 patients die of this tumor entity. Interestingly, a strong change in incidence rates in relation to the anatomical–topographic localization of the primary tumors in the stomach and esophagus has been experienced. While the frequency of proximal gastric carcinoma and adenocarcinoma of the cardiac and subcardiac region in Europe and North America has been constantly rising, distal gastric carcinomas have become less common (Torre et al. in JAMA 65:87–108, 2015). Furthermore, the relative incidence of esophageal adenocarcinoma (mostly localized in the distal esophagus) has strongly increased (Jemal et al. in JAMA 58:71–96, 2008; Crew and Neugut 31:450–464, 2004; Pohl and Welch 97:142–146, 2005).

Keywords Gastric cancer · Minimally invasive surgery · FLOT

The prognosis is dependent on tumor stage at the time of diagnosis and shows a strong international variability. Survival rates in North America and Europe are in the 20% range regarding 5-year survival and even in T2N0 it is only 50%. There are no evidence-based data for a sufficient prophylaxis of this cancer; thus, the only way to improve the prognosis is an earlier detection of tumor and more effective treatment, especially in the perioperative situation in potentially curative patients, candidates for an R0 surgical resection [1–6].

The next step in surgical development is minimally invasive surgery. Oncological principles with adequate lymphadenectomy and negative resection margin need to be equivalent as in open procedure. Surgery remains the only curative therapy. New association of surgery in even metastasized diseases is the subject of several research projects. We present with this review an updated view of the management for advanced gastric cancer.

Multimodal therapy concepts with curative intention

For each patient, as part of an interdisciplinary tumor conference, a treatment concept must be determined, respecting patient-related (performance status and comorbidities) and tumor-specific characteristics (extent of tumor, histological subtype and localization of the primary). As a part of multimodal concept for all potentially resectable gastric and gastroesophageal junction (GEJ) tumors, surgical resection is considered the standard therapy. Because surgical therapy alone has a 5-year survival less than 25% in the Western world, surgery alone is insufficient in curing these kinds of patients [6–8].

Combined modality therapies should be standard for ≥ stage T2, N0 patients with a localized adenocarcinoma of the stomach or esophagogastric junction (GEJ). Surgical

The article is part of the topical collection Gastric Cancer Surgery.

✉ Stefan Paul Mönig
Stefan.Moenig@hcuge.ch

[1] Institute of Clinical Cancer Research, UCT- University Cancer Center Frankfurt, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt, Germany

[2] Hôpitaux Universitaires de Genève, Service de Chirurgie viscéral, Geneva, Switzerland

therapy should normally include a D2-lymph node dissection with removal of at least 16, better 25, lymph nodes or a two-field lymph node dissection depending on the localization and surgical resection technique [8–12]. The surgical resection technique of the primary varies according to the localization of the tumor, stomach vs. GEJ type I–III and considers the mode of local and metastatic spread as well. The surgical spectrum ranges from subtotal- to total gastrectomy, transhiatal extended gastrectomy combined with a D2-lymph node dissection, up to esophagectomy with two-field lymphadenectomy for GEJ type I and possibly GEJ type II depending on surgeon's preferences.

There is often an uncertainty in differentiation between T2 and T3 cancer stage. Even more in T2 cancers, there is a high rate of about 40% positive lymph nodes. So, a multimodal approach (neoadjuvant or perioperative therapy) has to be an integral part in all tumors ≥ T2 N0 M0 stage. Depending on the localization of the primary tumor, gastric or gastroesophageal junction, a perioperative systemic chemotherapy or, in distal esophageal carcinoma and adenocarcinoma of the gastroesophageal junction (GEJ type I), alternatively chemoradiotherapy can be used. A pure adjuvant concept is no standard in the Western world.

