Palliation of Esophageal Adenocarcinoma

13

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Abbreviations

5-FU	5-Fluorouracil
BSC	Best supportive care
BT	Brachytherapy
CRT	Chemo radiation therapy
CT	Chemotherapy
(D)CF	(Docetaxel,) cisplatin, fluorouracil
EBRT	External beam radiation therapy
ECF	Epirubicin, cisplatin, fluorouracil
ECX	Epirubicin, cisplatin, capecitabine
EOF	Epirubicin, oxaliplatin, fluorouracil
EOX	Epirubicin, oxaliplatin, capecitabine
GEJ	Gastro-esophageal junction
FLOT	Fluorouracil, leucovorin, oxaliplatin, docetaxel
G-CSF	Granulocyte colony-stimulating factor
HER2	Human epidermal growth factor receptor 2
HRQoL	Health-Related Quality of Life
MET	Mesenchymal epithelial transition factor
MOS	Median overall survival
ORR	Overall response rate
PDT	Photodynamic Therapy
PEG	Percutaneous endoscopic gastrostomy
PFS	Progressive free survival
PPI	Proton Pump Inhibitor

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PS	Performance Status
RR	Risk rate
SEMS	Self-expanding metal stent
SEPS	Self-expanding plastic stent
TT	Targeted therapy
TTP	Time to progression
VEGFR-2	Vascular endothelial growth factor receptor 2

Adenocarcinoma of the esophagus and gastro-esophageal junction is a highly aggressive and deadly disease. In Western countries, the incidence is rising and has already surpassed the numbers of squamous cell carcinoma in some areas [1]. In a population-based study less than 50% of patients were eligible for surgical treatment (42% received esophageal resection) [2]. Therefore, more than 50% of patients are in palliative setting. This number increases over time, since patients with recurrent disease or incomplete resection most likely will enter palliative treatment with developing efficacy. The group of patients not qualifying for curative surgical resection comprises of those with locally advanced unresectable tumors (T4 invading neighboring organs, predominantly trachea, heart, vessels), distant metastatic disease, carcinosis, and individuals, who deny surgery or suffer on severe comorbidities. The most frequent problem, we have to deal with, is dysphagia (Table 13.1), which finally can lead to complete disability to swallow, malnutrition, loss of body weight, aspiration, and of course to a massive reduction of quality of life. Weight loss of more than 10% worsens the prognosis, in particular this concerns advanced cases. Other tumor-related complications are pain, bleeding, and fistulation, either to the tracheobronchial tree and/or mediastinum (Figs. 13.1 and 13.2). A variety of therapeutic approaches are used, especially to alleviate dysphagia [4], but there is no single "best treatment option" existing, so therapeutic alternatives have to be discussed with the patient and adapted to his/her needs as well to PS. In a survey with 55 gastric and GEJ cancer patients, under palliative CT ability of self-care and tolerability of therapy were rated highest in importance [5]. So patients' view is not necessarily in congruence with specialists' opinion. Palliative therapy needs a multimodal and multidisciplinary approach and should be reviewed in an oncological tumor conference.

Table 13.1 Dysphagia score (Mellow and Pinkas [3]) to assess therapeutic efficacy

0 = able to eat normal diet/no dysphagia
1 = able to swallow some solid foods
2 = able to swallow only semi-solid foods
3 = able to swallow liquids only
4 = unable to swallow anything/total dysphagia

