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ASPECTS OF CHEMOTHERAPY AND PHOTON AND PROTON RADIOTHERAPY IN PATIENTS WITH GASTRIC CANCER

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Aspects of Chemotherapy and Photon and Proton Radiotherapy in Patients with Gastric Cancer

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my parents

ABSTRACT

Gastric cancer remains a major health problem worldwide. The addition of chemotherapy alone or in combination with radiotherapy to surgery in local gastric cancer improves outcome. In more advanced stages, the optimal palliative chemotherapy remains unknown, as well as the effect of different regimens on the patients' quality of life. The aim of this thesis was to explore a new concept in chemotherapy, i.e. the sequential approach, and a new modality in radiotherapy, i.e. proton therapy, in the treatment of patients with gastric cancer. Quality of life (QoL) in patients treated with chemotherapy, and target delineation in radiotherapy of gastric cancer, were also studied.

In Paper I, we evaluated the efficacy of sequential chemotherapy in patients with locally advanced and/or metastatic gastric cancer, with alternating irinotecan and docetaxel in combination with infusion 5-Fu. Eighty-one patients were randomized. No differences favoring either arm were found with respect to response rate, overall survival (OS), or toxicity. The median OS of 11 months indicated that the sequential approach was effective and similar to triple combinations, with potentially less toxicity. In Paper II, we evaluated the effect of sequential chemotherapy on the QoL in the same cohort. It was measured before, during, and after treatment. There were no statistically significant differences in QoL scores between the two treatment arms and no changes in mean scores during treatment. During the last 8 weeks of treatment, a significantly larger portion of patients with radiological response reported sustained or better QoL scores than those with no radiological response.

In Paper III, we investigated the effect of inter physician variation on the delineation of target volumes in gastric cancer patients treated with perioperative chemoradiotherapy (CRT). Despite the use of a delineation atlas, we found a large variation in CTV and PTV volumes. There was only a small variation in target coverage and doses to organs at risk (OARs) in the corresponding plans. In Paper IV, we compared proton therapy to modern photon radiotherapy with respect to doses to OARs in gastric cancer patients treated with perioperative CRT. Protons offered significantly lower doses to the left kidney, liver, and spinal cord, and statistically lower risks for all types and malignant secondary neoplasms compared to photons. In Paper V, we evaluated the importance of daily anatomical variations, i.e. intestinal gas filling, on the dose distribution of proton beam therapy. The effect of intestinal gas variations on the PTV/CTV coverage was large. The sparing effect of protons was, however, sustained or the dose to the OARs did not significantly exceed the dose delivered with photons.

In conclusion, sequential chemotherapy and proton radiotherapy are attractive alternatives in the treatment of gastric cancer. Standardization of target definitions in CRT, e.g. by reducing the inter physician variation, is important and should also be further investigated.

LIST OF SCIENTIFIC PAPERS

- I. Randomized phase II study of sequential docetaxel and irinotecan with 5-fluorouracil/folinic acid (leucovorin) in patients with advanced gastric cancer: the GATAC trial. Gubanski M, Johnsson A, Fernebro E, Kadar L, Karlberg I, Flygare P, Berglund A, Glimelius B, Lind PA; Gastric Cancer. 2010 Aug; 13(3): 155-61.
- II. Quality of life in patients with advanced gastric cancer sequentially treated with docetaxel and irinotecan with 5-fluorouracil and folinic acid (leucovorin). Gubanski M, Glimelius B, Lind PA. Med Oncol. 2014 Apr; 31(4): 906.
- III. Interobserver variation of CTV delineation in Gastric Cancer. Jansen EP, Nijkamp J, Gubanski M, Lind PA, Verheij M. Int J Radiat Oncol Biol Phys. 2009 Oct 14; 77(4): 1166-1170.
- IV. Influence of scanned proton treatment on doses to organs at risk and secondary cancer in patients with gastric cancer. Gubanski M, Siegbahn A, Mondlane G, Lind PA (In manuscript).
- V. Variation in gastrointestinal gas filling and dosimetric feasibility of proton radiotherapy in patients with gastric cancer. Gubanski M, Siegbahn A, Mondlane G, Lind PA (In manuscript).

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LIST OF ABBREVIATIONS

5-Fu	5-fluorouracil
BSC	Best supportive care
CRT	Chemoradiotherapy
CT	Computed tomography
CTV	Clinical target volume
DNA	Deoxyribonucleic acid
DVH	Dose volume histogram
EAPC	Estimated annual percent changes
FDG-PET	Positron emission tomography with fluorodeoxyglucose
HR	Hazard ratio
HP	Helicobacter Pylori
HU	Hounsfield units
ICRP	International Commission on Radiological Protection
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
LQ	Linear Quadratic
MI	Maruyama Index
MLC	Multi leaf collimator
MRI	Magnetic resonance imaging
MUs	Monitor units
NKI	Nederlandse Kanker Instituut
NTCP	Normal tissue complication probability
OARs	Organs at risk
OS	Overall survival
PBS	Pencil beam scanning
PFS	Progression-free survival
PT	Proton therapy
PTV	Planning target volume
QoL	Quality of life
RBE	Relative biological effectiveness

RT	Radiotherapy
SAE	Serious adverse event
SFUD	Single field uniform dose
SOBP	Spread out Bragg peak
TPS	Treatment planning system
TTP	Time to tumor progression
VMAT	Volumetric modulated arc radiotherapy

1 INTRODUCTION

1.1 EPIDEMIOLOGY

Gastric cancer is the fifth most common cancer type worldwide, with almost one million new cases diagnosed annually. Due to late detection and remaining therapeutic challenges, the case fatality ratio remains at the high 75%. Thus, gastric cancer is the third most common cause of cancer related death worldwide, with 9% of cases[1]. The disease is most common in parts of Asia, particularly in Japan, China and South Korea, which account for 60% of all gastric cancer cases worldwide. It is also relatively common in most Eastern European countries and in parts of South America[2, 3].

Both the incidence and mortality in gastric cancer have decreased during the last few decades in a majority of the world's countries, although local differences appear within regions. As late as in 1975, gastric cancer was rated as the most common malignancy worldwide, dropping to the fourth most common in 2008[1]. In Sweden, the number of reported cases of gastric cancer declined from 2176 in 1970 to 743 in 2012 [4].

According to a recently published WHO report on mortality data (1980-2011) and 2003-2007 Cancer Incidence in Five Continents data[5], the regression of the estimated annual percent changes (EAPC) was during recent years -3% for most European countries, Japan and Korea and -2% for major countries in North and South America. The EAPC has lately shown a trend for lower numbers in most countries, but estimations for 2015 suggest a leveling off in both mortality and incidence for some countries, including the US, thus breaking the favorable trends seen worldwide since the mid 20th century.

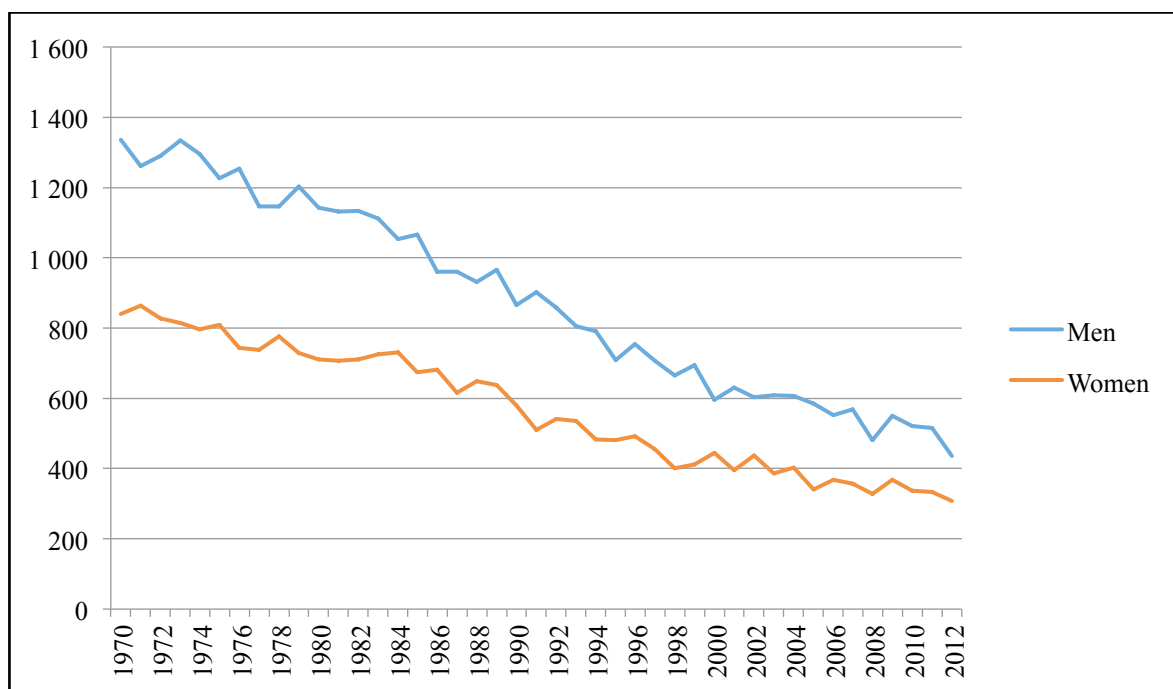


Figure 1. Annual number of reported cases of gastric cancer in men and women in Sweden 1970-2012.

