Quality assurance in the surgical treatment of gastric cancer

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PART IV

DIRECTIONS FOR THE FUTURE

CHAPTER 9

NEOADJUVANT TREATMENT OF GASTRIC CANCER

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INTRODUCTION

Gastric cancer remains a significant health problem. Despite the fact that the incidence of gastric cancer over the last decades decreased considerably, it is still the fifth most common malignancy in the world with approximately one million new cases each year. With over 700.000 deaths yearly it is the third leading cause of cancer deaths in both sexes worldwide, with the highest mortality rates reported in Eastern Asia (14.0 per 100,000 males and 9.8 per 100,000 females).[1]

Surgery is still the cornerstone in treatment of curable gastric cancer. Nowadays, gastrectomies are increasingly minimally invasive performed. The results of gastrectomies have improved over the last years with respect to morbidity, postoperative mortality, and survival.[2] However, whether the extended lymph node dissection contributed to this improvement is still unclear as the last decades the role of extended lymph node dissection has been controversial. In Asian countries an extended lymph node dissection (D2) has been the standard procedure for the last two decades, whereas in Western countries only a limited lymph node dissection (D1) was common practice until recently.[2] Many studies have investigated the benefit of an extended lymph node dissection (D2) over the standard limited (D1) lymphadenectomy for Western patients, including three methodologically well performed randomized clinical trials, the UK Medical Research Council (MRC) surgical trial, the Dutch Gastric Cancer Trial (DGCT), and the Italian Gastric Cancer Trial.[3-5] Initially none of these trials showed a difference in overall survival, though a D2 lymphadenectomy was associated with a significant higher morbidity- and mortality rate.[3-5] Long term follow up in the Dutch trial, however, did show a benefit for the more extended lymph node dissection, especially if morbidity and mortality could be minimalized.[4,6] Furthermore, the Italian trial showed that an extended lymph node dissection was beneficial for patients with node positive disease.[5] Nevertheless, survival after surgery alone with a D2 lymph node dissection remains poor with a 5-year survival rate around 50% in Western countries.[2]

As no further great improvements were expected in the field of surgery, new treatment strategies were urgently needed to improve survival rates of gastric cancer. In order to achieve this, numerous studies were conducted with multimodal treatment strategies, such as (neo)adjuvant chemotherapy and/or radiotherapy, in addition to surgery. First, adjuvant chemotherapy was tested in several trials with limited patients, but with promising results.[7] Later on, the role of chemotherapy in neoadjuvant setting was evaluated, starting in the Dutch FAMTX trial, and developed to an essential part of the treatment of gastric cancer.[8] Application of radiotherapy in neoadjuvant setting has also gained space over time. The last years attention has risen increasingly for chemotherapy combined with targeted agents. Consequently, in the last 15 years, major advances in the field of multimodal treatment strategies have changed clinical management of gastric cancer.

This chapter comprises the current status of neoadjuvant therapy in treatment of gastric cancer in the Western world. Future directions in the treatment of gastric cancer are addressed.

NEO-ADJUVANT/ PERIOPERATIVE CHEMOTHERAPY

The use of preoperative chemotherapy in gastric cancer was considered to achieve downstaging of the tumor, to improve resectability, and to increase the likelihood of completing multimodal treatment, because surgery is associated with substantial morbidity rates. An overview of studies investigating the impact of neo-adjuvant/ perioperative chemotherapy in gastric cancer is shown in *Table 1*. One of the first randomized clinical trials investigating the added value of neoadjuvant chemotherapy in resectable gastric cancer was the Dutch FAMTX trial (also known as the POCOM (Preoperative Chemotherapy for Operable Gastric Cancer) trial).[8] The aim of this trial was to investigate whether pre-operative chemotherapy leads to a 15% higher curative resectability rate in patients with operable gastric cancer. After adequate staging, patients were randomized to receive either four courses of FAMTX (5-fluorouracil, doxorubicin, and methotrexate), followed by surgery or surgery alone. With a two-sided significance level of 5% and a power of 90%, 225 patients were required in each arm.