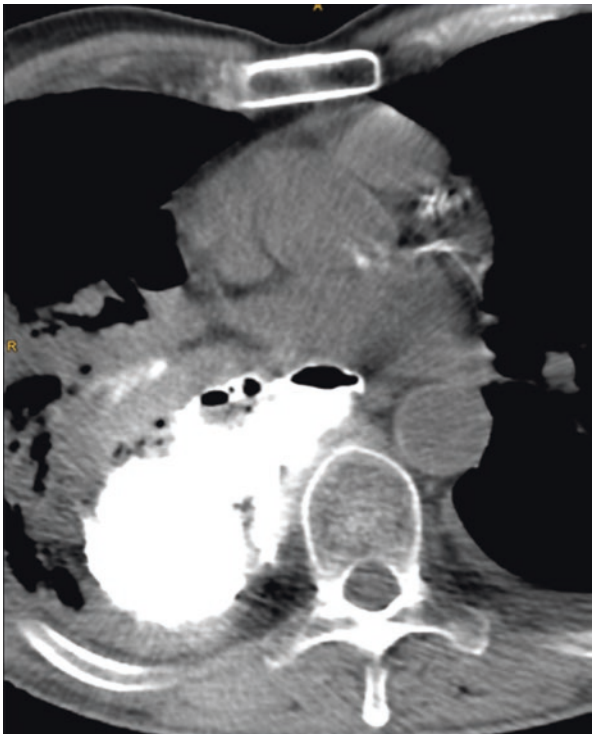

Fig. 13.1 CT scan of a patient with esophageal cancer, showing the spacious and devastating distribution of the contrast media within the mediastinum caused by a tracheo-esophageal/mediastinal fistulation

Extracting data and further more drawing conclusions for options of palliative treatment have to be done very carefully. This is mainly due to different design of the studies. Prognosis in patients on palliative track seems mainly dependent on possibilities to apply antitumor therapy [6]. Knowledge of prognostic factors (e.g., weight loss, PS, ability to swallow, pain) will help to determine the right choice of therapy [7]. Clinical outcome and patient-related outcome are not necessarily linked together. Surprisingly, as example, DCF compared to CF gives better results of HRQoL, although DCF is accompanied by higher toxicity [8]. One possible explanation for this unexpected finding is that more aggressive therapy might increase patient's hope and tolerance.

13.1 Palliative Chemotherapy

Adenocarcinoma of the esophagus and GEJ is assumed to have a very similar profile as gastric cancer [9] and therefore frequently dealt together. Restrictively it must be admitted that differences seem to exist [10].

There is consensus that a CT should be offered to patients with incurable tumors and physical fitness [11]. The goal is to extend survival time [10], improve/maintain HRQoL, and restore/maintain organ function. This benefit is questioned for

