Neoadjuvant Treatment of Esophageal and Gastro-Esophageal Cancer

4

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4.1 Introduction

The incidence of adenocarcinoma of the esophagus and gastroesophageal (GE) junction has increased rapidly in Western countries, while numbers of squamous cell carcinoma (SCC) have gradually declined. For locally advanced esophageal cancer, surgery remains the mainstay of treatment. However, esophagectomy is historically associated with relatively high rates of irradical resection margins and high numbers of patients presenting with recurrent disease within 2 years after surgery. Therefore, the last decades several multimodality treatment regimens have been developed. Numerous studies evaluated the value of neoadjuvant as well as adjuvant strategies, especially chemotherapy and chemoradiation. In most countries advanced esophageal cancers are treated nowadays by neoadjuvant multimodality treatment regimens. It is thought that neoadjuvant chemotherapy and neoadjuvant chemoradiation eliminate micrometastases and induce locoregional tumor regression which leads to a higher rate of radical esophagectomies due to a reduction in the number of R1 and R2 resections (downstaging). However, its value has been debated for several decades. Up to a few years ago, the majority of the studies did not show any statistically significant benefit for neoadjuvant therapy, but these studies were frequently criticized because of inadequate trial design, limited statistical power (small sample size), and poor outcomes in the surgery alone group. However, in recent years, many different neoadjuvant regimens have been developed and tested. Historically, in the United Kingdom neoadjuvant chemotherapy was advocated while in Continental Europa and the USA neoadjuvant CRT was the preferred treatment. Ultimately the question which modality is superior will hopefully be answered by the Neo-AEGIS study, which compares perioperative chemotherapy (MAGIC) with neoadjuvant chemoradiation (CROSS). This trial design is discussed later on. The present chapter focuses on the different neoadjuvant treatment regimens.

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4.2 Neoadjuvant Chemotherapy

Studies in the 80s and 90s of the previous century revealed that patients with esophageal cancer who underwent surgical resection with curative intent had a dismal prognosis, with a 2-year

M.A. Cuesta (ed.), *Minimally Invasive Surgery for Upper Abdominal Cancer*,
DOI 10.1007/978-3-319-54301-7_4

survival rate of only 20–30%. Factors that contributed to these poor outcomes were the presence of locally advanced disease reflected by a high number of irradical resections and (distant) micrometastases at the time of surgery, which could not be detected with the available imaging techniques. To increase survival rates after esophagectomy, there was interest in the combination of chemotherapy and surgical treatment.

Multiple randomized trials have evaluated the benefit of chemotherapy administered prior to resection in patients with esophageal cancer. For example, the European EORTC 40954 trial in which 144 patients with adenocarcinoma of the stomach or GE-junction were randomized to neoadjuvant chemotherapy (5-FU, leucovorin, cisplatin) followed by surgery or surgery alone [1]. This trial was stopped for poor accrual, which limited the power of the study. A significantly increased R0 resection rate was found for patients treated with chemotherapy, however this did not translate into a survival benefit. Other studies such as the OEO2 trial demonstrated a survival benefit compared with resection alone. The OEO2 trial, in which patients (SCC or adenocarcinoma of the esophagus or GE-junction) were randomized to preoperative chemotherapy (cisplatin and fluorouracil) followed by surgery or surgery alone, revealed a survival benefit (HR 0.79, p 0.004) in combination with increased R0 resection rates (60% vs. 54%) [2]. In addition, a 30-day mortality of 10% was observed in both treatment groups. Long-term follow-up revealed a modest improvement in 5-year survival (36% vs. 23%, p = 0.03) [3]. These results can explain why neoadjuvant chemotherapy became standard of care for esophageal cancer in the United Kingdom. For squamous cell carcinoma of the esophagus a Dutch trial randomized patients for preoperative chemotherapy (cisplatin and etoposide) followed by surgery or surgery alone [4]. The 5-year survival was significantly improved after chemotherapy (26% vs. 17%). On the other hand, the USA intergroup 113 trial, which randomly assigned patients with SCC and adenocarcinoma to preoperative chemotherapy (cisplatin and fluorouracil) and surgery or surgery alone, failed to show a survival benefit for patients treated with preoperative chemotherapy [5]. They reported a 2-year survival rate of 35% for patients who received chemotherapy and 37% for those who underwent surgery alone. Postoperative mortality was 6% in both treatment groups. Long term results showed no difference in overall survival for patients receiving preoperative chemotherapy compared with surgery alone [6]. These results can explain why neoadjuvant chemotherapy did not become standard of care for esophageal cancer in the USA. The difference in outcome between the OEO2 trial and the USA intergroup 113 trial is difficult to explain as almost the same chemotherapy regimens have been applied.