1.2 RISK FACTORS

The incidence of gastric cancer rises with age, with a worldwide mean age at diagnosis between 70-74 years. The disease very rarely occurs before the age of 30. Men are twice as often afflicted as women in Asian countries, but this ratio is smaller in Western populations. There are no differences between genders in the case fatality rates, i.e. mortality/incidence during a specific time period[1].

The most important risk factor for gastric cancer is *Helicobacter Pylori* (HP) infection, which is estimated to cause approximately 60 - 70% of all cases worldwide[6]. This is thought to be a result of a chronic inflammatory process and/or an oncogenic effect of the bacterial virulence factor cytotoxin-associated gene A (CagA)[7, 8]. According to a pooled analysis of Asian trials, eradication treatment of HP reduces the incidence of gastric cancer[9]. There are, however, unexplained variations in the relationship between HP and adenocarcinoma of the stomach. In Indian and African populations, both with a high HP infection prevalence, the occurrence of gastric cancer still remains low[10]. The HP infection alone is not sufficient to cause gastric cancer and the carcinogenesis is thought to be a result of multiple factors[9].

Other risk factors for gastric cancer include smoking and dietary factors such as low fruit and vegetable intake. Furthermore, previous gastric surgery, especially Bilroth II, increases the risk[11]. Hereditary predisposition is estimated to account for approximately 10% of all cases, with higher risk in families with hereditary non-polyposis colorectal cancer or the Peutz-Jegher syndrome.

The global decrease in gastric cancer incidence has mainly been attributed to the increased refrigeration of food and the parallel decrease in dependence on salted or preserved dietary products, resulting in intake of fresher foods[1]. Furthermore, decrease in smoking, HP eradication, increased sanitation, and in some countries screening programs may explain the lower numbers of cases.

1.3 PATHOPHYSIOLOGY

The vast majority of gastric tumors are adenocarcinomas (90-95%). Lymphomas and carcinoid tumors are unusual[12]. Adenocarcinomas are malignant epithelial tumors, which originate from the gastric mucosa and have glandular differentiation. They are divided into two main histological subgroups, according to the Lauren classification, i.e. the intestinal type and the diffuse type[13]. The carcinogenesis of the intestinal type follows a sequence of tissue transformation starting with superficial gastritis, followed by atrophic gastritis, intestinal metaplasia, dysplasia, and finally ending with invasive cancer[14]. The carcinogenic pathway of the diffuse type remains unclear. There is a predominance of the intestinal type in men, elderly patients, and in the high-risk regions, while the diffuse type is relatively more common in low-risk countries[15]. The WHO classification is also commonly used alongside the Lauren system.

Approximately 15% of gastric cancers are located in the fundus, and the remaining ones are evenly distributed between the pylorus and corpus. In 10% of the cases the tumor involves more than one part of the stomach[16]. The majority of tumors in the gastric corpus are located along the major curvature. Adenocarcinoma in the cardia region is generally classified as gastric cancer, however, the etiology resembles the one of adenocarcinoma of the esophagus[17].

1.4 PREVENTION AND EARLY DETECTION

Population screening with gastroscopy, or other methods, e.g. barium meal radiology, differs worldwide due to both cost and variations in incidence. There is a long experience of screening programs in several Asian countries, foremost in Japan. This is reflected in the higher detection rates of early stage gastric cancers of 30-50% compared to 16-24% in Western populations[15, 18-20]. In Scandinavia, the incidence of gastric cancer is too low to motivate general screening. It can, however, be recommended in high-risk individuals[21].

In several Asian countries, HP eradication therapy in accordance to national guidelines has been introduced[9]. The efficacy of eradication treatment is, however, highly dependent on whether precancerous lesions are present. Due to limitations in present eradication treatment and the multifactorial nature of carcinogenesis, general treatment, other than in high-risk individuals, is not recommended in European guidelines[22, 23].

1.5 CLINICAL PRESENTATION

The clinical manifestations and the findings at the physical examination are often unspecific and overlap with common non-malignant diseases. This frequently results in late diagnosis. In Western countries, around two-thirds of the patients with gastric cancer present with advanced disease[24, 25]. Early symptoms include upper abdominal discomfort or a dull and unspecific pain, which is often combined with dyspepsia. Typically, these symptoms initially respond to anti-peptic treatment, which may further delay the diagnosis. As the tumor progresses, additional symptoms such as anorexia, nausea, and weight loss may appear. Proximal tumors in the cardia are often associated with dysphagia, while the ones close to the pylorus or antrum may lead to gastric outlet obstruction syndrome associated with nausea and vomiting. Tumors infiltrating large portions of the gastric wall affect the ability for distention, which results in early satiety. Gastric bleeding occurs with variable intensity but melena has been reported in only one-fourth of the patients[24]. However, patients with unexplained iron-deficiency anemia should be liberally referred for an endoscopic examination. Physical findings on examination may include an abdominal mass, ascites, or palpable, typically supraclavicular or periumbilical nodes. These are all, however, signs of locally advanced and/or metastatic disease.

Biochemical markers, e.g. carcinoembryonic antigen (CEA), CA125, CA19-9, CA72-4 and α -fetoprotein, are elevated in 15-60% of patients[26, 27]. They are, however, not specific for gastric cancer and are, thus, presently of limited value in the diagnostic situation. Elevated CEA and CA72-4 levels at diagnosis are associated with poor outcome[28, 29].

1.6 DIAGNOSTICS AND STAGING

Endoscopy is the most sensitive and specific diagnostic method for detecting gastric cancer. This examination should include the esophagus, the stomach, and the duodenum. The sensitivity of endoscopy in early gastric cancer is not well studied, but according to Japanese data, a substantial amount of lesions can be missed[30]. A histological sensitivity of over 98% can be reached if at least 7 biopsies are obtained[31]. The T stage and the Borrmann classification of the tumor are obtained with the endoscopic evaluation of the growth pattern in combination with histological analysis of the depth of invasion, possibly assisted by an endoscopic ultra sound examination. Other radiological methods have not yet been shown reliable as means for T-staging other than detecting a thickening of the gastric wall and direct tumor invasion into surrounding tissues. Computer tomography scanning detects 26-56% of early gastric tumors and correctly evaluates wall invasion in only 15% of these cases. Detection rates in advanced gastric cancer are higher, i.e. 88-100% [32, 33]. Dedicated CT scans are reliable for predicting tumor resectability[34] and the evaluation of bulky disease. T-stage evaluation with modern MRI techniques is promising but still remains investigational.

Most commonly, CT is used for N-staging. However, the method's specificity and sensitivity for detecting metastatic lymph nodes are widely questioned. This is due to the fact that the diagnosis of pathological nodes is based on nodal size only, rendering an accuracy of 25 to 70% in different series[35]. Endoscopic ultra sound, especially when combined with fine needle aspiration cytology, is more sensitive for detecting nodal metastases in the proximity of the stomach than CT alone and can be used as a complementary technique[36]. The risk of involvement of regional lymph nodes increases with the depth of tumor penetration in the gastric wall[37]. Lymph node involvement is reported in 3-5% of tumors confined to the mucosa, in 11-25% of those extending to the submucosa, in 50% of those reaching the muscularis, and finally, in 83% of those involving the serosa[38, 39].

The most widely used radiological modality for detection of distant metastases (M-staging) is CT, with a reported sensitivity rate of 90%[40]. Routinely, the examination includes the lower neck, the thorax, and the abdomen. Brain metastases are uncommon and CT of the brain has therefore not been considered cost-effective. Positron emission tomography with fluorodeoxyglucose (FDG-PET) has a superior sensitivity in detecting distant metastases compared to CT[41]. However, MRI, and possibly contrast-enhanced ultrasonography (CEUS), have been reported to have higher sensitivity than FDG-PET in detecting liver metastases[42, 43]. Furthermore, it remains uncertain whether CT or PET-CT is more reliable in detecting peritoneal metastases[44].

Parallel to the staging process, a careful evaluation of the patients' general physical condition should be undertaken, due to the high intensity and toxicity of the treatments. A detailed patient history and physical examination should be performed and, if necessary, additional evaluations of the heart, lung, and kidney functions.

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1. TNM-staging for gastric cancer.

1.7 PROGNOSIS

The prognosis for the general population of patients with adenocarcinoma of the stomach and the gastroesophageal junction is poor. Furthermore, it is highly dependent on tumor stage and localization, patient age, and comorbidity. Patients with tumors confined to the mucosa and submucosa layers of the stomach have 5-year survival rates of 86% following surgical gastrectomy[1, 45]. This number drops dramatically when the tumor extends through the gastric wall and/or metastasizes to the regional lymph nodes, i.e. 5-year survival rates of 30%[45, 46].

There are large geographical differences in 5-year survival rates between Eastern Asia and the Western countries, i.e. 20-30% in Europe and the US compared to 40-60% in Japan[1, 46, 47]. These differences have been attributed to variations in the proportion of early gastric cancers at the time of diagnosis, tumor biology, and localization[48]. Between 1995 and 2000, the proportion of patients with early gastric cancer at the time of diagnosis in Eastern Asia was 53% compared to 14-20% in Western populations[49]. In a population based European report, the majority of gastric cancer patients presented with irresectable or metastatic disease. The curative resection rate was less than 50% and 5-year survival rates were 28-42%[50].