Table 1. Overview of studies investigating the impact of neoadjuvant/ perioperative chemotherapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
FAMTX trial[8]					
	1993 - 1996	29	FAMTX - S	Median survival : 18 months	0.17
		30	S	Median survival : 30 months	
MAGIC trial[9]					
	1994 - 2002	250	ECF - S - ECF	HR 0.75 (CI: 0.60-0.93)	0.009
		253	S		
FNLCC/ FFDC trial[10]					
	1995 - 2003	113	CF - S - CF	HR 0.69 (CI: 0.50-0.95)	0.02
		111	S		
EORTC 40954[11]					
	1999 - 2004	113	CF - S	HR 0.84 (CI: 0.52-1.35)	0.466
		111	S		

N=number, P= p-value, FAMTX=5-fluorouracil, doxorubicin, and methotrexate, S=surgery, ECF=epirubicin, cisplatin, and 5-fluorouracil, HR=hazard ratio, CI= 95% confidence interval, CF= cisplatin and 5-fluorouracil

Due to poor accrual an interim analysis was prematurely performed where no difference in resectability rates was observed between both arms. Based on these results and poor accrual, the trial was prematurely closed. Between 1993 and 1996, 59 patients were randomized of which 29 patients were allocated to the FAMTX regimen and 30 patients

to surgery alone. A beneficial effect of the pre-operative FAMTX could not be shown as the results showed equal resectability rates in both groups. The response rate (complete or partial) in the FAMTX group was only 32%, which was comparable with lower results of previous reported data. The median survival was 18 months in the FAMTX group compared to 30 months in the surgery alone group (p=0.17). At initiation of this trial in the early 90s, a FAMTX regimen was chosen because of its repeatedly demonstrated steady response rates, lower toxicity compared with EAP (etoposide, 5-fluorouracil (5-FU) and methotrexate), lower costs, and lower toxicity compared with FEMTX-P (5-FU, epidoxorubicin, methotrexate, and cisplatin). Moreover, at that time FAMTX was considered the golden standard for future randomised trials. After prematurely closing the study investigators suggested that more active regimens than FAMTX are required for future randomised trials, such as epirubicin, cisplatin, and 5-fluorouracil (ECF).

A landmark study in the field of perioperative chemotherapy for gastric cancer is the United Kingdom Medical Research Council MAGIC study in which Dutch participants contributed significantly.[9] This trial was the first randomized clinical trial showing a survival benefit for perioperative chemotherapy in gastric cancer compared to surgery alone. Patients with resectable adenocarcinoma of the stomach, esophagogastric junction (GEJ), or lower esophagus were included. Between 1994 and 2002, 250 patients were randomly assigned to perioperative chemotherapy and 253 patients to surgery alone. Chemotherapy consisted of 3 preoperative and 3 postoperative cycles of intravenous epirubicin (50 mg/m^2 body surface) and cisplatin (60 mg/m^2) on day 1, and a continuous intravenous infusion of 5-fluorouracil (200 mg/m^2/day). The primary endpoint was overall survival. Postoperative complications rates were similar in the perioperative and the surgery alone group (46% vs. 45%), as were the numbers of death within 30 days (6% vs. 6%). In the perioperative chemotherapy group more patients were able to undergo surgery (79% vs. 70%) and tumors were significantly smaller (T1/T2 52% vs. 37%) with less involved lymph nodes (N0/N1 84% vs. 71%). The perioperative chemotherapy group improved both overall survival (HR 0.75; 95% CI: 0.60-0.93, *P*=0.009; 5-year survival rate 36% vs. 23%) as disease-free survival (HR 0.66; 95% CI: 053-0.81, *P*<0.001) compared to surgery alone. Despite these promising results, this trial was criticized for the fact that only 54% of the patients completed the entire treatment, suggesting that the benefit found was largely derived from neoadjuvant ECF.