The OEO2 trial was followed by the OEO5 trial, which hypothesized that adding a fourth cycle of chemotherapy to the neoadjuvant regimen would lead to better survival rates compared with a short neoadjuvant chemotherapy regimen. The preliminary results of this so called OEO5 trial, which compared prolonged neoadjuvant chemotherapy (4 cycles of epirubicin, cisplatin, capecitabine) with standard chemotherapy (2 cycles of cisplatin and 5-FU) in 895 patients with esophageal or GE-junction cancer have only been published in abstract form at the time of writing this chapter [7]. The OEO5 trial showed that prolonged chemotherapy resulted in increased R0 resection rates, better disease free survival, and progression free survival. The 3-year overall survival rate was 42% after prolonged neoadjuvant chemotherapy versus 39% after the classical OEO2 regimen, i.e. not significantly different, but with a higher toxicity rate in the group receiving 4 cycles of chemotherapy. Survival rates in the OEO5 trial are higher compared with the historical OEO-2 trial data. This may be explained by better patient selection and improved surgical techniques/outcome.

A recent meta-analysis showed a survival benefit for neoadjuvant chemotherapy relative to surgery alone for patients with esophageal or GE-junction cancer (HR all-cause mortality for neoadjuvant chemotherapy (HR 0.88 (95% CI 0.80–0.96), p = 0.003)) [8]. In addition, it was thought that neoadjuvant chemotherapy could result in an increase of surgery related morbidity

and mortality, since preoperative therapy might weaken the patient. A recent prospective study in patients with SCC of the esophagus or GEJ indeed showed that neoadjuvant chemotherapy increased the risk of postoperative complications compared with surgery alone [9]. However, a meta-analysis showed that neoadjuvant chemotherapy does not increase the risk of postoperative morbidity and perioperative mortality [10].

4.3 Neoadjuvant Chemoradiation

The role for neoadjuvant chemoradiation has also been debated for many years because of varying results of different studies. The high locoregional and systemic failure after surgery alone urged the need for new treatment options and resulted in combined modality treatment using systemic chemotherapy and locoregional radiotherapy. The goal of combining both neoadjuvant chemotherapy and neoadjuvant chemoradiation is mainly based on the possibility to downstage the primary tumor, resulting in higher R0 resection rates. In addition, neoadjuvant chemotherapy may also eradicate micro-metastatic disease by decreasing cancer-cell dissemination.

Studies on the effect of neoadjuvant chemoradiation for esophageal and GE-junction tumors showed variable results. The French FFCD 9901 trial which randomly assigned 195 patients with stage 1 or 2 esophageal or GE-junction cancer to preoperative chemoradiation (5-FU, cisplatin, and 45 Gy radiation therapy) followed by surgery versus surgery alone did not improve 3-year survival (47.5 vs. 53%) [11]. Chemoradiation prior to surgery did not improve the complete R0 resection rate and was associated with a significantly increased postoperative mortality. However, interpretation of these results is confounded by the fact that the study is underpowered to show a possible survival benefit. A Swedish trial randomized 181 patients with esophageal or GE-junction tumors (SCC and adenocarcinoma) to chemotherapy (cisplatin, FU) with or without radiotherapy (40 Gy) followed by surgical resection (4–6 weeks after completing neoadjuvant treatment) [12]. Chemoradiation significantly increased pathologically complete response (pCR) (28 vs. 9%) and complete R0 resection rate (87 vs. 74%). However, no significant difference in 3-year survival was found (47 vs. 49%). An Australian study randomized 256 patients to chemoradiation (cisplatin, fluorouracil, 35 Gy radiotherapy) followed by surgery or surgery alone [13]. Chemoradiation resulted in a significant increase of R0 resections (80% vs. 59%, p = 0.0002). However, no difference in overall survival was shown.