2 TREATMENT

2.1 CURATIVE TREATMENT

Until recently, radical surgery was the only hope for cure in gastric adenocarcinoma of the stomach and the gastroesophageal junction. However, the high rates of relapse after resection led to an interest in more effective strategies. The different methods used were:

1. Altered, more radical surgical techniques
2. Combination of chemotherapy with surgery
3. Combination of chemoradiotherapy with surgery

2.1.1 Surgery

2.1.1.1 Gastric resection

Curative treatment always involves a tumor resection with a subtotal or total gastrectomy. The decrease in incidence of gastric cancer combined with a decrease in benign gastric surgery during the last decades of the previous century, have high-lighted the necessity for concentrating surgery in these patients to high-volume centers. Today, the subtotal resection is used routinely in the majority of patients with intestinal type gastric cancer in the distal or mid portion of the stomach, in which a margin of at least 2 cm, and preferably larger, can be obtained[51-54]. In patients with proximal tumors, a total gastrectomy is commonly performed with resection of the distal portion of the esophagus. In the diffuse type gastric cancer, a R0 situation is difficult to achieve with limited surgery and thus total gastrectomy is generally recommended. This procedure is followed by a construction of a gastric reservoir in order to minimize the postoperative weight loss due to low calorie intake and losses through diarrhea, and to improve the postoperative quality of life [55, 56]. The reconstruction can be achieved by a long Roux-en-Y esophagojejunostomy.

2.1.1.2 Lymphadenectomy

A major point of discussion in terms of gastric cancer surgery has been the extent of lymph node dissection. The Japanese Gastric Cancer Association (JGCA) defined 16 nodal stations commonly involved in the lymphatic drainage of the stomach[57]. These stations are further divided into three levels of increasing distance to the stomach, and thus defining the extent of nodal resection (D1-3) (Table 2). Several prospective randomized trials have investigated the effect of a more extensive lymphadenectomy (D2) compared to the standard D1 resection, in which only the perigastric lymph nodes are removed. The Dutch Gastric Cancer Group trial, including 711 patients, did not show any difference in survival, but significantly higher operative mortality and morbidity in the extended resection group[58]. A later subgroup analysis showed a trend for better survival among N2-positive patients in the D2 group. These results were confirmed by the British MRC trial[59]. In both trials, the increases in complication rates were thought to be associated with the pancreatectomy and/or

splenectomy rather than the extent of the lymphadenectomy. However, in a later, European study with a higher grade of centralization of surgery no difference in morbidity was found between D1 and D2[60]. A highly centralized trial from Taiwan, comparing D1 and extended D2 resections, reported no perioperative mortality and higher 5-year survival in the extended resection group[61].

Regional lymph node stations
No. 1 Right paracardial LN No. 2 Left paracardial LN No. 3 LN along the lesser curvature No. 4 LN along greater curve (short gastric vessels, left and right gastroepiploic vessels) No. 5 Suprapyloric LN No. 6 Infrapyloric LN No. 7 LN along the left gastric artery No. 8 LN along the common hepatic artery (anterosuperior and posterior group) No. 9 LN around the celiac artery No. 10 LN at the splenic hilum No. 11 LN along the splenic artery (proximal and distal tract) No. 12 LN in the hepatoduodenal ligament (along hepatic artery, bile duct and portal vein) No. 13 Retropancreatic LN No. 14 LN along superior mesenteric vessels (vein and artery) No. 15 LN along the middle colic vessels No. 16 LN paraaortic (of upper, middle and lower abdominal aorta, in relation to the intragastric tumor site) The classification includes also the following lymph node compartments: No. 17 LN on the anterior surface of the pancreatic head No. 18 LN along the inferior margin of the pancreas No. 19 Infradiaphragmatic LN No. 20 LN in the esophageal hiatus of the diaphragm No. 110 Paraesophageal LN in the lower thorax No. 111 Supradiaphragmatic LN No. 112 Posterior mediastinal LN
D1 No.1-6 D2 D1+No.7-12 D3 D2+No.13-16

Table 2. Regional lymph nodes according to the Japanese Research Society for Gastric Cancer (1998) and corresponding levels of surgical dissection. LN = lymph nodes.

In conclusion, in the Asian countries, with high rates of incidence and high volumes of gastric cancer patients operated by specialized surgeons, D2 lymphadenectomy is considered as standard procedure. In Western countries, with low incidence and, thus, fewer cases per center the question of D1 vs. D2 resection remains to some extent unresolved[62]. However, after the report of 15-year follow up from the Dutch Gastric Cancer Group, which showed a lower rate of locoregional recurrence and gastric-cancer-related death with D2 resections compared to D1[63], the extended lymphadenectomy is becoming the preferred procedure even in Western countries.

2.1.2 Adjuvant therapies

Local recurrences after radical gastric cancer surgery occur in 40-60% of the patients, both as the only site of disease recurrence and as a part of a disseminated disease[64]. The most frequently involved sites of recurrence include the areas previously occupied by the tumor, the regions in the proximity of the anastomoses and the non-resected regional lymph nodes. This fact suggests that surgery, as a single modality treatment, cannot fully address the microscopic tumor residues around the primary site and those disseminated during the operative procedure, thus creating a rationale for systemic and radiation therapy. A recent review on the extent of lymphadenectomy suggested, that surgery has reached or almost reached its full potential as a curative treatment in gastric cancer and further development should be pursued in non-surgical perioperative treatment modalities[62].

2.1.2.1 Postoperative chemotherapy

There are many published randomized controlled clinical trials on adjuvant postoperative chemotherapy. In later years some trials also combined chemotherapy with immunotherapy. Various regimens were investigated and many of the early chemotherapy combinations are today considered outdated. Only a few trials managed to demonstrate any benefit in survival for adjuvant chemotherapy compared to surgery alone[65, 66] and none in a Western population[67]. In meta-analyses of trials conducted in a Western population, no improvement of survival was detected[67-69]. However, in the Asian CLASSIC trial with 1035 patients, adjuvant chemotherapy with capecitabine in combination with oxaliplatin significantly increased 3-year survival compared to surgery alone (74% vs. 59%, $p < 0.0001$)[66]. Another recent large Japanese randomized trial of adjuvant S-1 demonstrated a 3-year survival rate of 80.1% in the surgery plus S-1 group compared to 70.1% in the surgery only group ($p = 0.003$)[65]. These results have not been replicated in a Western population. S-1 has not been registered in the US due to high toxicity in a Caucasian population. The latter data raise the question of patient ethnicity and different response to treatment as well as variations in tumor biology of gastric cancer in Asian and Western populations. In conclusion, the role of adjuvant chemotherapy in gastric cancer in a Western population remains unclear and a subject of further investigation.

2.1.2.2 Postoperative radiotherapy

In a trial by the British Stomach Cancer group, 436 patients were randomized between three treatment arms: surgery alone, surgery with chemotherapy (FAM), or surgery with radiotherapy (RT) to 45-50 Gy. The trial failed to show any survival differences between the three arms[70].

2.1.2.3 Perioperative chemotherapy

Perioperative chemotherapy, a commonly used strategy in Europe, was introduced due to the results of two major randomized trials. Firstly, the British MAGIC trial randomized 500 resectable Stage \geq II gastric or distal esophageal adenocarcinoma patients to surgery alone or surgery plus pre- and postoperative chemotherapy with epirubicin, cisplatin and 5-Fu[71]. There was a significantly improved 5-year survival (36% vs. 23%, $p=0.009$), progression-free survival, and decreased tumor size and stage in the perioperative chemotherapy group. It is, however, worth noticing that only 42% of all patients completed the entire treatment. The main reasons for not proceeding with the postoperative chemotherapy were disease progression or patient choice. Secondly, the French ACCORD07/FFCD-9703 trial[72] randomized 224 patients to either surgery alone or surgery with perioperative chemotherapy, i.e. cisplatin and 5-Fu. The 5-year disease-free survival was significantly better in the combined treatment arm, 34% vs. 21%. Furthermore, chemotherapy significantly improved the curative resection rate, 84% vs. 73%.

2.1.2.4 Perioperative targeted therapy

Several case reports with trastuzumab containing preoperative chemotherapy regimens in HER2 positive gastric cancer have been published with promising outcomes[73, 74]. Following the results in colorectal cancer, bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor, has been included in trials of gastric cancer. In the AVAGAST trial, the addition of bevacizumab in first line therapy in advanced gastric cancer patients showed no improvement in overall survival, but prolonged progression-free survival, and response rates[75]. The British MAGIC B trial is accruing patients to compare perioperative chemotherapy with or without bevacizumab in patients with resectable gastric cancer.

2.1.2.5 Perioperative chemoradiotherapy

Trials investigating chemoradiotherapy (CRT) in gastric cancer have been reported since the nineteen-eighties. One of the first randomized trials on this subject was published in 1984. Although small, the authors reported a staggering difference in 5-year survival of 4% vs. 23% between patients treated with surgery only ($n=23$) and surgery followed by 5-Fu in combination with RT ($n=39$)[76].

The efficacy of cisplatin and 5-Fu in gastric cancer is well established[77] and the mechanisms of synergy between these drugs and RT are also well described. Cisplatin inhibits the repair of radiation-induced injury and directly enhances DNA injury by formation

of DNA-adducts. In the case of 5-Fu, it has been suggested that RT sensitizes the cells to the DNA interfering effect of the drug[78, 79].