Similar outcomes as the MAGIC trial were achieved in the French FNCLCC and FFCD multicentre phase III trial.[10] A total of 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ, or stomach were randomized to receive either 2-3 cycles of preoperative and 3-4 cycles of perioperative chemotherapy (5-fluorouracil 800 mg/m^2 daily for five days plus cisplatin 100 mg/m^2 on day 1 or 2, every four weeks; n=113) or surgery alone (n=111). The perioperative chemotherapy group had a better overall survival (HR 0.69; 95% CI: 0.50-0.95, *P*=0.02; 5-year survival rate 38% vs. 24%) and a better disease-free survival (HR 0.65; 95% CI: 0.48-0.89, *P*=0.003; 5-year rate 34% vs. 19%).

The European Organisation for Research and Treatment of Cancer randomized trial (EORTC 40954) was closed due to poor accrual and was not able to demonstrate a survival benefit for neoadjuvant chemotherapy compared to surgery alone (HR 0.84; 95% CI: 0.52-1.35, *P*=0.466).[11] Possible explanations according the study investigators were a low statistical power, a high rate of proximal gastric cancer, and a better outcome than expected after surgery alone. This trial, however, did show a significantly increased R0 resection rate in favour of the neoadjuvant chemotherapy group (82% vs. 67%, *P*=0.036).

A recent meta-analysis of Yang *et al*. investigated the effect of neoadjuvant chemotherapy on the survival outcomes of resectable gastric cancer.[12] Results showed that perioperative chemotherapy led to an increase in progression-free survival (HR=0.66; 95% CI: 0.55-0.78, *P*=<0.001) and reduction in distant metastases (RR=0.72, 95% CI: 0.59-0.87, *P*=0.001) compared to surgery alone. A trend toward favouring neo-adjuvant chemotherapy compared to no neo-adjuvant chemotherapy was observed in overall survival, but was not significant (HR=0.68, 95% CI: 0.44-1.05, *P*=0.08).[12]

NEOADJUVANT CHEMORADIOTHERAPY

Application of radiotherapy in the neoadjuvant setting has gained ground over the years. In theory, the gastric tumor remains intact leading to a facile treatment planning by the conserved normal anatomy and there is limited toxicity to adjacent organs. An overview of studies investigating the impact of neoadjuvant chemoradiotherapy is provided in *Table 2*. A German phase III randomized clinical trial (POET trial) aimed to address the question of whether adding chemoradiotherapy to neoadjuvant chemotherapy (cisplatin, 5-fluorouracil, and leucovorin) in tumors of the lower esophagus and gastric cardia would lead to survival benefit compared to chemotherapy alone.[13] The study was planned according a two-stage adaptive design. The alternative hypothesis was superiority of 10% in 3-year survival of the chemoradiotherapy arm compared with the chemotherapy arm. With one-sided significance level of 5% and power of 80% the required amount of 263 patients each arm was not achieved resulting in prematurely closing of the trial. From 2000 and 2006, 126 patients were randomly assigned. A significant higher probability of showing pathological complete response was found in favour of the chemoradiotherapy group (15.6% vs. 2.0%, *P*= 0.03). This study found a trend toward improved 3-year survival with the addition of chemoradiotherapy to chemotherapy alone (27.7% vs. 47.4%, *P*= 0.07). However, no statistical significance was seen, most likely due to prematurely closing of the study.

Later on, the Dutch CROSS trial was conducted to demonstrate the benefit of neoadjuvant chemoradiotherapy in esophageal or esophagogastric-junction cancer.[14] It should be notified that this study included primarily patients with esophageal cancer (76%) and a smaller part tumors of the GEJ (24%). Between 2004 and 2008, patients were

randomly assigned to carboplatin (doses titrated to achieve an area under the curve of 2mg/ml/minute) and paclitaxel (50mg/m^2/body surface) and concurrent radiotherapy (41.4 Gy in 23 fractions, 5 days per week), followed by surgery or surgery alone. Overall survival improved in the chemoradiation group (HR 0.66; 95% CI: 0.50-0.87, *P*=0.003). Complete resection (R0) was achieved in 92% of the chemoradiation group versus 69% in the surgery alone group (*P*<0.001). Acceptable adverse event rates were observed.