Several other trials and meta-analyses have demonstrated improved survival with preoperative concurrent chemoradiation as compared to surgery alone, for potentially resectable stage II or III localized cancer of the thoracic esophagus. However, the optimal regimen is not established yet. A relatively old Irish trial randomized patients to chemotherapy (fluorouracil and cisplatin) and radiotherapy (40 Gy) followed by surgery or surgery alone. This study in 113 patients revealed 25% complete response and a significantly increased 3-year survival after neoadjuvant chemoradiation followed by surgery (32% vs. 6%) [14]. Postoperative 90-day mortality of both groups combined was 6%. However, this study was criticized because of the unusually low survival rate in the surgery alone group. An American trial (CALGB 9781) randomized patients to chemotherapy (cisplatin and fluorouracil) and radiotherapy (50.4 Gy) followed by surgery or surgery alone. This study, which was closed prematurely after 3 years and only 56 patients (of the planned 475 patients) due to poor accrual, showed an increased 5-year survival (39% vs. 16%), however this did not reach statistical significance [15]. More recently, the Dutch Cross trial randomized 363 patients comparing preoperative chemotherapy consisting of carboplatin (doses titrated to achieve an area under the curve of 2 mg per millilitre per minute) and paclitaxel (50 mg per m^2 body-surface area) and radiotherapy (41.4 Gy in 23 fractions, 5 days per week) followed by surgery with surgery alone in patients with potentially curable esophageal or

GE-junction cancer (SCC and adenocarcinoma) (Fig. 4.1) [16]. This combination of chemotherapy and radiotherapy was well tolerated by the patients and significantly increased the percentage of R0 resections up to 92% compared with 69% in the surgery alone group. In addition, 29% percent of the patients with chemoradiation had a pCR. The median overall survival was also significantly higher in the combined treatment arm than in the surgery arm (49 months vs. 24 months; $P = 0.003$). (Fig. 4.2a, b) The long-term results confirmed the overall survival benefit for neoadjuvant chemoradiation (5-year survival 47 vs. 33%, HR for death 0.67, 95% CI 0.51–0.87) [17]. Due to the overall survival benefit, low toxicity, and high R0 resection rate (91%) of the neoadjuvant chemoradiation, the CROSS regimen is now the preferred multimodality treatment in the Netherlands and several other Western European countries.

The German POET trial suggested a possible superiority of neoadjuvant chemoradiation over chemotherapy. This trial randomized 126 patients with GE-junction tumors to chemotherapy alone (cisplatin, FU, leucovorin) followed by surgery or the same chemotherapy regimen (cisplatin, FU, leucovorin) followed by low-dose RT concurrent with chemotherapy (cisplatin and etoposide) [18]. Induction chemotherapy followed by chemoradiation significantly increased complete pathological response (15.6% vs. 2.0%, p = 0.03) and (non-significantly) increased 3-year survival (47 vs. 28%, p = 0.07). Recently the long-term results showed a 5 year overall survival of 24.4%