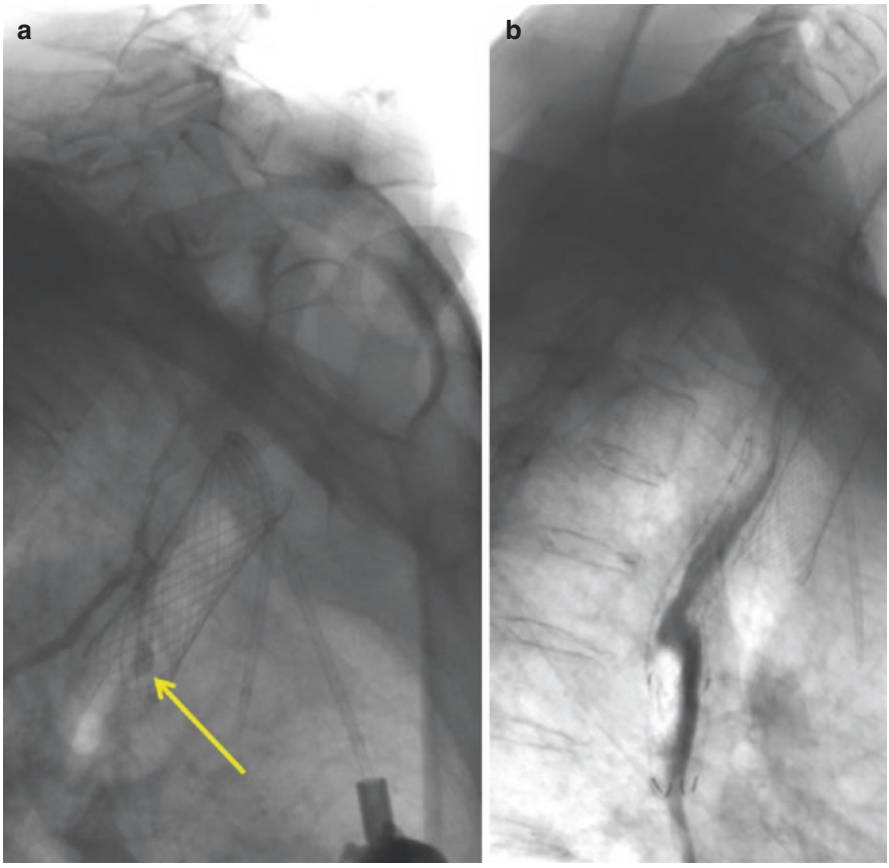

Fig. 13.2 Effect of stenting on a tracheoesophageal fistula. (**a**) Depicts a residual leakage (arrow) after a tracheal stent (Leufen aerstent® TBS, fully covered, 16/40 mm) was placed. (**b**) An additional esophageal stent (Niti-S™ Esophageal Stent, fully covered, 18/100 mm) was implanted, which led to a separation of the esophageal and tracheal compartment, preventing aspiration

individuals with reduced PS. There is some ongoing debate, whether CT is able to improve or just slow down deterioration of HRQoL [12]. It is still a controversy, which combination and substances should be applied, and also guidelines with slightly different recommendations exist. Most used chemotherapeutic regimens are based on combination of cisplatin and 5-FU. A randomized study comparing capecitabine with fluorouracil and oxaliplatin with cisplatin confirmed noninferiority. PFS and RR were comparable, and median survival was ECF: 9.9 months, ECX: 9.9 months, EOF: 9.3 months, and EOX: 11.2 months with a HR for death of 0.8 for EOX over ECF. Toxicity was similar for fluorouracil and capecitabine, whereas oxaliplatin caused more neuropathy and less renal toxicity [13]. If a standard of care is combination of platins and fluoropyrimidines, expanding this to a

triplet with docetaxel achieves better results (DCF vs. CF, ORR: 37% vs. 25%; median TTP 5.6 vs. 3.7 months; MOS: 9.2 vs. 8.6 months) [14, 15], although having to pay the toll of higher hematologic toxicity (Neutropenia Grade 3–4: 82% vs. 57%). DCF-treated patients also had better HRQoL [16] and clinical benefit in terms of maintaining PS and body weight. There was no measurable impact on pain or opioid need [17].

Various modifications have been developed, searching for better tolerability than the DCF regimen, e.g., FLOT [18] or adding G-CSF [19]. Since capecitabine was found to be equal to 5-FU [13], most patients, if possible, prefer oral administration and furthermore implantation of a venous access device can be avoided or at least delayed. A meta-analysis including almost 3500 patients, searching for optimal first-line CT demonstrated an advantage of triplet over doublet CT (OS: HR 0.90; PFS: HR 0.80; objective response rate risk ratio: 1:25). In contrast, risk of thrombocytopenia, mucositis, and infection increased [16]. No statistical significance was found with adding anthracycline to a doublet. This contrasts with Wagner's publications [20, 21], whereas all other results mainly conform.

After failure of first-line therapy, the COUGAR-02 trial proved the efficacy of second-line monotherapy with docetaxel versus BSC. MOS was found 5.2 versus 3.6 months as well as reduced dysphagia and pain [22]. In a comparison between irinotecan and paclitaxel, no relevant differences were detected, so both can be applied as second-line therapy [23]. Reliable data to second-line CT are still scarce and it remains an individual therapeutic decision depending on patient's preference and PS [24].

In a recently published Cochrane review, it has been shown with high quality of evidence that in palliative setting CT and/or TT increase OS (MOS: 6.7 vs. 5.7 months, HR 0.75), furthermore adding only TT improved also PFS (HR 0.64, moderate quality of evidence). These therapies seem to increase toxicity grade ≥3, whereas there was no clear proof for increased treatment-related mortality. Only very low evidence was found in a small sample for the improvement of HRQoL [10].