Since the publication of the results of the Intergroup 0116 trial in 2001, the combination of chemotherapy and RT has become the routine treatment after radical resection of gastric cancer in the United States[80]. In this study, 556 patients with resectable Stage \geq II disease were randomized between surgery only and surgery followed by CRT. The latter, experimental arm consisted of chemotherapy with three courses of 5-Fu perioperatively and two shortened courses during RT (45 Gy in 25 fractions in five weeks). Radiotherapy planning was 2-D based. The results were highly encouraging; with an increase of median overall survival from 27 to 36 months and the disease-free survival from 19 to 30 months in the CRT arm. This study has, however, been heavily criticized on several points, and CRT has not become the standard treatment in Europe. In more than 50% of cases the extent of the surgical procedures was ruled as less than a D1 resection suggesting that the additional treatment only compensated for suboptimal surgery. The rationale for this criticism can be put into question in the light of the results in rectal cancer, where the relative effect of CRT becomes more pronounced when more adequate surgery is performed. Furthermore, the patients included in the Intergroup 0116 trial had an increased risk of relapse due to higher disease stage (more than two thirds had a T3 or T4 tumor and 85% were node positive) than patients in most published surgical series. Additionally, there was a considerable toxicity in the CRT arm, resulting in 54% hematological and 33% gastrointestinal Grade III or IV toxicity. This resulted in only 62% of the patients completing the entire treatment. A considerable part of the toxicity was considered due to the use of an outdated chemotherapy regimen and radiotherapy technique. The updated results on the Intergroup 0116 trial were published in 2009[81] and 2012[82] after a median follow up time of over ten years. The overall and disease free survival ($p=0.001$) as well as recurrence rates ($p<0.001$) were still significantly better in the experimental arm.

The role of perioperative CRT in relationship to the extent of lymphadenectomy was addressed in a Korean observational trial of 1000 patients after a R0 D2 gastric resection, which was published in 2005[83]. Five hundred and forty-four patients received similar postoperative CRT as in the Intergroup 0116 trial, while the control group of 446 patients had no additional treatment. The two groups differed by higher rates of undifferentiated carcinomas ($p=0.0021$), Stage IIIA ($p=0.005$), and Stage IV ($p=0.0011$) in the CRT arm. Despite the difference in the patient populations, the median overall survival (95.3 vs. 62.6 months) and disease-free survival (75.6 vs. 52.7 months) were significantly better in the CRT arm. Seventy-five percent of the patients completed the entire treatment protocol in the CRT arm.

A meta-analysis including five randomized clinical trials and 868 patients investigated the benefit of perioperative CRT compared to surgery alone[84]. The CRT group had a significantly lower overall risk for mortality than the control group ($p=0.00001$). The protocol completion rate was 73.3%.

In the ARTIST trial[85], including 458 patients, the authors compared perioperative chemotherapy with perioperative CRT after D2 gastric resection. No statistically significant differences were found in the recurrence rate or the 3-year disease-free survival (78.2% in CRT group vs. 74.2%, $p=0.086$). However, a significantly longer disease-free survival was found in the CRT arm among patients with node positive disease (77.5% vs. 72.3%, $p=0.035$).

Presently, two large ongoing multicenter trials, the European CRITICS trial (CRITICS; clinicaltrials.gov NCT 00407186) and the Australian TOP-GEAR trial (TOP-GEAR; clinicaltrials.gov NCT 01924819) address the role of perioperative CRT in gastric cancer. Furthermore, since the publication of the Intergroup 0116 trial, the concept of CRT has been better established in several other diagnoses, e.g. rectal, head-neck and lung cancers.

2.2 PALLIATIVE TREATMENT

At the time of diagnosis, the majority of gastric cancer patients in the Western countries, present with irresectable and/or metastatic disease. Furthermore, many patients previously treated with curatively intended gastric resection recur. In these patients, palliative treatment is of importance to control tumor related symptoms and to improve survival while preserving or preferably improving quality of life (QoL).

The symptoms of locally advanced and/or metastatic disease are both of general and local nature and vary among individuals. While chemotherapy has the potential to alleviate general symptoms, surgery and radiotherapy can be used to treat local symptoms caused by obstruction or tumor overgrowth.

2.2.1 Surgery

Endoscopic stent treatment is by far the most common method of surgical palliation in gastric cancer. Tumors located in the distal portion of the esophagus, the cardia or the proximal portion of the stomach, often cause inadequate nutritional intake and swallowing problems. Stent treatment is both safe and more effective than nasogastric sond nutrition in terms of avoiding weight loss. This facilitates the initiation of oncological treatment and stabilizes serum albumin levels[86]. Severe gastric outlet obstruction syndrome, typically leading to nausea, vomiting and inadequate nutritional intake, can also be treated with surgical open or laparoscopic gastroenteroanastomosis. Stent treatment is, however, less invasive and, thus, less strenuous for the patient. It is, however associated with higher frequency of re-obstruction and lower long-term nutritional intake and predominantly the treatment of choice for patients with short expected survival[87, 88].

2.2.2 Chemotherapy

Patients with metastatic, inoperable, or recurrent gastric cancers have a median survival time of 3 - 5 months with only best supportive care (BSC). Randomized trials have shown that the median survival time in this patient group can be prolonged by 4 – 6 months with chemotherapy compared to BSC alone[89-91], but the benefit has to be weighed against

treatment-induced toxicity. The most commonly used combinations contain either continuous infusion or bolus 5-fluorouracil (5-Fu), or oral capecitabine. In addition, the drugs cisplatin, doxorubicin or epirubicin, etoposide, and more lately irinotecan, docetaxel and oxaliplatin have been used in various combinations[67, 77]. In the Cochrane meta-analysis from 2010[77], combinations of two or three cytostatic drugs had a survival benefit (HR 0.86) compared to single agent treatment, but resulted only in a further modest increase of 2 months in time to progression (TTP) and 1.5 months in overall survival, and in increased toxicity and risk of toxic death (HR 1.22). The meta-analysis by the GASTRIC group concluded that the addition of any new chemotherapeutic agent to the standard control regimen resulted in slight improvements in overall and progression free survival, this effect being foremost visible for cisplatin and irinotecan[92].

Despite a multitude of performed randomized trials and meta-analyses, there is no international consensus on the optimal regimen in palliative therapy of gastric cancer[93]. This is due to inter trial variations in study populations and the lack of head-to-head comparisons for all used combinations. In the routine treatment, double or triple combinations are generally recommended. In Sweden, patients with good performance status were previously treated with a combination of etoposide and 5-Fu (ELF)[91], while elderly patients or those with poor performance status received single agent bolus 5-Fu. Superior response rates have, however, been reported for the irinotecan/5-Fu/leucovorin (ILF) combination compared to the ELF regimen (35% vs. 17%). Internationally, cisplatin based double or triple combinations have previously been dominating, i.e. epirubicin/cisplatin/5-Fu (ECF)[94] and cisplatin/5-Fu (CF). More aggressive combinations have also been studied, i.e. in the phase III TAX325 trial[95]. The authors of the latter article reported that the combination of cisplatin, docetaxel and 5-Fu (DCF) increased median survival, 10.2 vs. 8.5 months, and response rates, 39% vs. 23%, compared to CF. There was, however, a considerable amount of toxicity associated with the triple combination, e.g. Grade 3-4 toxicity present in 69% of cases and complicated neutropenia in 29%.

The dominating role of cisplatin in the treatment arsenal for gastric cancer was questioned after the publication of the British REAL-2 trial[96]. This four-arm study demonstrated the equivalence of oxaliplatin to cisplatin and capecitabine to infusion 5-Fu. The latter relationship was also confirmed in another controlled trial[97]. Furthermore, a Cochrane meta-analysis[77] reported that anthracyclines had an effect in gastric cancer independent of platinum based therapy. A recently published meta-analysis reported improved response rates and outcome in drug combinations where cisplatin was replaced with irinotecan, oxaliplatin, or taxanes compared to cisplatin based double or triple combinations[98]. This analysis failed, however, to identify the subgroups of patients who would gain most from cisplatin-free therapy.

2.2.2.1 Irinotecan

The efficacy of irinotecan, a topoisomerase 1 inhibitor, has been evaluated in gastric cancer both as single agent and in combinations. As a single agent, response rates of 23% have been

reported[99], which is comparable to other drugs with activity in this disease. In gastric cancer irinotecan is mostly combined with either 5-Fu or cisplatin. A response rate of 23% and a median survival of 6.3 months have been reported for the combination of irinotecan and 5-Fu[100]. Response rates of 31-58% have been reported for the combination irinotecan and cisplatin, with a feasible toxicity profile and with median survival of 5-10.7 months[101-104]. In a randomized phase II study, ILF yielded higher response rates (35% vs. 17%, n = 104) than the classical ELF-regimen, which previously was frequently used in Sweden[105]. Another randomized phase II study compared irinotecan in combination with fluorouracil to irinotecan in combination with cisplatin, and demonstrated an overall response rate of 34% and 28% respectively and a median survival of 10.7 months vs. 6.9 months. Thus, a superior efficacy was shown for the less toxic cisplatin-free combination[106]. Furthermore, irinotecan has been reported effective in second line palliative treatment of gastric cancer compared to BSC after previous tumor progression on cisplatin-based regimens[107].

2.2.2.2 Docetaxel

As single agent, docetaxel yields response rates of 17-24% in first line treatment of advanced gastric cancer[108, 109]. The most common docetaxel combinations include 5-Fu and/or cisplatin. Docetaxel in combination with cisplatin has produced response rates of 37-56%, while docetaxel in combination with 5-Fu has shown response rates of 28-86%[110-112]. A phase II study compared docetaxel in combination with cisplatin (TC) to docetaxel in combination with 5-Fu and cisplatin (TCF) with response rates of 35 vs. 54% and median survival 10.5 vs. 9.6 months, respectively. There were more gastrointestinal toxicities with 4.3% diarrhea in the TCF arm compared to 1.2% in the TC arm. Neutropenia was more common in the TCF arm with 59.6% vs. 49% in the TC arm. Noticeably, 2.5% of the patients in the TCF arm died due to febrile neutropenia[113]. The results of the large controlled trial TAX 325, in which the triple combination docetaxel, cisplatin, and 5-Fu was compared to cisplatin and 5-Fu, is discussed above (section 2.2.2).