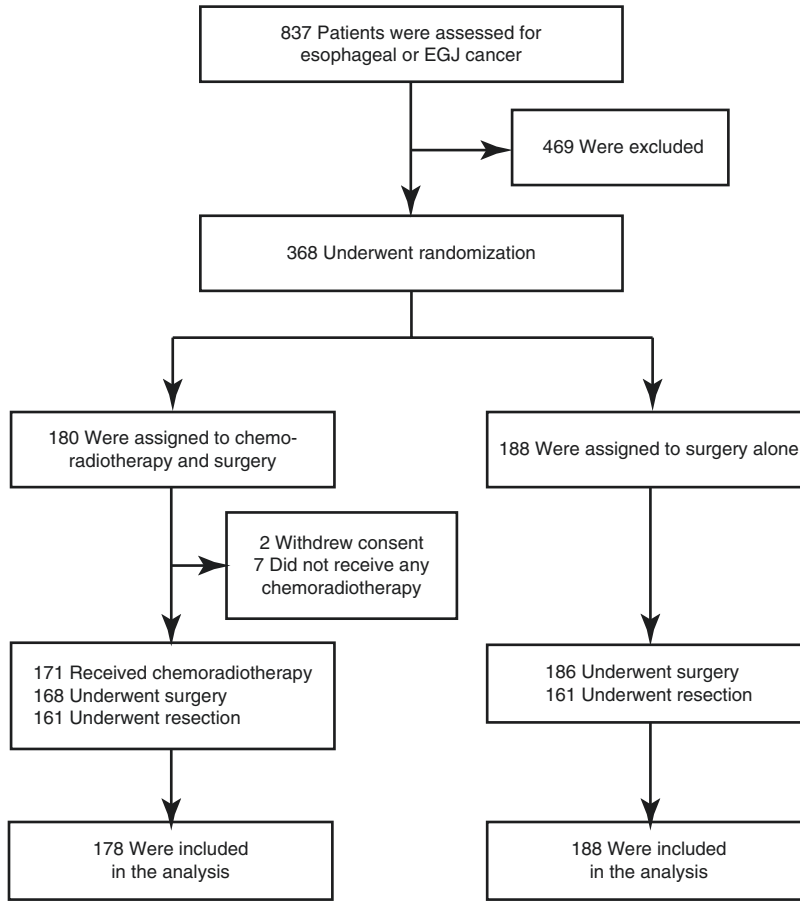
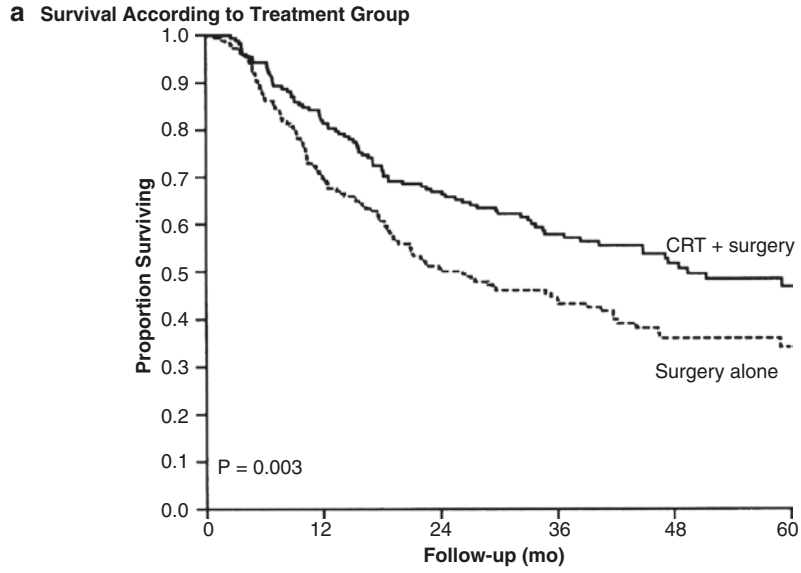
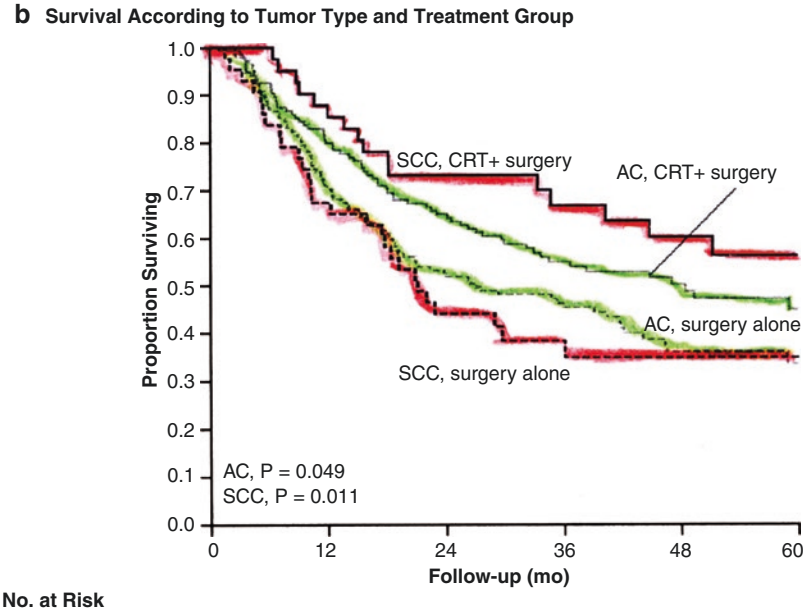