Since 2009, the TOPGEAR trial is accruing. Patients with resectable adenocarcinoma of the stomach or GEJ are eligible for this trial. The hypothesis of this randomized phase III trial is that adding chemoradiation to standard perioperative chemotherapy (3 cycles of ECF preoperative and postoperative) will have a positive effect on overall survival rates.[15]

Table 2. Overview of trials investigating the impact of neoadjuvant chemoradiotherapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
POET trial[13]					
	2000 - 2005	60	PLF - CRT[1] - S	HR 0.67 (CI: 0.41-1.07)	0.07
		59	PLF - S		
CROSS trial[14]*					
	2004 - 2008	178	CRT[2] - S	HR 0.66 (CI: 0.50-0.87)	0.003
		188	S		
TOPGEAR trial[15]					
	2009 - 2020**		ECF - CRT[3] - S	Ongoing	
			ECF - S		

N=number, P= p-value, PLF= cisplatin, 5-fluorouracil, and leucovorin, CRT[1]= cisplatin, etoposide, and radiotherapy (30 Gy), S=surgery, HR=hazard ratio, CI= 95% confidence interval, CRT[2]=carboplatin, paclitaxel, and radiotherapy (41.4 Gy), ECF=epirubicin, cisplatin, and 5-fluorouracil, CRT[3]= 5-fluorouracil and radiotherapy (45 Gy)

**= trial including esophageal or esophagogastric-junction cancer*

***= estimation*

ADJUVANT THERAPY

Although the primary goal of this chapter is to focus on neoadjuvant treatment strategies in gastric cancer, a description of the present evidence for adjuvant therapy in gastric cancer is necessary to obtain a complete overview of the current multimodal treatment strategies of gastric cancer. Results of below mentioned studies are shown in *Table 3*.

In 2001, the SWOG/Intergroup 0116 trial showed an improvement in survival and locoregional control with the introduction of postoperative chemoradiotherapy.[16] In this trial, 556 patients were randomized to surgery and postoperative chemoradiotherapy

(45 Gy in 25 fractions in 5 weeks and 3 cycles of 5-fluorouracil and leucovorin; n=281) or surgery alone (n=275). A survival benefit was seen in the chemoradiotherapy group with a median overall survival of 36 months compared to 27 months in the surgery group (HR 1.35; 95% CI: 1.09-1.66, *P*=0.005). Relapse free survival was prolonged in the chemoradiotherapy group (19 months compared to 30 months in surgery alone group (HR 1.52; 95% CI: 1.23-1.86, *P*<0.001)). This study was criticized for its poor adherence to the surgical protocol, as only 10% of the included patients underwent the intended D2-lymphadenectomy.

Table 3. Overview of trials investigating the impact of adjuvant therapy in resectable gastric cancer

Trial	Years	N	Treatment	Results	*P*
Intergroup 0116 trial[16]					
	1991 - 1998	281	S - CRT[1]	HR 1.35 (CI: 1.09-1.66)	0.005
		275	S		
ARTIST trial[17]					
	2004 - 2008	211	S - XP - CRT[2] - XP	HR 1.130 (CI: 0.78-1.65)	0.527
		204	S - XP		
CRITICS trial[19]					
	2007 - 2015	395	ECC - S - CRT[3]	Median survival: 3.3 year	0.99
		393	ECC - S - ECC	Median survival: 3.5 year	

N=number, P= p-value, S=surgery, CRT[1]= 5-fluorouracil, leucovorin, and radiotherapy (4500 cGy), HR=hazard ratio, CI= 95% confidence interval, XP=capecitabine and cisplatin, CRT[2]=capecitabine and radiotherapy (45 Gy), ECC= Epirubicin, Cisplatin/Oxaliplatin, and Capecitabine, CRT[3]= 5-fluorouracil, cisplatin, and radiotherapy (45 Gy)