2.2.2.3 Sequential chemotherapy

Combinations of several drugs, thus, result in higher response rates than single drug treatment, but are generally more toxic. There is a lack in convincing evidence of clinical benefit in terms of improved QoL, when multiple drug combinations are used rather than sequential treatment, even if subgroups of patients are likely to benefit from the most aggressive upfront therapy. Furthermore, according to the Goldie and Coldman hypothesis, using active drugs in a predefined alternating sequence, may reduce the risk of inducing drug resistance[114]. This hypothesis is based on a mathematical model relating the drug sensitivity of a tumor to its own spontaneous mutation rate towards phenotypic drug resistance. According to this model, the proportion as well as the absolute numbers of resistant cells will increase with time and the fraction of resistant cells within tumor colonies of the same size will vary depending on whether mutation occurs early or late. The probability of the appearance of a resistant phenotype increases with the mutation rate. Furthermore, for any population of tumors with a non-zero mutation rate the likelihood of

there being at least one resistant cell will go from a condition of low to high probability over a very short interval in the tumor's biologic history.

Sequential chemotherapy may allow the delivery of a greater number of drugs, the dose of each drug to be optimized, and limitation of toxicity. In a sequential schedule, the evaluation of the response to each drug or drug combination, in order to identify the most active drug(s) as an *in vivo* chemo sensitivity test, may potentially guide the selection of individually tailored consolidation or maintenance chemotherapy. In addition, the “worst drug rule” can be applied[115]. According to this rule, in order to kill clones resistant to the most active regimen when two non-cross-resistant regimens are available with different activities, the less active regimen should be administered first. However, the dismal outcome and the rapid deterioration observed in patients with advanced gastric cancer following first line chemotherapy do not support the application of the “worst drug rule” in this setting.

The concept of sequential chemotherapy has, to some extent, been used in palliative breast cancer treatment and has now become a part of the routine chemotherapy arsenal in the adjuvant setting[116]. A recently published Cochrane meta-analysis[117], found twelve randomized trials, with a total of 2317 patients, comparing combinations of drugs to the same drugs used in a sequential setting in first, second, and third line treatment in metastatic breast cancer. The authors did not find any difference in survival ($p=0.45$) according to how the treatment was given. Furthermore, the risk of progression was significantly higher in the combination group ($p=0.01$), as were the response rates ($p=0.001$). The latter difference was, however, largely heterogeneous between the analyzed trials. The risk of febrile neutropenia was higher in the combination group ($p=0.01$), but no statistically significant differences were found regarding neutropenia, nausea, vomiting, or treatment related deaths. There were also no differences in QoL, but this had been reported in only three of the twelve trials. Similar results, with lower toxicity and lack of differences in survival for sequential treatment compared to combination treatment, have been reported in other malignant diseases, i.e. colorectal cancer[118] and in lymphoma[119].

2.2.3 Quality of life

Despite increased response rates, the median survival of patients with advanced gastric cancer remains low, rarely exceeding 10 months, even with triple combinations of cytotoxic drugs or with the addition of biological agents. Due to the poor prognosis of this patient population and relatively limited and similar gains in median OS with the use of various cytotoxic therapies, it is important to evaluate the effect of any new anticancer treatment not only on its life prolonging ability but also on the QoL. This fact has been given increasing attention during the last decade, driven by the development of the toxic double and triple drug combinations. As most patients with advanced gastric cancer are not cured and many regimens have similar efficacy, differences in QoL may help to determine which regimen is preferred. Several authors suggested that QoL measurement should be used as an independent measure in evaluating the outcome of new treatments[120] and the American Society of

Clinical Oncology recommended already in its 1996 guidelines that survival and QoL are of more importance in evaluation of efficacy than response rates and biomarker changes.

In a review of 19 trials in advanced gastric cancer[121], the authors reported that no significant gain in QoL was obtained with chemotherapy. Scores were maintained for approximately half of the patients for a period of six months but deteriorated for the remaining patients. The effect of therapy on QoL appeared to be connected with the objective treatment response rather than with the toxicity. In three of the randomized phase III trials, cisplatin/5-Fu in combination with either docetaxel or epirubicin improved QoL scores compared to the control groups.

In the updated Cochrane analysis of chemotherapy in advanced gastric cancer[77], QoL is one of the main variables reported when comparing treatments. However, many randomized clinical trials still do not report outcomes in QoL, which limits the possibility of analyzing QoL in an adequate meta-analysis. Furthermore, studies assessing QoL in tumors of the upper gastrointestinal tract have often reported poor accrual and poor collection rates of the QoL assessments[94, 122, 123]. Consequently, poor compliance and reporting of the QoL data might bias and influence the conclusions[124]. Attempts to improve compliance have focused on improvement of assessment tools, i.e. questionnaires, and on computer-based methods of reporting and have led to encouraging results[125, 126].

The most commonly used QoL assessment tool is the European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30). It is used worldwide and for a large number of malignant diagnoses[127]. The Swedish version of the EORTC QLQ-C30 has been validated [128]. This questionnaire has been further developed to include site-specific modules for better evaluation of anatomically relevant complaints, including a module for gastric- (QLQ-STO22) and esophageal cancer (QLQ-OES18). Both modules have been internationally validated[129, 130]. There are alternative questionnaires for assessment of QoL, i.e. the SF-36[131]. The advantage of the EORTC QLQ-30 is, however, its cancer- and site-specificity in combination with the high grade of validity and popularity, which increases the comparison reliability.

3 RADIOTHERAPY IN GASTRIC CANCER

Radiotherapy (RT) may be an important treatment modality for patients with gastric cancer, especially in the adjuvant setting. Its role in this patient group has been in the perioperative setting in combination with chemotherapy (CRT), as described above (section 2.1.2.5), and is now also the subject of two large multicenter trials, i.e. the European CRITICS and the Australian TOPGEAR trials. In gastric cancer irradiation, generally doses of 1.8 Gy per fraction to a total dose of 45 Gy are used, to treat potential residual microscopic disease[80, 132]. The position of CRT as standard treatment in the United States is based on the results of the previously described Intergroup 0116 trial[80], a trial that has received criticism for its outdated planning techniques and consequently considerable toxicity. In this trial, two dimensional (2D) treatment planning was used, and two opposed antero-posterior, posterior-anterior photon beams, with an attempt to spare one of the kidneys from incidental irradiation. Since the start of enrollment in this trial in 1991, the development and implementation of new irradiation techniques has been a fast growing field. This includes progress in treatment planning, methods of patient immobilization, and compensation for patient movement by image guided RT.

3.1 PHOTON TECHNIQUES

During the 1990-ies, 3D conformal RT became the standard RT technique. This planning strategy requires planning capabilities such as 3D target and organs at risk (OARs) volume definition. Structures of interest are delineated on cross-sectional images (CT, MRI, or PET) on a slice-by-slice basis as opposed to drawing beam portals on a simulator radiograph, which was used in 2D planning. The treatment plan is further constructed by the application of a number of fields shaped by multi leaf collimators (MLCs) and their fluence can be further optimized by the addition of wedges and physical modulators, i.e. compensation filters. These modifications are performed manually in a planning system, thus making this method of planning highly sensitive to the individual creativity and experience of the dose-planner.

The 3D conformal RT planning has been further developed, resulting in the intensity modulated radiotherapy (IMRT) planning technique[133], which has been increasingly adopted into standard RT since the late 1990-ies. It is based on inverse treatment planning, where an interactive computer optimization algorithm calculates for all given beam directions, the optimal fluence profiles necessary to obtain the desired dose distribution within the patient. The fluence of each beam is shaped through the continuous movement of the MLCs during irradiation[134] and the resulting plan shows higher levels of dose to target conformity. Further developments of IMRT include the rotational irradiation techniques such as volumetric modulated radiotherapy (VMAT) and tomotherapy, where dose delivery is modeled by infinite number of beam directions and a variable dose-rate combined with continuous MLC movement, providing shorter or longer treatment times, respectively, with equal or enhanced conformity[135]. However, both IMRT and the rotational techniques demand larger amounts of monitor units (MUs) and, consequently, the delivery of the same dose to the target results in a higher integral dose to the patient. This is seen as large volumes

of “low-dose-bath” in the patient and it may potentially lead to an increased risk of treatment-induced secondary neoplasms.

A dose planning trial comparing 3D conformal RT with nine-field IMRT in gastric cancer revealed satisfactory coverage of the clinical target volumes by the 95% iso-dose with either technique. Furthermore, IMRT was only marginally better than 3D-RT at protecting the spine and kidneys from incidental radiation[136]. This suggests that only a small subgroup of patients would benefit clinically from more advanced planning techniques. However, a recently published Dutch trial[137], which compared 2D planning technique according to the Intergroup 0116 trial to 3D-conformal and IMRT in 87 gastric cancer patients, found a significantly lower dose to the left kidney for the IMRT plans. This difference was also shown to be of clinical significance, as the kidney function was decreasing in the total population, but at a lower rate in patients treated with IMRT, thus establishing a dose-effect relationship for the left kidney function. Of the 87 patients, 6 developed hypertension, but none in the IMRT group at the median follow up time of 4.7 years. In a recent retrospective analysis, adjuvant CRT with IMRT and modern chemotherapy doublets led to better survival in patients with advanced gastric cancer compared to the adjuvant combination of 3D conformal RT and conventional chemotherapy, also in the long-term follow-up[138]. This may be an effect of the compromise between kidney sparing and PTV coverage in 2D and 3D conformal RT planning, which can be avoided in IMRT.