13.2 Targeted Therapy

The ToGA [25] trial investigated the efficacy of adding trastuzumab to a CT, targeting human epidermal growth factor receptor 2. It showed an increased MOS of 13.8 over 11.1 months in HER2 positive tumors. So, a HER2 status should be determined for selecting cases, which will benefit from adding trastuzumab. Trastuzumab should not be administered with anthracycline simultaneously.

A further promising antibody is ramucirumab, which acts against VEGFR2, blocking angiogenesis. A significant better survival was shown in the REGARD [26] trial (Ramucirumab vs. BSC, 5.2 vs. 3.8 months) and RAINBOW [27] study (paclitaxel plus ramucirumab vs. paclitaxel monotherapy, 9.6 vs. 7.4 months). Ramucirumab was also proven to increase OS and PFS in patients previously treated with chemotherapeutic agents [10]. Other tested monoclonal antibodies and tyrosinkinase inhibitors did not show high antitumor effects, and a study directed

against hepatocyte growth factor receptor (MET) was interrupted due to high mortality in the treatment group [28, 29].

Taken together, application of targeted therapies increases MOS and even PFS in palliative setting. It is still somehow open, from which patient profile benefits the most.

13.3 Palliative Radiotherapy and Chemoradiotherapy

Radiotherapy definitely plays a role in the therapeutic spectrum of esophageal cancer. It is a valid alternative/addition for palliation. There is a reasonable effect reported on symptom control, particularly dysphagia. This can be accomplished by EBRT or BT and also by combination of both or other measures of recanalization of the esophagus. New techniques in planning and delivery of radiation are expected to allow higher precision in targeting the tumor and therefore reducing damage to surrounding healthy tissue [30]. Probably RT, stent placement, or a combined management of both are mostly applied. Two randomized studies [31, 32] compared BT with stent placement, and the bottom line was that initially stents are more effective, whereas the esophageal patency of BT lasts longer [33], latter is in line with HRQoL [34]. Complications were less in the BT group (21% vs. 33% [31] or 13% vs. 25% [34]). Stenting appears very appropriate in patients probably expecting short survival. In a further randomized trial, increasing evidence emerges supporting the combination of SEMS and BT [35] as a very efficient method. Adding EBRT (30 Gy/10 fractions) to high-dose-rate BT (8 Gy/2 fractions 1 week) proved superiority to BT alone in a randomized study. This affects dysphagia, odynophagia, regurgitation, pain, PS, and HRQoL, whereas MOS and severe adverse events did not differ [36, 37]. The efficacy and safety of BT are reviewed in a recent meta-analysis [38] with resolution of symptoms in 87% after one month, a low mortality rate of 0.3%, and adverse effects of 23.4%. A more frequent use of BT is advocated, but it must be admitted that availability of BT is not everywhere.

A comparison between CRT (50 Gy) and RT alone (64 Gy) clearly demonstrated an advantage in favor of CRT (MOS 14.1 vs. 6.3 months) [39]. These results also get supported by a retrospective study comparing survival of SEMS versus CT versus RT versus CRT with MOS of 6.92, 7.75, 8.56, and 13.53, respectively. The only independent predictor in the multivariate analysis was the treatment modality [40]. Similar supporting results were obtained by a review primarily focusing on patient-related outcome [8].

13.4 Stenting

Introduction and continuous further development of expandable stents have brought a big advancement in treating dysphagia. Easy handling during placement, better results, and less complications led to a nearly complete replacement of the older plastic tubes. Such tubes were associated with high clinical mortality (>10%) and