The South Korean ARTIST trial was the first study investigating the addition of radiotherapy to adjuvant chemotherapy for patients who underwent a curative gastric resection with a D2 lymph node dissection.[17] Between 2004 and 2008, 458 patients were randomized between either capecitabine plus cisplatin followed by chemoradiotherapy and two additional cycles capecitabine (n=230) or only capecitabine plus cisplatin regime (n=228). Overall, addition of chemoradiotherapy did not lead to a significant difference with regard to disease free survival (HR 0.740; 95% CI: 0.52-1.05, *P*=0.092) nor overall survival (HR 1.130; 95% CI: 0.78-1.65, *P*=0.527). Though, results showed a significant benefit in disease free survival benefit of chemoradiation in the subset of patients with node-positive disease. As a follow up of this trial the ARTIST 2 is ongoing and will evaluate the value of adjuvant chemotherapy and chemoradiation after a D2 lymph node dissection in patients with node positive gastric cancer. It should be notified that these trials are being performed in the Eastern world. Gastric cancer in the Eastern world differs compared to the Western world, regarding biology, epidemiology, stage, and prognosis. In the Eastern world gastric cancer is characterised by a higher

incidence, more distal located tumors, more often found in an early stage of the disease, more standardized surgery with a D2 lymph node dissection, and better prognosis.[18]
In order to determine the most optimal adjuvant therapy for the Western gastric cancer patient with advanced disease, the CRITICS trial was conducted and recently completed. In this randomized clinical trial patients with resectable gastric cancer were treated with three cycles of preoperative epirubicin, cisplatin/oxaliplatin, and capecitabine (ECC/EOC) and surgery with adequate lymph node dissection, followed by either three cycles of ECC/EOC (CT) or concurrent chemoradiation (CRT; 45 Gy in 25 fractions with 5- fluorouracil and cisplatin).[19] The first study results were presented during the ASCO convention in 2016 but are not published yet. The median follow up was 4.2 years. The 5-year overall survival was equal in both arms: 40.8% for CT and 40.9% for CRT, with a corresponding median survival of 3.5 years and 3.3 years. No differences were observed with regard to progression free survival across both arms (5-year 38.5% (CT) and 39.5% (CRT) with a median progression free survival of 2.3 years (CT) and 2.5 years (CRT)). Sixty-one % of the patients in the CT group and 63% in the CRT group started with postoperative treatment whereas 47% and 52% of the patients respectively were able to complete treatment. Further analyses of this trial are currently being performed. In the near future, the CRITICS-II trial aims to establish the most optimal preoperative regimen in resectable gastric cancer by comparing chemotherapy, chemotherapy and subsequent chemoradiotherapy, and chemoradiotherapy.

In 2014, Cao *et al.* aimed to assess the value of adjuvant chemotherapy in patients with gastric cancer after radical surgical resection in a meta-analysis.[20] Results showed that adjuvant chemotherapy can improve overall survival rate (RR=1.09, 95% CI: 1.06-1.23), as well as disease-free survival rate (RR=1.11, 95% CI: 1.07-1.15), and can reduce the relapse rate after curative resection (RR=0.79, 95% CI: 0.74-0.84).[20]

TARGETED THERAPY

Biomarker-targeted therapy has received increased attention in the recent years. Although high expectations, until this moment, targeted agents have no place in the standard care of curable Western gastric cancer patients after several trials obtained negative trial results. Currently, the INNOVATION trial is being conducted to investigate whether trastuzumab (a humanized monoclonal IgG antibody which inhibits the HER-2/neu receptor) or trastuzumab with pertuzumab shows more activity against standard chemotherapy after surgery in patients with HER-2 positive resectable gastric cancer and whether it can be safely administered (NCT02205047). The HER-2 positive rate in resectable gastric cancer is around 15%. Some studies suggested that HER-2 positive status is associated with a worse prognosis although the sample sizes of these studies were relatively small. Primary completion date for the INNOVATION trial is estimated for September 2020.

In contrast with the negative trial results of targeted therapy for curable gastric cancer, positive results are being achieved in trials with targeted therapy for incurable gastric cancer. The most important trials with targeted therapy in metastatic gastric cancer are discussed here and shown in *Table 4*.