Fig. 4.1 Consort scheme of patients of CROSS trial



No. at Risk

CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45



No. at Risk

AC, CRT+surgery	134	107	87	53	34	18
AC, surgery alone	141	99	73	50	25	10
SCC, CRT+surgery	41	35	30	21	15	8
SCC, Surgery alone	43	29	19	11	8	4
Total	359	270	209	135	82	40

Fig. 4.2 (**a**) Estimated overall 5-years survival according to treatment group (CROSS trial); (**b**) estimated overall 5 year survival, according to tumor type and treatment group (CROSS trial)

in the chemotherapy versus 39.5% in the chemoradiation group (p = 0.055) [19]. An Australian trial randomized 75 patients to neoadjuvant chemotherapy (cisplatin and 5-FU) followed by surgery or neoadjuvant chemoradiation (cisplatin and 5-FU in combination with 35 Gy radiation therapy) followed by surgery [20]. After neoadjuvant chemoradiation pCR was significantly increased compared with neoadjuvant chemotherapy, 31 vs. 8% (p = 0.01) respectively. No significant difference in median overall survival was observed, possibly because of the low number of included patients.

Overall, a recent meta-analysis based on 6072 patients found that neoadjuvant chemoradiation followed by surgery compared with surgery alone was the only regimen to significantly improve survival (HR 0.77 (95% CI 0.68–0.87), p < 0.001) [21]. This network meta-analysis states that neoadjuvant chemoradiation followed by surgery is the most effective strategy in improving survival of resectable esophageal cancer. Earlier, a meta-analysis based on 4188 patients included in RCTs (CROSS, FFCD, CALGB 9781) found that neoadjuvant chemotherapy and neoadjuvant chemoradiation reduced overall mortality as compared to surgery alone in patients with T1-3 esophageal adenocarcinoma [22]. In addition, it has been debated that neoadjuvant chemoradiation may enhance the occurrence of postoperative complications, which for example has also been observed after neoadjuvant radiotherapy in rectal surgery. A recent prospective study in patients with SCC of the esophagus or GEJ indeed showed that neoadjuvant chemoradiation increased postoperative mortality compared with surgery alone [9]. However, a meta-analysis showed that neither neoadjuvant chemotherapy nor neoadjuvant chemoradiation increases the risk of postoperative morbidity and mortality [10].

4.4 Perioperative Chemotherapy

For gastric cancer a strategy of perioperative chemotherapy, which is also known as the "sandwich approach", is the predominant approach in Europe. This regimen was based primarily on the United Kingdom Medical Research Council MAGIC trial which randomized 503 patients with adenocarcinoma of the stomach, GE-junction and esophagus, to perioperative ECF (epirubicin/cisplatin/5-FU) and surgery or surgery alone [23]. Perioperative chemotherapy improved 5-year survival rate (36% vs. 23%, p = 0.009). However, only 42% of the patients intentionally treated with chemotherapy completed the full regime. Perioperative mortality (death within 30 days) was similar between both groups (5.6% vs. 5.9%). This study was criticized because of the lack of a standardized surgical procedure as well as the late inclusion of GE-junction and esophageal tumors in the protocol. The initial trial design was for stomach cancer, however due to low accrual, distal esophageal tumors and GE-junction tumors were also included in a later phase. Only one fourth of the patients had esophageal or GE-junction cancers. The inclusion of these last subgroups may have biased the results. Moreover, no clear evidence has been given about the additional value of the adjuvant phase of the study, and long term results have never been published.

The French FNCLCC-FFCD trial randomized 224 patients with adenocarcinoma of the esophagus, GE-junction, or stomach to perioperative chemotherapy (cisplatin and fluorouracil) and surgery or surgery alone [24]. Perioperative chemotherapy significantly improved 5-year survival (38% vs. 24%, p = 0.02), curative resection rate, disease-free survival (5-year rate: 34% vs. 19%, P = 0.003), while there was no difference in 30-day mortality (4.5% vs. 4.6%). In this study 75% of the patients had esophageal or GE-junction tumor.