3.2 PROTON TECHNIQUES

The possibility to use proton radiotherapy (PT) for medical purposes was suggested already in 1946[139] and in 1954 the first patient was treated for a pituitary disorder. Since that year, several laboratories, among them the Svedberg Laboratory in Uppsala, continued to treat patients with protons (and/or ions) on a small scale. Today, PT is an increasingly available alternative in cancer treatment as new centers are being built around the world. In July 2005, there were 23 active proton centers and 3 centers using ions, and 43 000 and 4 500 patients were reported to have been treated with protons and ions, respectively[140]. By the end of 2012, 42 facilities were reported to be in operation and the total number of patients treated was 107 792[141].

Protons, as opposed to photons, are charged particles with a defined mass, which leads to a different behavior in tissue. This difference is mainly in the physical properties of both modalities, while the biological effect can be seen as similar, due to the proximity of the clinical relative biological effectiveness of protons ($RBE = 1.1$) compared to photons[142]. The depth of maximum dose deposition of a proton beam can be made to coincide with the depth of the targeted disease. The treatment depth can be chosen arbitrarily by varying the proton beam energy. The main physical difference between radiotherapy with photons and protons can be described by the difference in the dose distribution as a function of depth in tissue produced by these two types of particles (Fig. 2). The presence of the Bragg peak in the proton beam dose profile is normally an advantage for proton beams compared to conventional photon beams because the region of maximum energy deposition can be

positioned within the targeted volume, which results in a highly conformal high-dose region. Furthermore, with proton beams, the dose rapidly drops to zero beyond the depth of dose maximum, since the protons have then reached their maximum range in tissue. This also means that sensitive structures posterior to the target are protected from irradiation. In treatments with photons a considerable fraction will ionize beyond the target adding to total dose deposited both proximally and distally of the target.

The techniques of delivery of protons have undergone considerable refinement since their introduction in medical applications. Up to recently, the only method was passive scattering. The beams extracted from the accelerator were mono-energetic and could not provide a uniform dose to a target of any significant size. Methods of modification by scattering foils, absorbers and filters, in order to broaden the Bragg peak, resulting in an extended spread out Bragg peak (SOBP) (Fig. 2), were used to obtain tumor coverage[143]. This posed a dose-related problem, since the tissues inside the beam proximal to the tumor received higher radiation doses, and a logistical one, since a specific absorber had to be manufactured for each field, and for shifts in the patient's anatomy during treatment.

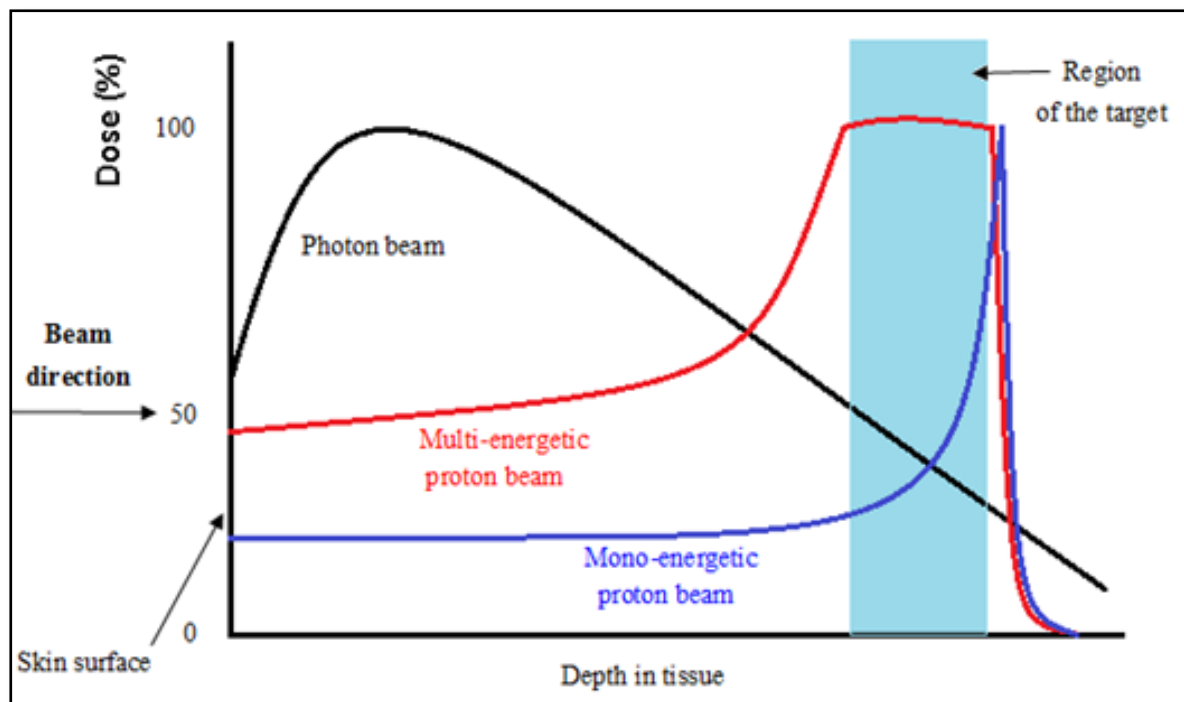


Figure 2. Central axis depth dose for photons and protons. The SOBP is illustrated in the multi energetic proton beam.

A novel method of proton delivery, used at the Paul Scherrer Institute in Switzerland since over a decade, is the spot scanning proton beam technique. With this procedure, small sub volumes within the patient can be selected and irradiated one by one by adjusting the beam energy. The method is more selective compared to the previously used passive scattering delivery technique. With spot scanning, it is possible to reduce the unwanted radiation doses in healthy tissues surrounding the targeted disease even more than what is possible with previously used techniques[144, 145]. The dose reduction in healthy tissue, which is even

more accentuated when compared with standard photon RT, provides the potential for fewer side effects compared to what is observed after today's treatments.

Although patients have been treated with proton beams since half a century, the evidence of clinical benefits for PT remains very limited[146, 147]. This stresses the need of identifying potential groups of patients who might benefit from the different dose distribution pattern offered by PT compared to photons for future clinical trials. The dosimetric advantages of PT compared to photons have been described in a number of dosimetric studies, which compared doses to OARs and the risks of therapy-induced secondary cancer[148]. The majority of these reports have studied relatively small treatment volumes, i.e. intracranial lesions, prostate, and head-neck cancers. Tumors in these areas have long been considered as "traditional" proton targets. There are, however, limited data on the reduction of doses to OARs in larger treatment volumes in PT. Several simulation studies[149-152], mostly for intra-thoracic tumors, have explored the potential advantages of applying proton planning on large PTV volumes. However, among the latest reports, the scattering technique was used almost exclusively. An exception to this is the report by Radu et al[153], in which scanned proton beam planning for large volumes in rectal cancer resulted in decreased doses to the OARs compared to 3D conformal photon planning. In a recently published trial[154], the authors compared IMRT plans to 2-3 field plans in gastric cancer, and they reported lower doses to all OARs outside the PTV with PT.

A large amount of skepticism was directed at the prospect of treating targets in the vicinity of bowels with protons, foremost with the active scanning technique, due to unpredictable bowel movements and bowel gas in particular. The radiation therapy planning is based on information about the electron density inside the patient. This density data is obtained from CT images, on which the position of the different tissues identified in relation to treatment beams. The dose calculation algorithms incorporated in the treatment planning system (TPS) include a correction for tissue inhomogeneities, which is based on differences in electron density for different types of tissue. This correction is, however, static. Respiratory motion and changes in the organ composition and position, e.g. due to variations in intestinal gas filling, during the course of RT in gastric cancer can introduce large changes in tissue composition along the path of the beam. These anatomical inconsistencies may cause deviations in the dose distribution during the dose delivery due to variations in attenuation for photon beams and range for proton beams. For protons, there is in particular a high susceptibility for the dose prediction at the proximal and distal end of the intra-abdominal PTV in the beam. These uncertainties have been commented upon in published trials but have not been quantified[149, 153].

3.3 TARGET DEFINITION

The target volume in gastric cancer consists of the gastric bed and remnant, the anastomoses, and lymph nodes (Table 2). In the case of large tumors (T3-T4), with invasion or close relationship with the abdominal wall, the abdominal wall is included. Recommendations for 2D target construction were published following the Intergroup 0116 experience[155]. These

recommendations are, however, inadequate in order to construct a 3D based CTV. A 3D approach, with higher degree of treatment conformity, resulting in lower doses to the OARs[156], requires in addition to strictly defined regions of interest, information from the preoperative gastroscopy and CT scan as well as the postoperative CT scan and renal scintigraphy. Furthermore, following the experience from the Japanese surgical patient material, the Maruyama Index (MI) was constructed, with the ability to predict the risk of involvement of any given lymph node station depending on the anatomical location of the primary tumor[157, 158]. This has lead to further individualization of the CTV delineation. The inclusion of the lymph node stations into the CTV, based on the tumor location is presented in Table 3.