In both neoadjuvant as adjuvant settings, trastuzumab has been shown to be effective regarding the treatment of HER-2 positive breast cancer. In 2010, the ToGA (Trastuzumab for Gastric Cancer) trial is conducted to evaluate the benefit of combining trastuzumab with chemotherapy versus chemotherapy alone for treatment of HER-2 positive incurable gastric or GEJ cancer.[21] Chemotherapy regimen consisted of either capecitabine plus cisplatin or 5-fluorouracil plus cisplatin every 3 weeks for six cycles or this chemotherapy regimen in combination with intravenous trastuzumab. Addition of trastuzumab significantly prolonged median overall survival compared to chemotherapy alone (HR 0.74; 95% CI: 0.60-0.91, *P*=0.005). Rates of overall grade 3 or 4 adverse events did not differ between both groups. [21] Since the results of this trial were published, trastuzumab in combination with chemotherapy could be considered as a new standard option for patients with HER-2 positive incurable gastric of GEJ cancer.

Table 4. Overview of studies investigating the impact of neoadjuvant chemotherapy combined with targeted agents in incurable gastric cancer

Trial	Years	N	Regimen	Results	*P*
ToGa trial[21]					
	2005 - 2008	298	tra - CT	HR 0.74 (CI: 0.60-0.91)	0.005
		296	CT		
AVAGAST trial[22]					
	2007 - 2008	387	bev - CT	HR 0.87 (CI 0.73-1.03)	0.100
		387	CT		
REGARD trial[23]					
	2009 - 2012	238	ram	HR 0.776 (CI: 0.60-1.00)	0.047
		117	placebo		
RAINBOW trial[24]					
	2010 - 2012	330	ram - pac	HR 0.81 (CI: 0.68-0.96)	0.017
		335	placebo - pac		

N=number, P= p-value, tra = trastuzumab, CT= chemotherapy, HR=hazard ratio, CI= 95% confidence interval, bev = bevacizumab, ram = ramucirumab, pac = paclitaxel

Additional targeted therapies for metastatic diseases have been investigated the latest years with promising results. Bevacizumab, a vascular endothelial growth factor A (VEGF-A) inhibitor, has earlier been adding to chemotherapy in colon- and rectal cancer. In 2011, the results of the AVAGAST trial (Avastin in Gastric Cancer) have been published.[22] This randomized, double-blind, placebo-controlled phase III trial evaluated the addition of an antiangiogenic agent to chemotherapy with regard to survival in patients with incurable gastric cancer. Patients received bevacizumab (vascular endothelial growth factor A, VEGF-A, inhibitor) 7.5mg/kg or placebo followed by cisplatin 80mg/m^2 on

day 1 plus capecitabine 1,000 mg/m^2 twice daily for 14 days every 3 weeks. Cisplatin was given for six cycles; capecitabine and bevacizumab were administered until disease progression of unacceptable toxicity. In total, 774 patients were enrolled, both equally assigned to each treatment group. Overall survival improved in the bevacizumab plus fluoropyrimidine-cisplatin group compared to the placebo plus fluoropyrimidine-cisplatin (HR 0.87; 95% CI 0.73-1.03; *P*=0.100). Although this trial did not reach its primary objective, it was shown that both median progression-free survival (6.7 vs. 5.3% months; HR 0.80; 95% CI: 0.68-0.93, *P*=0.004) and overall response rate (46.0% vs 37.4%; *P*=0.032) significantly improved with bevacizumab versus placebo.[22]

Furthermore, increasing attention has been given to ramucirumab, a vascular endothelial growth factor (VEGF) receptor-2 antagonist. Recently the REGARD trial aimed to assess whether ramucirumab prolonged survival in patients with incurable gastric cancer.[23] Between 2009 and 2012, 355 patients were randomly assigned to receive either ramucirumab (8mg/kg, n=238) or best supportive care (n=117). Ramucirumab improved overall survival (HR 0.78; 95% CI: 0.60-1.00, *P*=0.047) and adverse events were mostly similar between groups.[23] This international trial showed that ramucirumab, as a single drug, is the first biological treatment prolonging survival in patients with advanced gastric or GEJ adenocarcinoma after first-line chemotherapy. Between 2010 and 2012, 665 patients were randomized in the RAINBOW trial with previously treated advanced gastric cancer to receive either ramucirumab (n=330) or placebo (n=335), plus paclitaxel.[24] Overall survival was significantly higher in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (HR 0.81; 95% CI: 0.68-0.96, *P*=0.017).[24] From that moment, this combination of targeted therapy is regarded as a new standard second-line treatment for patients with advanced gastric cancer.