4.5 Neoadjuvant Versus Adjuvant Strategies

Relatively few studies focused on postoperative strategies. In general, the data suggest that postoperative regimens fail to improve survival. There are only a few randomized trials of adjuvant chemotherapy for resected esophageal adenocarcinoma and only a few Japanese studies in

resected esophageal squamous cell carcinoma that showed no survival benefit [25, 26]. Recently, the superiority of neoadjuvant as compared to adjuvant chemotherapy was shown in the Japanese JCOG9907 trial [27]. Patients (n = 330) with SCC of the esophagus were randomly assigned to surgery preceded or followed by chemotherapy (cisplatin and 5-FU). Five-year overall survival was significantly higher after preoperative chemotherapy (55% vs. 43%, p = 0.04). One of the reasons that neoadjuvant chemotherapy may lead to better results is the fact that many patients do not tolerate adjuvant chemotherapy after an esophagectomy.

4.6 Future Perspectives

Over the last decades multiple trials have indicated that multimodality treatment of patients with esophageal and GE-junction cancer is necessary to obtain optimal results. At the moment several phase 3 trials are ongoing to further determine the optimal (neo)-adjuvant treatment regimen. The NeoAegis trial is recruiting patients to evaluate survival of patients treated with perioperative chemotherapy plus surgery versus neoadjuvant chemoradiation plus surgery (MAGIC vs. CROSS) in esophageal and junctional adenocarcinoma. The French PROTECT trial, investigates the effect of preoperative radiotherapy (41.4 Gy) in combination with two different chemotherapy regimens, namely FOLFOX (folinic acid, fluorouracil, oxalipatin) versus paclitaxel and carboplatin [28].

The recurrence patterns after CROSS followed by surgery for esophageal or GE-junction cancer reveal that isolated infield locoregional recurrence is very rare [29]. This indicates that increase of the dosis of radiotherapy is reasonless. Isolated outfield lymphatic recurrence is also very rare which counters a possible positive effect of enlargement of the radiation field. The occurrence of distant metastases, whether or not in combination with locoregional recurrence, is the major problem. Therefore, a more effective systemic therapy is needed to improve long-term survival. However, it is unlikely that much can be expected from new combinations or adjusted doses of the classical chemotherapeutic agents.

Several studies investigate the possible beneficial effects of monoclonal antibodies as neoadjuvant treatment for different types of cancer. For example in metastatic colorectal cancer and metastatic breast cancer the addition of monoclonal antibodies to standard chemotherapy regimens has improved survival [30, 31]. However, up to now, for esophageal cancer no beneficial effects of monoclonal antibodies have been reported. A recent study added bevacizumab and erlotinib to neoadjuvant chemoradiation for patients with esophageal or GE-junction cancer [32]. The addition of bevacizumab and erlotinib did not demonstrate any survival benefit. Another phase 2 trial showed that for patients with gastric or GE-junction adenocarcinoma the addition of bevacizumab to perioperative epirubicin, cisplatin, and capecitabine is feasible [33]. However, the phase-3 part of this STO3 trial is still ongoing. Also other monoclonal antibodies, for example against the vascular endothelial growth factor receptor 2 (ramucirumab), are promising additions to the standard of care for gastric or gastro-oesophageal cancer.

The success of immunotherapy for other tumors gives high expectations for a possible beneficial effect in esophageal and GE-junction tumors. Just as e.g. melanoma, esophageal cancer has a relatively high burden of genetic mutations which probably act as “neoantigens” and could be tested as potential targets for immunotherapy [34, 35].

The CROSS trial revealed that following chemoradiation, 49% of patients with SCC and 23% of patients with an adenocarcinoma had a pCR in the resection specimen. Also other studies described the effect of neoadjuvant chemoradiation on the occurrence of pCR. Several trials showed that this “sterilizing” effect is increased after chemoradiation compared with chemotherapy alone [12, 18, 20]. The occurrence of pathologically complete response opens the possibility for new (organ sparing) treatment options. It can be hypothesized that patients with pCR do not benefit from esophagectomy. Those patients could undergo an organ sparing approach if

identified correctly. Such approach would consist of active surveillance if clinically complete response (cCR) has been accomplished by chemoradiation. These effects of neoadjuvant chemoradiation on the occurrence of pCR raises questions about the timing and necessity of esophagectomy after application of the CROSS regimen. Therefore, a prospective trial (preSANO) is ongoing in the Netherlands which analyzes the optimal diagnostic set for determining the presence or absence of residual disease after chemoradiation [36]. If the preSANO trial shows that the presence or absence of residual tumor can be predicted reasonably after chemoradiation, a subsequent randomized controlled trial will compare chemoradiation plus standard surgery with chemoradiation plus surgery as needed (SANO trial). In this active surveillance group surgery will only be performed after CROSS if residual disease has been proven or is highly suspected. A comparable randomized trial (Esostrate trial) has recently been initiated in France.