complication rate [41, 42]. There are many expandable stent models offered, made either of an alloy of nickel and titan or steel or plastic (SEPS). The use of SEPS is highly decreased because of a higher migration rate and therefore need of further interventions. At the time being, SEMS are mostly used, fully or partially covered with synthetic covering—to prevent tumor ingrowth, with or without a reflux valve. Double-layered (second external metal mesh around a covered stent) is expected to reduce migration. Alternatively, biodegradable models are available, which in first-line seem more appropriate for benign diseases. To discuss different brands of stents goes beyond the scope of this chapter due to different availability, variety and rapid change in design and technical aspects. Selection of the most appropriate stent has to be done depending on the tumor location, size, configuration, and length of stenosis [43]. Placement is performed endoscopically or radiologically in sedoanalgesia or in general anesthesia, in selected cases with expected difficult stent placement or high risk of aspiration. Typical complications in the early phase are perforation, aspiration, pneumonia, pain, migration, and reflux. Late complications are migration, recurrent dysphagia due to tumor in- and overgrowth, food impaction, bleeding, formation of an esophageal fistulation, particularly to the airways, migration, perforation, and reflux. Stents placed over the GEJ form an open channel allowing reflux of gastric juice. To overcome this problem, stents with integrated reflux valves were introduced. The value of these is not clearly defined [44] and has to be compared with PPI administration. Although stents provide a rather rapid relief of dysphagia, the disadvantage is recurrent dysphagia within a few weeks. So, it appears reasonable to combine stent with BT notably for patients with estimated longer life span [31]. Feasibility and safety of this additive treatment have been shown, although a substantial increase of HRQoL except relieving dysphagia was not observed [45, 46]. Further promising results are expected with SEMS covered with ^{125}I seeds providing prolonged survival compared to covered SEMS (MOS 177 days vs. 147 days) with comparable side effects [47].

13.5 Other Palliative Treatment for Alleviation of Dysphagia

Different further measures are used to achieve relief from dysphagia. Thermal and chemical methods are locally applied like laser, photodynamic therapy, argon plasma coagulation, and injection of ethanol. Probably APC is the most used thermoablative method, which seems technically easier to apply with a reduced risk of perforation compared to laser [48]. In a randomized comparison of APC alone to a combination with either BT or PDT, a longer dysphagia-free period was observed for combined modalities, whereas these did not differ from each other. As well less complication as better HRQoL was shown in the APC-BT group [49]. In addition, availability of laser and PDT is limited and also requires specialized experience. Photosensitization of the skin and a distinct danger of perforation as side effects of PDT also must be taken into account [50].

In a meta-analysis, comparing the outcome between SEMS and other locoregional palliative treatment methods, stents needed less recurrent interventions,

whereas a survival advantage was observed for the others [44]. So, recanalization with other methods apart from SEMS are mainly used, if stents cannot be placed, e.g., in situation where the tumor is very close to the upper esophageal sphincter.

Mechanical dilation can be applied as an adjunct to widen the esophageal lumen before inserting a stent. The sole use of dilation is only recommended for selected cases with poor prognosis.

13.6 Role of Surgery

Besides attempts of rescue surgery, mainly due to perforation or bleeding, nearly all of palliative surgery and bypasses became obsolete because of high rates of morbidity (30–70%) and mortality (20–40% in the literature) [51–53]. This in turn leads to prolonged hospital stay and reduced HRQoL.

Nevertheless, some reports advocate palliative resection. Independent prognostic variables, which lead to poor survival, were identified as local or diffuse peritoneal carcinosis, solid organ matastases, signet cell histology, ASA III–IV, and advanced tumor stage [54]. This management applies only for a very small and highly selected group of patients. And it has to be noted that this study mainly focuses on OS but not on HRQoL.

One has also to bear in mind that development of new drugs, targeted therapies, and radiation techniques might offer new therapeutic approaches [55]. So, the border of unresectability might shift towards potential radical resectability due to downsizing and/or downstaging of the tumor. This could affect locally advanced tumors as well as metastatic ones in selected cases. The role of ablative therapy of metastases needs still to be defined.

13.7 General Supportive Measures

Pain medication, psychooncological support, and if required social help must be offered to patients with esophageal cancer. This should help these individuals to alleviate problems induced by this heavily aggressive disease. Nutritional status plays a major role and it has been shown that it is predictive for the course of the disease [56]. In some cases, a PEG tube is required, where oral intake cannot be achieved with other measures. This mainly applies for tumors highly located.