Perioperative chemotherapy

Perioperative chemotherapy with fluoropyrimidine and cisplatin (with epirubicin—ECF scheme—or without epirubicin) over about 2 months was the former established standard in GEJ or gastric adenocarcinomas, based on the data of two randomized landmark trials. Two studies, ACCORD-07 and MAGIC, show an improvement in the 5-year overall survival with a delta of 13–14% with neoadjuvant and perioperative systemic therapy, respectively, compared with surgery alone without changes regarding postoperative complications and 30-day mortality [6, 7].

Noteworthy in these studies is the limited feasibility of the postoperative (adjuvant) part of therapy, by the delayed reconvalescence after oncological resection of GEJ or gastric carcinoma. This clearly suggests starting perioperative therapy necessarily preoperatively, and not only adjuvant.

According to recent studies, the role of epirubicin in combination chemotherapy regimen is critical. Only the British MAGIC study used this drug as a combination partner with platin and fluoropyrimidine. Another randomized study of the British Group (OE05) showed no advantage in the same setting for the "classic" ECF regimen compared with a regimen of only two cycles of cisplatin and fluoropyrimidine alone, similarly to that used in the French ACCORD 07 trial [13]. If there is a need for triplet therapy in the perioperative situation, a taxane-based therapy should be used. The already fully published phase II data of the German FLOT4 study on 300 patients and the corresponding phase III data currently shown at the ASCO 2017 of the FLOT-4 study on 716 patients showed that a taxane-based triplet regime leads to a significant benefit in all end points [14, 15]. According to the FLOT4 data, FLOT (docetaxel/5FU/leucovorin/oxaliplatin) showed a significantly higher rate of complete pathological remissions compared to ECF/ECX (16%, 95% CI 10–23% vs. 6%, 95% CI 3–11%; $p = 0.02$). The phase III data show, moreover, that FLOT significantly improves 3-year overall survival (57 vs. 48%) and the progression-free survival (PFS, 30 vs. 18 months) compared to the former standard ECF/ECX.

Based on this data, FLOT regimen is the new standard in perioperative therapy of gastric or esophagogastric adenocarcinomas and the basis for the forthcoming and already recruiting studies, FLOT 6 (PETRARCA, phase II, $n = 100$; phase III $n = 304$), FLOT 7 (RAMSES, phase II $n = 150$; phase III $n = 758$) and FLOT 8 (DANTE, phase II).

Perioperative therapy in HER2-positive patients

Based on the data from the HER-FLOT study (4 cycles FLOT and trastuzumab, followed by another 6 months trastuzumab), the addition of trastuzumab to FLOT regimen is feasible and related with a high pathological complete remission rate (22%) [16]. The monoclonal antibody trastuzumab binds to the subdomain IV of epidermal growth factor receptor HER2, and another monoclonal antibody called pertuzumab binds to the extracellular dimerization domain (subdomain II) and thus prevents receptor dimerization in combination with trastuzumab as a double blockade. The EORTC has recently started the INNOVATION study (NCT02 205 047) for HER2-positive GEJ and gastric adenocarcinomas with fluoropyrimidine/cisplatin as backbone in combination with trastuzumab or with trastuzumab and pertuzumab. On the other hand, there is the mentioned FLOT 6-PETRARCA trial comparing the 15–20% HER-2+ patients in a perioperative setting as in FLOT4, FLOT ± trastuzumab and pertuzumab; this trial is also currently recruiting patients.

Perioperative anti-angiogenesis therapy

Based on the positive data of the REGARD and Rainbow study [17, 18], in second-line therapy of gastric carcinoma with the VEGF-R2 antibody ramucirumab—showing a significant improvement in OS—the evaluation of this substance in combination with FLOT perioperative is more than justified. However, we need to consider that anti-VEGF-/R antibodies in the context of first-line therapy in

AVATAR, AVAGAST (both bevacizumab), MEGA (ziv-aflibercept) and Rainfall (ramucirumab) trial showed negative results [19–21]. Also, the currently fully published data of the ST03 study showed no improvement with the addition of bevacizumab to ECX/ECF in a neoadjuvant setting [22]. Against the background of the questionable surgical quality, regarding resection margins, the data of ST03 should be interpreted with caution. More data should be generated in the perioperative setting with this promising antibody in the German RAMSES trial, combining FLOT ± ramucirumab in a randomized fashion.