Tumor location in the stomach	Node station number	Lymph node stations
GE-junction / Cardia / proximal 1/3	stations 1-4; 7; 9-11	para-oesophageal, perigastric, hepatogastro lig, celiac (left gastric artery, celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal
Corpus / Middle 1/3	stations 3-13	perigastric, suprapyloric, infrapyloric, celiac (left gastric artery, common hepatic artery and celiac axis), splenic hilum, suprapancreatic, porta hepatis, pancreaticoduodenal
Antrum / Distal 1/3	stations 3-9; 11-12	perigastric, suprapyloric, infrapyloric, splenic artery, pancreaticoduodenal, porta hepatis, celiac (left gastric artery, common hepatic artery and celiac axis), suprapancreatic

Table 3. Inclusion of lymph nodes in the CTV (based on CRITICS trial recommendations).

The increasing conformity of dose coverage and the progressively shorter dose-fall-off obtained with new treatment techniques, such as IMRT and VMAT[138], stresses the need for standardized delineation in both trials and in clinical practice. There are also large inter physician variations in CTV contouring[159]. As a result, radiotherapeutic organizations proceeded to establish consensus guidelines to increase the grade of standardization in CTV delineation in the most common targets of RT[160, 161]. Recommendations for 3D CTV delineation in gastric cancer have been published by the Trans-Tasman Radiation Oncology Group (TROG)[162], a group in Boston[163], and also the CRITICS study group (CRITICS; clinicaltrials.gov NCT 00407186).

3.4 NTCP AND RISK OF SECONDARY CANCER

The adverse health effects of RT may be grouped into two general categories: the deterministic effects, i.e. harmful tissue reactions and the stochastic effects, i.e. cancer and inheritable effects[164]. The induction of deterministic tissue reactions is characterized by a threshold dose, above which the severity of the damage increases with dose. When the

threshold dose has been exceeded, early and late tissue reactions can be observed. The early tissue reactions appear days to weeks after exposure to radiation and are often of the inflammatory type, a result of the release of cellular factors and/or the treatment-induced cell death[164]. The late reactions appear months to years after exposure. The induction of stochastic effects is of the genetic type and due to the survival of mutated cells. Contrary to the deterministic effects, it does not have a threshold dose from which it starts to be observed.

The evaluation of a treatment plan with regard to the risk of acute and late side effects is commonly done by assessing the 3D dose distribution, and reduced to dose-volume histograms (DVHs), which give information about the dose-volume frequency distribution for the target and the OARs. However, the DVH does not provide information about the expected biological response or the spatial information about which parts of the irradiated structures that received a dose deviating from the prescribed one. Therefore, models of NTCP have been developed which can provide estimates of the biological response in the OARs to RT. The biological evaluation of the treatment plans for RT with either photon or proton beams can be calculated with the DVHs generated by the TPS[165]. This calculation model utilizes the tolerance levels reported in the Emami data[166].

Fulfilling the delineation criteria stated in recommendations for CTV construction in gastric cancer, results in large and relatively complex PTVs (Fig. 3), in the direct vicinity of both kidneys, the liver, the bowel, and the heart. Furthermore, the dose to the bone marrow, in particular in combination with chemotherapy, and, in the case of tumors in the proximal section of the stomach, the dose to the lungs has to be considered. The applied total dose of 45 Gy is below the spinal cord tolerance. Dose limiting organs for acute toxicity in gastric CRT are the stomach remnant, the bowel, and the bone marrow and for late toxicity the liver and kidneys[138].

The radiation-induced secondary neoplasms, a stochastic late-term effect, can be the cost of a successful treatment of a primary malignancy[167, 168]. With the increasing numbers of cancer survivors[169], there is an increasing need to assess, by means of an accurate model, the risk of radiation-induced secondary neoplasms. There is furthermore, a need to compare the estimated risk of induced cancer after traditional photon beam therapy with the risk estimated for proton and heavier ions therapy[170].

Several models are used to estimate the risk of radiation-induced secondary tumors. The International Commission on Radiological Protection (ICRP 60)[171] proposed a calculation scheme for the prediction of total mortality due to late effects. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) has proposed a general equation that takes into account both the effects of radiation-induced DNA mutations and also the survival of the irradiated cells[172].

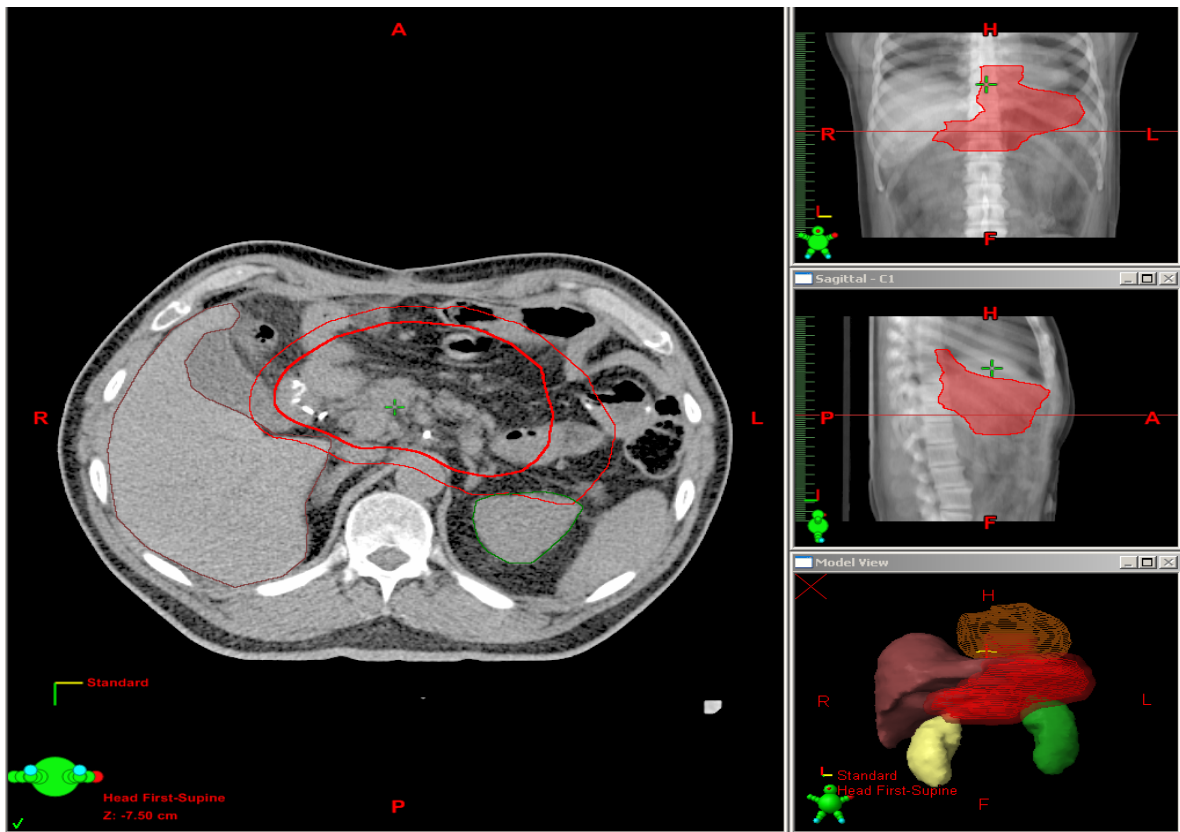


Figure 3. Typical CTV and PTV in gastric cancer according to the CRITICS trial delineation atlas.

Schneider et al[167] used the ICRP 60 calculation scheme to assess the total mortality of the patients due to late side effects after therapy with either photon or proton beams in Hodgkin's disease. This risk assessment model uses the average organ dose and does not take the heterogeneity of the dose distributions in the different organs into account. The results from this study showed that the competition between the induction of the DNA mutations and cell survival should be included for risk estimations of radiation-induced secondary cancers and suggested a decrease in the cancer incidence after proton beam treatment compared to photon treatment.

Dasu et al[173] performed a study of radiation-induced secondary cancer based on the equation proposed by UNSCEAR (1993). The authors modified this equation to take into account the treatment fractionation and also the non-uniform dose distributions to the irradiated organs. The results from the calculations of radiation-induced secondary risk with this modified equation were then compared with risk estimates obtained with two alternative methods. The results showed the importance of using the heterogeneous dose distribution in the organs at risk combined with the non-linear model for risk prediction to obtain improved risk estimations.

4 AIMS OF THE STUDIES

4.1 OVERALL AIMS

The overall aim of the work presented in this thesis was to explore a new concept in chemotherapy, i.e. the sequential approach, and a new modality in radiotherapy, i.e. proton therapy, in the treatment of patients with gastric cancer. Quality of life in patients treated with chemotherapy, and delineation in radiotherapy of gastric cancer, were also investigated.

4.2 SPECIFIC AIMS

The specific aims were

- to evaluate the efficacy of sequential chemotherapy in patients with locally advanced and / or metastatic gastric cancer, with alternating irinotecan and docetaxel in combination with infusion 5-Fu,
- to evaluate the effect of sequential chemotherapy on the quality of life of patients with locally advanced and / or metastatic gastric cancer,
- to investigate the impact of inter observer variations on the delineation of CTV volumes in gastric cancer patients treated with perioperative CRT,
- to evaluate the influence of proton therapy compared to modern photon radiotherapy on the doses to organs at risk in gastric cancer patients treated with perioperative CRT, and
- to evaluate the impact of daily anatomical variations, i.e. intestinal gas filling, on the dose distribution of proton beam therapy.