13.8 Conclusion

Palliative therapy of esophageal cancer has to be adapted to PS, concomitant diseases, organ function, morphology, and complications of the tumor. It should minimize the requirement for multiple therapeutic sessions and of course be in concordance to needs and wishes of the patient. This therapy is based on the concept

of multimodality and multidisciplinarity. If PS is good, a systemic CT and/or TT should be offered. This increases OS and has some positive effect on PFS and HRQoL. If first-line CT fails, a second-line CT and/or TT should be pursued. Oral food intake needs also to be restored. In case of reduced PS patency of the esophageal canal (e.g., stent/BT) and BSC are the foremost aim of palliation, providing the highest possible level of HRQoL. In some selected cases, a reduced systemic therapy might be appropriate.

13.9 Final Remark

This chapter was also crosschecked with selected published guidelines [11, 57–61].

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References

1. Castro C, Bosetti C, Malvezzi M, et al. Patterns and trends in esophageal cancer mortality and incidence in Europe (1980–2011) and predictions to 2015. Ann Oncol. 2014;25:283–90.
2. Sihvo EIT, Luostarinen ME, Salo JA. Fate of patients with adenocarcinoma of the esophagus and the esophagogastric junction: a population-based analysis. Am J Gastroenterol. 2004;99(3):419–24.
3. Mellow MH, Pinkas H. Endoscopic laser therapy for malignancies affecting the esophagus and gastroesophageal junction. Analysis of technical and functional efficacy. Arch Intern Med. 1985;145:1443–6.
4. Dai Y, Li C, Xie Y, et al. Interventions for dysphagia in oesophageal cancer. Cochrane Database Syst Rev. 2014;(10):CD005048.
5. Hofheinz R, Clouth J, Borchardt-Wagner J, et al. Patient preferences for palliative treatment of locally advanced or metastatic # cancer and adenocarcinoma of the gastroesophageal junction: a choice-based conjoint analysis study from Germany. BMC Cancer. 2016;16:937–45.
6. Gockel I, Kneist W, Junginger T. Incurable esophageal cancer: patterns of tumor spread and therapeutic consequences. World J Surg. 2006;30:183–90.
7. Frenken M. Best palliation in esophageal cancer: surgery, stenting, radiation, or what. Dis Esophagus. 2001;14:120–3.
8. Amdal CD, Jacobsen AB, Guren MG, et al. Patient-reported outcomes evaluating palliative radiotherapy and chemotherapy in patients with oesophageal cancer: a systematic review. Acta Oncol. 2013;52(4):679–90.
9. Chau I, Norman AR, Cunningham D. The impact of primary tumour origins in patients with advanced oesophageal, oesophago–gastric junction and gastric adenocarcinoma—individual patient data from 1775 patients in four randomised controlled trials. Ann Oncol. 2009;20:885–91.
10. Janmaat VT, Steyerberg EW, van der Gaast A, et al. Palliative chemotherapy and targeted therapies for esophageal and gastroesophageal junction cancer. Cochrane Database Syst Rev. 2017;11:CD004063.
11. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl 5):v50–7.
12. Al-Batran SE, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. Cancer. 2010;116(11):2511–8.

13. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358:36–46.
14. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 study group. J Clin Oncol. 2006;24:4991–7.
15. Chen X-L, Chen X-Z, Yang C, Liao Y-B, Li H, et al. Docetaxel, cisplatin and fluorouracil (DCF) regimen compared with non-taxane-containing palliative chemotherapy for gastric carcinoma: a systematic review and meta-analysis. PLoS One. 2013;8(4):e60320.
16. Haj Mohammad N, ter Veer E, Ngai L, et al. Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet versus doublet chemotherapy: a systemic literature review and meta-analysis. Cancer Metastasis Rev. 2015;34:429–41.
17. Ajani JA, Moiseyenko VM, Tjulandin S, et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal adenocarcinoma: the V-325 study group. J Clin Oncol. 2007;25:3205–9.
18. Al-Batran SE, Hartmann JT, Hofheinz R, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2008;19:1882–7.
19. Bojic M, Pluschnig U, Zacherl J, et al. Docetaxel, cisplatin and 5-fluorouracil plus granulocyte colony-stimulating factor prophylaxis in patients with metastatic adenocarcinoma of the stomach and gastrooesophageal junction: experience at the Medical University of Vienna. Anticancer Res. 2011;31:2379–82.
20. Wagner AD, Unverzagt S, Grothe W, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2010;(3):CD004064.
21. Wagner AD, Grothe W, Haerting J, et al. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24:2903–9.
22. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol. 2014;15(1):78–86.
23. Hironaka S, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol. 2013;31(35):4438–44.
24. Thallinger CM, Raderer M, Hejna M. Esophageal cancer: a critical evaluation of systemic second-line therapy. J Clin Oncol. 2011;29(35):4709–14.
25. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
26. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014;383(9911):31–9.
27. Wilke H, et al. 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. 2014;15(11):1224–35.
28. Pasini F, Fraccon AP, Modena Y, et al. Targeted therapies for advanced and metastatic adenocarcinoma of the gastroesophageal junction: is there something new? Gastric Cancer. 2017;20:31–42.
29. Behrens A, Ell C, Lordick F. Perioperative and palliative chemotherapy für esophageal cancer. Viszeralmedizin. 2015;31:341–6.

30. Hajj C, Goodman KA. Role of radiotherapy and newer techniques in the treatment of GI cancers. Clin Oncol. 2015;33:1737–44.
31. Homs MY, Steyerberg EW, Eijkenboomet WMH, et al. Single-dose brachytherapy versus metal stent placement for the palliation of dysphagia from oesophageal cancer: multicentre randomised trial. Lancet. 2004;364(9444):1497–504.
32. Bergquist H, Wenger U, Johnsson E, et al. Stent insertion or endoluminal brachytherapy as palliation of patients with advanced cancer of the esophagus and gastroesophageal junction. Results of a randomized, controlled clinical trial. Dis Esophagus. 2005;18:131–9.
33. Hanna WC, Sudarshan M, Roberge D, et al. What is the optimal management of dysphagia in metastatic esophageal cancer? Curr Oncol. 2012;19(2):e60–6.
34. Homs MY, Essink-Bot M L, Borsboom G J, et al., Dutch SIREC Study Group. Quality of life after palliative treatment for oesophageal carcinoma a prospective comparison between stent placement and single dose brachytherapy. Eur J Cancer. 2004;40:1862–71.
35. Amdal CD, Jacobsen AB, Sandstad B, et al. Palliative brachytherapy with or without primary stent placement in patients with oesophageal cancer, a randomised phase III trial. Radiother Oncol. 2013;107:428–33.
36. Rosenblatt E, Jones G, Sur RK, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multicentre randomized trial of the International Atomic Energy Agency. Radiother Oncol. 2010;97:488–94.
37. Welsch J, Kup PG, Nieder C, et al. Survival and symptom relief after palliative radiotherapy for esophageal cancer. J Cancer. 2016;7(2):125–30.
38. Fuccio L, Mandolesi D, Farioli A, et al. Brachytherapy for the palliation of dysphagia owing to esophageal cancer: a systematic review and meta-analysis of prospective studies. Radiother Oncol. 2017;122(3):332–9.
39. Al-Sarraf M, Martz K, Herskovic A, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15:277–84.
40. Sgourakis G, Gockel I, Karaliotas C, et al. Survival after chemotherapy and/or radiotherapy versus self-expanding metal stent insertion in the setting of inoperable esophageal cancer: a case control study. BMC Cancer. 2012;12:70.
41. Knyrim K, Wagner H, Bethge N, et al. A controlled trial of an expansile metal stent for palliation of esophageal obstruction due to inoperable cancer. NEJM. 1993;329:1302–7.
42. Fugger R, Niederle B, Jantsch H, et al. Endoscopic tube implantation for the palliation of malignant esophageal stenosis. Endoscopy. 1990;22(3):101–4.
43. Martinez JC, Puc MM, Quiros RM. Esophageal stenting in the setting of malignancy. ISRN Gastroenterol. 2011;2011:719575. https://doi.org/10.5402/2011/719575.
44. Sgourakis G, Gockel I, Radtke A, et al. The use of self-expanding stents in esophageal and gastroesophageal junction cancer palliation: a meta-analysis and meta-regression analysis of outcomes. Dig Dis Sci. 2010;55:3018–30.
45. Bergquist H, Johnsson E, Nyman J, et al. Combined stent insertion and single high-dose brachytherapy in patients with advanced esophageal cancer – results of a prospective safety study. Dis Esophagus. 2012;25:410–5.
46. Rueth NM, Shaw D, D'Cunha J, et al. Esophageal stenting and radiotherapy: a multimodal approach for the palliation of symptomatic malignant dysphagia. Ann Surg Oncol. 2012;19:4223–8.
47. Zhu HD, Guo JH, Mao AW, et al. Conventional stents versus stents loaded with ^{125}iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial. Lancet Oncol. 2014;15:612–9.
48. Homs MYV, Kuipers EJ, Siersema PD. Palliative therapy. J Surg Oncol. 2005;92:246–56.
49. Rupinski M, Zagorowicz E, Regula J, et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). Am J Gastroenterol. 2011;106:1612–20.