CONCLUSIONS

Gastric cancer is a common and highly lethal malignancy. The average age of patients has become higher in the past decades, leading to a higher rate of comorbidities to account for during treatment. This development gave rise to several new considerations to the approach of treatment of gastric cancer in the Western world.

Gastrectomy is considered as high-risk surgery in the Western world. Despite improved outcomes of gastric resections in centralized, high-volume centres, gastrectomies are still associated with surgical morbidity rates of 39% and mortality rates of approximately 4%.[25,26] It is well known that morbidity rates in gastrectomies are greatly influenced by age. Previous studies showed that sarcopenia and frailty of patients, which are frequently seen in older gastric cancer patients, are strong risk factors to experience severe problems once a complication occurs.[27] This emphasizes the need for careful consideration to perform a gastrectomy (and to receive adjuvant therapy) when patients are not able to complete neoadjuvant therapy.

Secondly, compliance of patients to therapy is an essential part in the multimodal treatment of gastric cancer. Several trials showed that protocol adherence to postoperative treatment is poor. For instance, treatment was completed as planned by 42% of patients in the MAGIC trial and in approximately 50% in the CRITICS trial.[9] Especially for the frail, older patient, the rate of postoperative therapy compliance is low, most likely due to the interplay between their pre-existing presence of comorbidity, diminished physical condition and postoperative morbidity. Protocol adherence to *preoperative* treatment is evidently higher because these patients did not (yet) undergo gastric resection, which is considered high-impact surgery. For instance, more than 80% of the patients in the CRITICS trial were able to complete preoperative treatment. Considering the growing population of elderly patients, neo-adjuvant treatment is therefore the future in the multimodal treatment of gastric cancer in the Western world. Ongoing and future studies will determine the most optimal neoadjuvant therapy (chemotherapy and/ or radiation) combined with optimal dose and timing.

Lastly, due to the heterogeneity of older gastric cancer patients, tailored treatment for these patients is needed. Diagnostic tools like staging/imaging, molecular/ genetic tools, and histological typing should be targeted, and should lead, together with the consideration of comorbidities, to a personalized treatment (*Figure 1*). This approach requires a multidisciplinary collaboration between medical oncologists, radiologists, nuclear oncologists, radiation oncologists, pathologists, nutritionists, and surgeons.

In conclusion, neoadjuvant therapy is a key element in the multimodal way of treatment of gastric cancer in the Western world. This is an inevitable consequence of the ageing population, since neoadjuvant treatment is associated with a better compliance. For this future personalized treatment of gastric cancer, a multidisciplinary approach remains crucial.

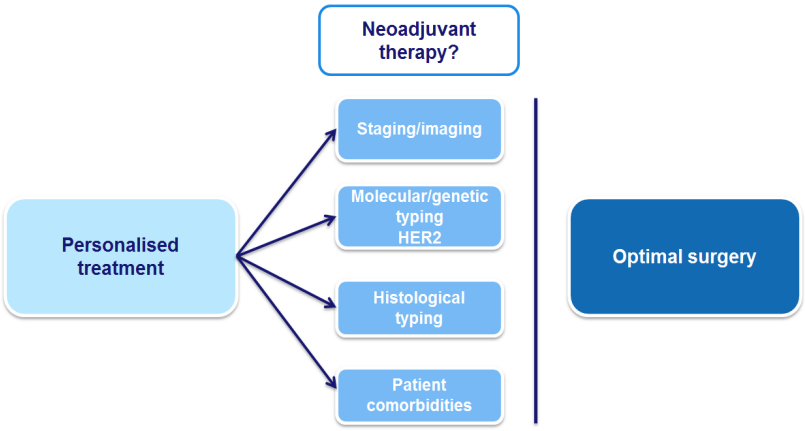

Figure 1. Tailoring treatment for gastric cancer patients in the Western world

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