Perioperative anti-EGFR therapy, anti-met therapy or PD/L1 therapy

Data for anti-EGFR therapy in first-line situation in gastric cancer showed no positive results for cetuximab (EXPAND) or panitumumab (Real-3) [23]. In the definitive irradiation situation without surgery, the RTOG 0436 phase III study showed, due to the addition of cetuximab to chemoradiation with paclitaxel/cisplatin, no gain in overall survival [24]. Further evaluation of the EGF-receptor in gastric carcinoma seems not to be justified according to the current status. The same applies to hepatocyte growth factor receptor (HGFR also known under MET). Studies on patients with MET-positive AEG or gastric carcinomas were not convincing or showed even detrimental effects in the first line (RILOMET, METgastric).

Interesting data, however, are related regarding evaluation of the PD1/-L1 mechanism. Promising data have also been generated in gastric carcinoma. The positive results of the ONO 4538-12 (ATTRACTION-2) study on gastric carcinoma after standard failure in palliative therapy give hope that this mechanism can also be effective in the perioperative situation [25]. Based on data of keynote 012 and 059, the US Food and Drug Administration (FDA) recently approved pembrolizumab for the treatment of patients with recurrent locally advanced or metastatic gastric or GEJ adenocarcinomas, whose tumors express PD-L1 (combined positive score [CPS] ≥ 1), determined by an FDA-approved test, and whose disease progressed while on or after ≥ 2 prior lines of therapy, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, human epidermal growth factor receptor 2-targeted therapy.

The FLOT 8 (DANTE) trail will evaluate patients in the perioperative curative setting with a regimen of FLOT ± atezolizumab (PD-L1 antibody) pre-and postoperatively. In keynote 585, pembrolizumab combined with chemotherapy will also evaluate this mechanism in potentially curative surgical candidates.

Neoadjuvant chemoradiation

While for the locally advanced squamous cell carcinoma of the esophagus neoadjuvant chemoradiotherapy and for the distal gastric carcinomas perioperative chemotherapy is an established standard of care, in GEJ tumors currently both modalities can be used.

Only two smaller randomized studies have directly compared neoadjuvant chemo- versus chemoradiation therapy in adenocarcinomas of the gastroesophageal junction so far. In the German POET study, a total of 119 patients received either three cycles PLF (cisplatin/leucovorin/5-fluorouracil) or two cycles of PLF followed by simultaneous chemoradiotherapy (30 Gy in 15 fractions in combination with cisplatin and etoposide) [26]. The rate of pathological complete remissions (pCR) was significantly higher in the chemoradiotherapy group versus after chemotherapy alone (15.6 vs. 2.0%). With non-significant increased postoperative mortality, the 3-year survival was 47.7% after chemoradiation compared to 27.7% after chemotherapy ($p = 0.07$). The study was due to sluggish recruitment that ended prematurely, and so it only shows a trend for longer survival in the chemoradiotherapy group.

Another study examined in one small group ($n = 75$) induction with two cycles of cisplatin and 5-FU compared to the same chemotherapy simultaneously with radiotherapy 35 Gy in 15 fractions [27]. Again, in the chemoradiotherapy group, the pCR rate was significantly higher than after chemotherapy alone (31 vs. 8%). Nevertheless, no improvement was shown regarding overall survival.