In conclusion, the use of preoperative chemoradiation or chemotherapy followed by surgery is currently the prevailing treatment for most patients selected for curatively intended treatment. However, up to now none of these two regimens has been proven superior. Possibly a treatment more individualized for each patient will further improve the results of neoadjuvant therapy in combination with surgery. Recently, three subtypes of esophageal adenocarcinoma have been described [37]. This subclassification may have therapeutic relevance and could result in individualized treatment regimens for patients with esophageal or GE-junction tumors to obtain the optimal results from neoadjuvant therapy and surgery.

References

1. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for research and treatment of cancer randomized trial 40954. J Clin Oncol. 2010;28(35):5210–8. Epub 2010/11/10.
2. Group MRCOCW. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–33. Epub 2002/06/07.
3. Allum WH, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. J Clin Oncol. 2009;27(30):5062–7. Epub 2009/09/23.
4. Boonstra JJ, Kok TC, Wijnhoven BP, van Heijl M, van Berge Henegouwen MI, Ten Kate FJ, et al. Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: long-term results of a randomized controlled trial. BMC Cancer. 2011;11:181. Epub 2011/05/21.
5. Kelsen DP, Ginsberg R, Pajak TF, Sheahan DG, Gunderson L, Mortimer J, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. N Engl J Med. 1998;339(27):1979–84. Epub 1998/12/31.
6. Kelsen DP, Winter KA, Gunderson LL, Mortimer J, Estes NC, Haller DG, et al. Long-term results of RTOG trial 8911 (USA intergroup 113): a random assignment trial comparison of chemotherapy followed by surgery compared with surgery alone for esophageal cancer. J Clin Oncol. 2007;25(24):3719–25. Epub 2007/08/21.
7. Cunningham D, Langley RE, Nankivell M, Blazeby J, Griffin M, Crelin A, et al. Neoadjuvant chemotherapy for resectable oesophageal and junctional adenocarcinoma: results from the UK Medical Research Council randomised OEO5 trial (ISRCTN 01852072). Ann Oncol. 2015;26(Suppl 4):iv117–iv21.
8. Kidane B, Coughlin S, Vogt K, Malthaner R. Preoperative chemotherapy for resectable thoracic esophageal cancer. Cochrane Database Syst Rev. 2015;5:CD001556. Epub 2015/05/20.
9. Klevebro F, Lindblad M, Johansson J, Lundell L, Nilsson M. Outcome of neoadjuvant therapies for cancer of the oesophagus or gastro-oesophageal junction based on a national data registry. Br J Surg. 2016;103(13):1864–73. Epub 2016/10/01.
10. Kumagai K, Rouvelas I, Tsai JA, Mariosa D, Klevebro F, Lindblad M, et al. Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers. Br J Surg. 2014;101(4):321–38. Epub 2014/02/05.
11. Mariette C, Dahan L, Mornex F, Maillard E, Thomas PA, Meunier B, et al. Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901. J Clin Oncol. 2014;32(23):2416–22. Epub 2014/07/02.
12. Klevebro F, Alexandersson von Döbeln G, Wang N, Johnsen G, Jacobsen AB, Friesland S, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of