50. Lindenmann J, Matzi V, Neuboeck N, et al. Individualized, multimodal palliative treatment of inoperable esophageal cancer: clinical impact of photodynamic therapy resulting in prolonged survival. Lasers Surg Med. 2012;44:189–98.
51. Meunier B, Spiliopoulos Y, Stasik C, et al. Retrosternal bypass operation for unresectable squamous cell cancer of the esophagus. Ann Thorac Surg. 1996;62:373–7.
52. DeMeester SR. Adenocarcinoma of the esophagus and cardia: a review of the disease and its treatment. Ann Surg Oncol. 2006;13:12–30.
53. Mariette C, Bruyére E, Messager M, et al. Palliative resection for advanced gastric and junctional adenocarcinoma: which patients will benefit from surgery? Ann Surg Oncol. 2013;20:1240–9.
54. Zacherl J. The current evidence in support of multimodal treatment of locally advanced, potentially resectable esophageal cancer. Dig Dis. 2014;32:171–5.
55. Schildberg CW, Weidinger T, Hohenberger W. Metastatic adenocarcinomas of the stomach or esophagogastric junction (UICC Stage IV) are not always a palliative situation: a retrospective analysis. World J Surg. 2014;38:419–25.
56. Paireder M, Asari R, Kristo I, et al. Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. Eur J Surg Oncol. 2017;43(2):478–84.
57. Porschen R, et al. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Diagnostik und Therapie der Plattenepithelkarzinome und Adenokarzinome des Ösophagus, Langversion 1.0, 2015, AWMF Registernummer: 021/023OL. Z Gastroenterol. 2015;53:1288–347. http://leitlinienprogramm-onkologie.de/Leitlinien.7.0.html.
58. Möhler M, et al. S3-Leitlinie „Magenkarzinom“ – Diagnostik und Therapie der Adenokarzinome des Magens und ösophagogastralen Übergangs (AWMF-Regist.-Nr. 032-009-OL). German S3-Guideline „Diagnosis and treatment of esophagogastric cancer“. Z Gastroenterol. 2011;49:461–531. http://www.leitlinienprogrammonkologie.de/fileadmin/user_upload/Downloads/Leitlinien/Magenkarzinom/S3-Magenkarzinom-OL-Langversion.pdf.
59. Esophageal Cancer Treatment (PDQ®)–Health Professional Version. https://www.cancer.gov/types/esophageal/hp/esophageal-treatment-pdq#section/all.
60. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Esophageal and esophagogastric junction cancers. Version 4.2017. 2017. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf.
61. Ajani JA, D’Amico TA, Almhanna K, et al. Esophageal and esophagogastric junction cancers, version 1.2015. J Natl Compr Cancer Netw. 2015;13(2):194–227.