The landmark study regarding chemoradiotherapy is the CROSS trail [28]. CROSS compared in patients with esophageal (squamous and adenocarcinoma as well) and adenocarcinomas of the gastroesophageal junction neoadjuvant chemoradiotherapy with 1.8 Gy single dose, to 41.4 Gy total dose and five weekly doses of carboplatin and paclitaxel, followed by resection versus resection without any neoadjuvant therapy. No induction chemotherapy were done before radiation in the CROSS trial. In the entire group of patients receiving chemoradiotherapy plus surgery (including esophageal squamous cell carcinoma; 23% of patients), there was a significant improvement in overall survival (HR 0.68, 95% CI 0.53–0.88; $p = 0.003$). The HR of chemoradiotherapy plus surgery versus surgery alone was only improved in the lymphonodal-negative tumors. In nodal-positive tumors there was no significant benefit which seems logical, because in a nodal-positive situation already a systemic disease is present, so a systemic therapy is needed. Studies with indiction chemotherapy before neoadjuvant chemoradiotherapy, as mentioned, were negative [29, 30]. In GEJ-I tumors, perioperative chemotherapy with an effective

chemotherapy protocol (FLOT) or neoadjuvant chemoradiation corresponding to CROSS regimen is therefore the current standard of care therapy. Against the background of additional toxicity, perioperative morbidity of the radiotherapeutic component, the worse effect in node-positive patients and the good results of FLOT in GEJ type I cancers, FLOT is moving into the spotlight, also in the adenocarcinomas GEJ type I, as an SOC. In contrast to squamous cell carcinomas of the esophagus, in this setting the component of radiotherapy is essential for the success of neoadjuvant therapy. An often-discussed surgical increase in morbidity or even mortality through the neoadjuvant concepts cannot be detected [31].

Adjuvant chemotherapy

Due to the clear indication for perioperative (neoadjuvant + adjuvant) therapy in the Western world, adjuvant chemotherapy should only be performed in exceptional cases, e.g., in patients with preoperative understaging of disease. A meta-analysis of therapy studies resulted in an improvement of the 5-year survival rate of only about 5–6% with a fluoropyrimidine-based therapy [32] versus surgery alone. The Japanese ACTS-GC study with 1-year lasting postoperative chemotherapy regimen with the fluoropyrimidine S1 results in a 5-year survival improvement of 71.7 versus 61.1% (HR 0.67, 95% CI 0.54–0.83) compared to surgery alone [33]. The high 5-year survival rate of 61% after surgery alone compared with only 19–23% in the European Studies after surgery alone seems remarkable [6, 7]. The Korean CLASSIC trial also showed a clear improvement in the 5-year survival rate due to 6 months of continued postoperative therapy with the doublet capecitabine and oxaliplatin versus surgery only (69% vs. 78%, HR 0.66, 95% CI 0.51–0.85; $p = 0.0015$) [34].

An intensification of adjuvant chemotherapy, as in the Italian ITACA-S study (4 cycles 5FU/FS and irinotecan, followed by three cycles of docetaxel and cisplatin) [35] or the French GISCAD study (weekly cisplatin, epirubicin, leucovorin and 5FU-wPELF) [36], however, did not improve the PFS and OS by an escalated adjuvant therapy in comparison to a therapy with 5-FU as an infusion or bolus, respectively. An adjuvant therapy can be recommended in accordance with the S3 Guideline in Germany and the ESMO-Guidelines with a fluoropyrimidine and platinum over 4.5–6 months, if no neoadjuvant therapy was given. The optimal therapy for the patient, however, is the perioperative (pre- and postoperatively combined) therapy.