the oesophagus or gastro-oesophageal junction. Ann Oncol. 2016;27(4):660–7. Epub 2016/01/20.
13. Burmeister BH, Smithers BM, Gebski V, Fitzgerald L, Simes RJ, Devitt P, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. Lancet Oncol. 2005;6(9):659–68. Epub 2005/09/01.
14. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462–7. Epub 1996/08/15.
15. Tepper J, Krasna MJ, Niedzwiecki D, Hollis D, Reed CE, Goldberg R, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. J Clin Oncol. 2008;26(7):1086–92. Epub 2008/03/04.
16. 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. Epub 2012/06/01.
17. Shapiro J, van Lanschot JJ, Hulshof MC, van Hagen P, van Berge Henegouwen MI, Wijnhoven BP, 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. Epub 2015/08/10.
18. Stahl M, Walz MK, Stuschke M, Lehmann N, Meyer HJ, Riera-Knorrenschild J, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. J Clin Oncol. 2009;27(6):851–6. Epub 2009/01/14.
19. Stahl M, Riera-Knorrenschild J, Stuschke M, Engenhart-Cabillic R, Bitzer M, Budach W, et al. Preoperative chemoradiotherapy and the long-term run in curative treatment of locally advanced oesophagogastric junction adenocarcinoma: update of the POET phase III study. J Clin Oncol. 2016;34(suppl; abstr 4031).
20. Burmeister BH, Thomas JM, Burmeister EA, Walpole ET, Harvey JA, Thomson DB, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. Eur J Cancer. 2011;47(3):354–60. Epub 2010/11/19.
21. Pasquali S, Yim G, Vohra RS, Mocellin S, Nyanhongo D, Marriott P, et al. Survival after neoadjuvant and adjuvant treatments compared to surgery alone for resectable esophageal carcinoma: a network meta-analysis. Ann Surg. 2017;265(3):481–91.
22. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681–92. Epub 2011/06/21.
23. 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. Epub 2006/07/11.
24. 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. Epub 2011/03/30.
25. Ando N, Iizuka T, Kakegawa T, Isono K, Watanabe H, Ide H, et al. A randomized trial of surgery with and without chemotherapy for localized squamous carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. J Thorac Cardiovasc Surg. 1997;114(2):205–9. Epub 1997/08/01.
26. Ando N, Iizuka T, Ide H, Ishida K, Shinoda M, Nishimaki T, et al. Surgery plus chemotherapy compared with surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study—JCOG9204. J Clin Oncol. 2003;21(24):4592–6. Epub 2003/12/16.
27. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). Ann Surg Oncol. 2012;19(1):68–74. Epub 2011/09/01.
28. Messager M, Mirabel X, Tresch E, Paumier A, Vendrely V, Dahan L, et al. Preoperative chemoradiation with paclitaxel-carboplatin or with fluorouracil-oxaliplatin-folinic acid (FOLFOX) for resectable esophageal and junctional cancer: the PROTECT-1402, randomized phase 2 trial. BMC Cancer. 2016;16:318. Epub 2016/05/20.
29. Oppedijk V, van der Gaast A, van Lanschot JJ, van Hagen P, van Os R, van Rij CM, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. J Clin Oncol. 2014;32(5):385–91. Epub 2014/01/15.
30. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92. Epub 2001/03/15.
31. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42. Epub 2004/06/04.
32. Bendell JC, Meluch A, Peyton J, Rubin M, Waterhouse D, Webb C, et al. A phase II trial of preoperative concurrent chemotherapy/radiation therapy plus bevacizumab/erlotinib in the treatment of localized esophageal cancer. Clin Adv Hematol Oncol. 2012;10(7):430–7. Epub 2012/08/17.
33. Okines AF, Langley RE, Thompson LC, Stenning SP, Stevenson L, Falk S, et al. Bevacizumab with

peri-operative epirubicin, cisplatin and capecitabine (ECX) in localised gastro-oesophageal adenocarcinoma: a safety report. Ann Oncol. 2013;24(3):702–9. Epub 2012/10/31.
34. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415–21. Epub 2013/08/16.
35. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480–9. Epub 2011/12/24.
36. Noordman BJ, Shapiro J, Spaander MC, Krishnadath KK, van Laarhoven HW, van Berge Henegouwen MI, et al. Accuracy of detecting residual disease after cross neoadjuvant chemoradiotherapy for esophageal cancer (preSANO Trial): rationale and protocol. JMIR Res Protoc. 2015;4(2):e79. Epub 2015/06/30.
37. Secrier M, Li X, de Silva N, Eldridge MD, Contino G, Bornschein J, et al. Mutational signatures in esophageal adenocarcinoma define etiologically distinct subgroups with therapeutic relevance. Nat Genet. 2016;48(10):1131–41. Epub 2016/09/07.