Postoperative chemoradiotherapy

An adjuvant chemoradiotherapy is common especially in the USA. The protocol is based on the data of INT 0116 study, in which after surgical resection a 5-FU bolus with accompanying radiotherapy up to 45 Gy total dose versus surgery alone was compared [37]. INT 0116 showed a significant advantage in overall survival, due to the adjuvant chemoradiotherapy. Against the background of the poor overall prognosis of the patient collective in the trial and the insufficient surgery within the trial (only 10% D2-lymphadenectomy), the conclusion of the trial must be interpreted with caution. The follow-up study CALGB 80101 with a similar approach and an intensification of the postoperative chemotherapy portion in the combination chemoradiotherapy (use of the ECF regime before/after radiation chemotherapy) failed to show effectiveness compared to 5-FU as a bolus [17]. Therefore adjuvant chemoradiotherapy according to INT 0116 is only an option after insufficient surgery in the form of a D1-lymph node dissection. The role of postoperative chemoradiotherapy even after a D2 dissection is still a matter of debate. The results of the Korean Phase III ARTIST study with six cycles of adjuvant capecitabine + cisplatin (XP) versus an adjuvant chemoradiotherapy (2xXP/XRT/2xXP) was negative [38]. As part of a perioperative concept, the Dutch phase III study—CRITIS showed no benefit, if as part of perioperative chemotherapy (ECX) the postoperative part of chemo was replaced by chemoradiotherapy (radiotherapy with 45 Gy in 25 fractions in combination with capecitabine + cisplatin). Again, as in ARTIST, there was a sufficient surgery in both trial arms.

The use of adjuvant chemoradiotherapy is currently extremely restrained, for example, in a "high-risk constellation" for a recurrence (e.g., extensive node-positive disease after resection, < D2-node-dissection and/or less than 25 nodes removed, R(+) resection). In this case, a protocol in conformity with the ARTIST study—especially with regard to the radiobiological, more meaningful continuous administration of fluoropyrimidine (e.g., by capecitabine)—should be used.

Conclusion

Patients with locally advanced, non-metastatic gastric or GEJ adenocarcinoma benefit from multimodal strategies. The survival advantage after 5 years is about 13–14% compared to the sole resection with insufficient regimen and is nearly doubled with FLOT compared to surgery alone. According to the FLOT-4 data, 5-year survival and

another 9% gain in overall survival compared to perioperative ECF/-X therapy was shown. ECF/-X showed the same survival within the FLOT-4 trial; so, the epirubicin-based triplet has not underperformed. The median OS was 50 months with FLOT versus 35 months with ECF/-X.

If there are no contraindications, patients must receive neoadjuvant or perioperative therapy. For GEJ, especially type I-tumors, preoperative chemoradiation according to CROSS is a standard option. Now due to the new data of the FLOT-4 trial, there is a second standard for GEJ type I cancers with an immediate more intensive systemic impact, especially important in potentially nodal-positive (up to 40% even in T2) diseases. In all other types of GEJ (type II–III) and especially in stomach cancer, perioperative FLOT is the new standard of care.

Currently published data of patients with mismatch repair deficiency and high microsatellite instability from the British MAGIC trial were associated with a positive prognostic effect in gastric cancer patients treated with surgery only and negative effect in the ones treated with additional perioperative ECF/-X. So, the molecular profile of patients even in perioperative trials will become important [39].

Surgery of oligometastatic adenocarcinoma of the stomach or GEJ

The only curative treatment for advanced gastric cancer is surgery. However, only 20% of patients are candidates for radical surgery with curative intent at the time of diagnosis in Western countries [40].

Chemotherapy is the standard treatment for incurable advanced gastric or GEJ adenocarcinomas. The role of patients with limited or so-called oligometastatic disease is not defined. Whether the addition of gastrectomy to chemotherapy improves the prognosis for patients with a single non-curable factor was examined in the REGATTA-trial [41]. It was the first randomized phase-III trial in this oligometastatic setting in stomach cancer, performed in Japan, South Korea and Singapore. Patients were randomized to palliative systemic chemotherapy alone or to upfront surgery including gastrectomy in the form of only a D1-resection, followed by adjuvant and additive systemic chemotherapy. Due to this concept with concessions regarding radicality to surgery, the concept has no curative approach in the systemic treatment arm or the surgical arm. The REGATTA-study failed to show a benefit for D1-gastrectomy followed by chemotherapy for gastric cancer patients with a single non-curable factor. Due to the study concept, REGATTA was not able to define the role of surgery in the oligometastatic setting of gastric cancer [41].

This principle has been called into question by a German prospective FLOT3-trial. In the non-randomized, stratified FLOT-3 trial [42], patients with a limited metastatic disease who received neoadjuvant FLOT-therapy and proceeded to radical tumor surgery including resection of all metastatic sites showed favorable survival compared to the other metastatic patients with palliative surgery or systemic therapy only. Limitations of this trial were the non-randomized character and therefore the selection bias. But the FLOT3-trial provides a strong rationale for currently recruiting German FLOT5-trial.

The FLOT5-RENAISSANCE trial [43] addresses potential benefits of surgical intervention in the stomach or esophagogastral junction adenocarcinomas with limited metastatic, so-called oligometastatic diseases. FLOT5 is a prospective, multicenter, randomized phase III trial. Previously untreated patients with oligometastatic disease (retroperitoneal lymph node metastases only or a maximum of one incurable organ site that is potentially resectable or locally controllable with or without retroperitoneal lymph nodes) receive four cycles of FLOT therapy. Patients without disease progression after four cycles are randomized in a 1:1 fashion to receive an additional four to eight cycles of FLOT or radical surgical resection of primary and all metastatic sites followed by subsequent FLOT cycles [43].

The results of this study should be able to determine the exact role of surgery in limited metastatic gastric cancer. This could potentially lead to a new standard of therapy. If the outcome for the surgical arm is negative, patients with adenocarcinoma of the stomach or GEJ with oligometastatic lesions will be no longer considered for curative or pseudo-curative surgery. Therefore, FLOT5 will lead to an answer to a long-lasting question.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study informed consent is not required.

References

1. Globocan (2012) Estimated cancer incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr
2. Torre LA, Bray F, Siegel RL et al (2015) Global cancer statistics 2012. CA Cancer J Clin 65:87–108
3. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics. CA Cancer J Clin 58:71–96
4. Crew KD, Neugut AI (2004) Epidemiology of upper gastrointestinal malignancies. Semin Oncol 31:450–464

5. Pohl H, Welch HG (2005) The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 97:142–146
6. Cunningham D, Allum WH, Stenning SP (2006) Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355:11–20
7. Ychou M, Boige V, Pignon JP et al (2011) Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 29:1715–1721
8. Songun I, Putter H, Kranenbarg EM et al (2010) Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 11:439–449
9. Wittekind C (2010) TNM-Klassifikation maligner Tumoren. 7. Auflage. Wiley-VCH, Weinheim
10. Wagner PK, Ramaswamy A, Ruschoff J et al (1991) Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br J Surg 78:825–827
11. Waddell T, Verheij M, Allum W et al (2013) Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):57–63
12. Moehler M, Al-Batran SE, Andus T et al (2011) German S3-guideline "diagnosis and treatment of esophagogastric cancer". Z Gastroenterol 49:461–531
13. Alderson D, Langley RE, Nankivell MG (2015) Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). J Clin Oncol 33(Suppl. 15):4002
14. Al-Batran SE, Hofheinz RD, Pauligk C et al (2016) Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol 17:1697–1708
15. Al-Batran SE, Homann N, Schmalenberg H et al (2017) Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol 35(Suppl. 15):4004
16. Hofheinz R, Hegewisch-Becker S, Thuss-Patience P (2014) HER-FLOT: trastuzumab in combination with FLOT as perioperative treatment for patients with HER2-positive locally advanced esophagogastric adenocarcinoma: a phase II trial of the AIO Gastric Cancer Study Group. J Clin Oncol 32(Suppl. 5):4073
17. Fuchs CS, Tepper J, Niedzwiecki D et al (2011) Postoperative adjuvant chemoradiation for gastric or gastroesophageal junction (GEJ) adenocarcinoma using epirubicin, cisplatin, and infusional (CI) 5-FU (ECF) before and after CI 5-FU and radiotherapy (CRT) compared with bolus 5-FU/LV before and after CRT: intergroup trial CALGB 80101. J Clin Oncol 29(Suppl. 15):4003
18. Wilke H, Muro K, van Cutsem E et al (2014) Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 15:1224–1235
19. Ohtsu A, Shah MA, Van Cutsem E et al (2011) Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 29:3968–3976
20. Shen L, Li J, Xu J et al (2015) Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastr Cancer 18:168–176
21. Yoon HH, Bendell JC, Braiteh FS et al (2016) Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter phase II trial. Ann Oncol. https://doi.org/10.1093/annonc/mdw423
22. Cunningham D, Stenning SP, Smyth EC et al (2017) Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2–3 trial. Lancet Oncol 18:357–370
23. Lordick F, Kang YK, Chung HC et al (2013) Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol 14:490–499
24. Ilson DH, SuntharalingamJM Mohan, Dicker A et al (2014) RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. J Clin Oncol 32(Suppl. 15):4007
25. Kang YK, Ryu MH, Chao Y et al (2017) Nivolumab (ONO-4538/BMS-936558) as salvage treatment after second or later-line chemotherapy for advanced gastric or gastro-esophageal junction cancer (AGC): a double-blinded, randomized, phase III trial. J Clin Oncol 35(Suppl. 4):2
26. Stahl M, Walz MK, Stuschke M et al (2009) Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol 27:851–856
27. Burmeister BH, Thomas JM, Burmeister EA et al (2011) Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer 47:354–360
28. Shapiro J, van Lanschot JJ, Hulshof MC et al (2015) Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial. Lancet Oncol 16:1090–1098
29. Leichman LP, Bohanes PO, Lenz HJ et al (2011) A phase II clinical and prospective molecular trial with oxaliplatin, fluorouracil, and external-beam radiation therapy before surgery for patients with esophageal adenocarcinoma. J Clin Oncol 29:4555–4560
30. Ajani JA, Xiao L, Roth JA et al (2013) A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. Ann Oncol 24:2844–2849
31. Sjoquist KM, Burmeister BH, Smithers BM et al (2011) Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol 12:681–692
32. Paoletti X, Ob K, Burzykowski T et al (2010) Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 303:1729–1737
33. Sasako M, Sakuramoto S, Katai H et al (2011) Five year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 29:4387–4393
34. Noh SH, Park SR, Yang HK et al (2014) Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 15:1389–1396
35. Bajetta E, Floriani I, Di Bartolomeo M et al (2014) Randomized trial on adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus 5-fluorouracil and folinic acid for radically resected gastric cancer. Ann Oncol 25:1373–1378
36. Cascinu S, Labianca R, Barone C et al (2007) Adjuvant treatment of high-risk, radically resected gastric cancer patients with

5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. J Natl Cancer Inst 99:601–607
37. Smalley SR, Benedetti JK, Haller DG et al (2012) Updated analysis of SWOG-directed intergroup study 0116: a phase III trial of adjuvant radiochemotherapy versus observation after curative gastric cancer resection. J Clin Oncol 30:2327–2333
38. Park SH, Sohn TS, Lee J et al (2015) Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol 33:3130–3136
39. Smyth EC, Wotherspoon A, Peckitt C et al (2017) Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial. JAMA Oncol 3(9):1197–1203
40. Everett SM, Axon AT (1997) Early gastric cancer in Europe. Gut 41:142–150
41. Fujitani K, Yang HK, Mizusawa J et al (2016) Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol 17(3):309–318
42. Al-Batran SE, Homann N, Pauligk C et al (2017) 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 3(9):1237–1244
43. Al-Batran SE, Goetze TO, Mueller DW et al (2017) The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction—a phase III trial of the German AIO/CAO-V/CAOGI. BMC Cancer 17(1):893