5 MATERIALS AND METHODS

5.1 PATIENTS

All patients included in Paper I and II were recruited and treated in Swedish oncology centers participating in the GATAC trial. The participating centers and the numbers included by each site are listed in Table 4. All patient data were centrally collected and coded at the Department of Oncology, Uppsala University Hospital, Uppsala, Sweden.

Site	No. of patients
Uppsala	13
Stockholm	13
Karlstad	1
Lund	26
Eskilstuna	1
Malmö	6
Sundsvall	5
Västerås	5
Örebro	3
Umeå	6
Luleå	2
Total	81

Table 4. Patients included in Paper I and II by participating center.

5.2 CT SCANS

All CT scans utilized for the purpose of treatment simulation in Paper IV and V were obtained from patients included in the CRITICS trial at the Department of Radiotherapy at Karolinska University Hospital, Stockholm, Sweden. The CT scan used for CTV comparisons in Paper III was obtained at the Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands.

5.3 THE GATAC TRIAL

5.3.1 Inclusion and exclusion criteria

The study was a multicenter phase II trial aiming at randomizing 80 chemo-naïve patients, older than 18 years, with histologically verified metastatic or locally advanced adenocarcinoma of the stomach or cardia. Adjuvant therapy, including chemoradiotherapy after radical surgery, was allowed if finished more than 6 months before registration. Patients

with CNS-metastases or a history of other malignancies than gastric cancer, except curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix or prior malignancies treated more than 5 years ago without recurrence, were not included.

All patients had radiologically measurable lesions according to the RECIST-criteria, good performance status (WHO ≤ 2), and adequate hematological, renal, and liver functions. The latter was defined as hemoglobin (Hb) > 100 g/L, neutrophils (ANC) $> 2.0 \times 10^9$ /L, platelets $> 150 \times 10^9$ /L, total bilirubin $< 1.25 \times$ upper normal limit (UNL), creatinine $< 1.25 \times$ UNL, ASAT and ALAT $< 3 \times$ UNL; in case of liver metastases, ASAT and ALAT $< 5 \times$ UNL. Patients with unresolved bowel obstruction, uncontrolled Crohn's disease or ulcerative colitis, or a current history of chronic diarrhea were excluded. All hematological and radiological assessments were done within 8 days and 3 weeks prior to randomization, respectively. The patients started treatment within 10 days from randomization.

5.3.2 Chemotherapy scheme

Patients were randomly assigned to start with either four courses of docetaxel 45 mg/m² (arm T) or irinotecan 180 mg/m² (arm C) with the simplified de Gramont regimen of 5-Fu/Lv (d1,2 q 2 w) (Fig. 4). After 8 weeks, i.e. 4 courses of treatment, patients switched to the other regimen, thus receiving an additional four courses of docetaxel (arm C) or irinotecan (arm T) with the same 5-Fu/Lv-schedule. The cross-over design of the GATAC trial is illustrated in Figure 4.

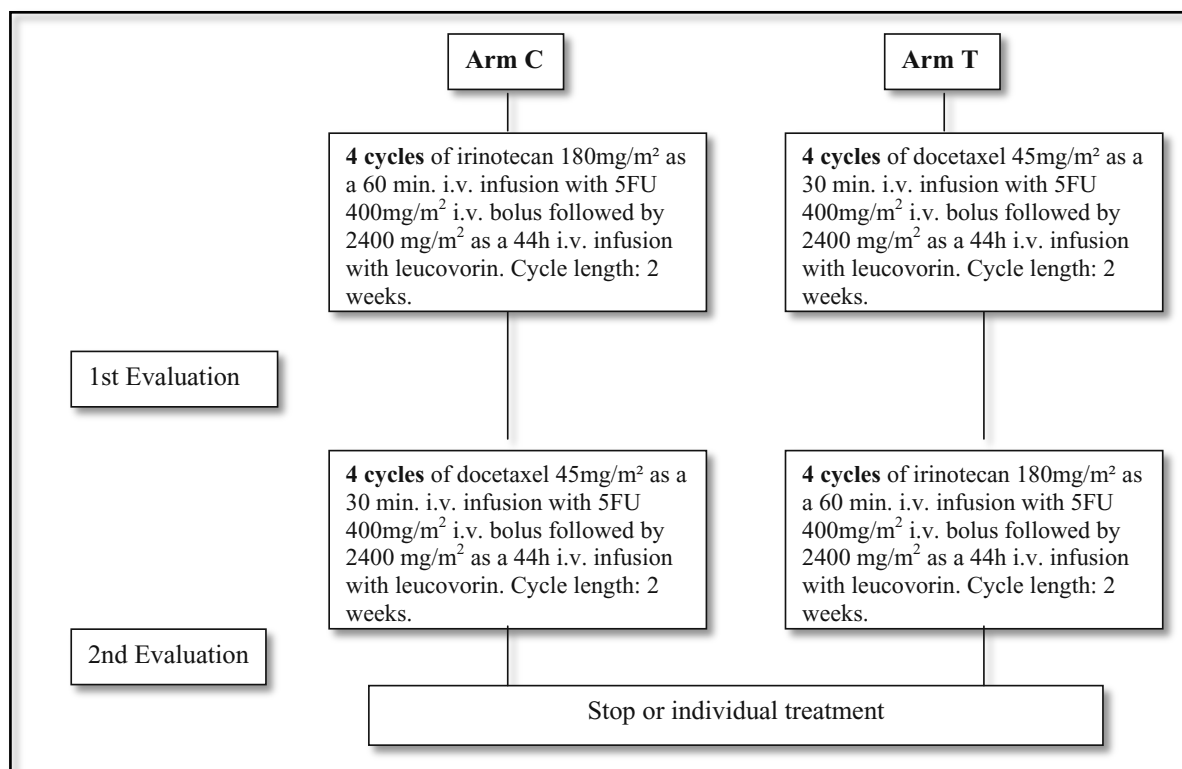


Figure 4. The GATAC trial design.

Dose adaptations for toxicity were predefined in the study protocol. In case of Grade ≥ 2 hematological or non-hematological toxicity at the day of infusion, the treatment was delayed until recovery (Grade <2). In case of febrile neutropenia or Grade 4 neutropenia, thrombocytopenia or leukopenia, the doses of both drugs were reduced by 20% for the next and subsequent courses of treatment. In cases of cumulative skin toxicity or peripheral neuropathy of Grade 3-4, only the docetaxel dose was reduced by 20%.

Prior to treatment with docetaxel all patients received corticosteroids, most commonly dexamethasone. Prophylactic treatment with atropine was allowed before the administration irinotecan in order to prevent cholinergic symptoms.

5.3.3 Evaluation of response – RECIST criteria

Radiological evaluations were conducted by means of CT or MRI at base line and after four courses (8 weeks), i.e. at the switch of combinations, and after eight courses (16 weeks), i.e. at the conclusion of the 2nd drug combination. Patients must have received a minimum of four cycles of treatment with a minimum of one tumor assessment to be considered evaluable for response, unless “early progression” occurred in which case they were scanned earlier to be considered evaluable.

Tumor response was evaluated with the efficacy criteria according to the EORTC Response Evaluation Criteria in Solid Tumors (RECIST)[174, 175]. All measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, were identified as target lesions and recorded and measured at baseline. Target lesions were selected on the basis of their size, i.e. those with the longest diameter, and their suitability for accurate repeated measurements either imaging techniques or clinically. A sum of the longest diameter for all target lesions was calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter was used as the reference by which to characterize the objective tumor response.

All other lesions, or sites of disease, were identified as non-target lesions and were also recorded at baseline. Measurements of these lesions were not required, but the presence or absence of each was noted throughout the follow-up.

The target lesions were evaluated according to following definitions:

- Complete response (CR) = the disappearance of all target lesions.
- Partial response (PR) = at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
- Progressive disease (PD) = at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of the longest diameter recorded since the treatment started or the appearance of one or more new lesions.

- Stable disease (SD) = Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

The non-target lesions were further evaluated according to following definitions:

- Complete response (CR) = the disappearance of all non-target lesions and normalization of tumor marker levels.
- Stable disease (SD) = the persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits.
- Progressive disease (PD) = the appearance of one or more new lesions or unequivocal progression of existing non-target lesions.

Evaluation of overall response was a combined assessment of the changes in both target and non-target lesions (Table 5).

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Table 5. Evaluation of overall response according to RECIST.

5.3.4 Assessment of adverse events

An adverse event is defined as any symptom, sign, illness, or experience, which develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Adverse events were recorded and graded according to National Cancer Institute Common toxicity Criteria (NCI-CTC) Version 2.0[176] before each new treatment course and up to 30 days after last study drug infusion. In case these criteria were not applicable, the event was defined as 1=mild, 2=moderate, 3=severe, 4=life-threatening. Grade 3 and 4 adverse events were defined as serious adverse events (SAE).

An adverse event is classified as serious if it is:

- Fatal
- Life-threatening

- Requires or prolongs hospitalization
- Results in a persistent or significant disability or incapability
- A congenital anomaly or birth defect
- An important medical defect

5.3.5 Quality of life assessment

Patient QoL was measured at baseline, before the fifth cycle and after the eight cycle of treatment. If the therapy was modified, the questionnaire was also filled in, thus, at the same points as the radiological evaluation.

The evaluation tool used was the Swedish version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 items (QLQ-C30) version 3. This tool consists of 30 questions, which cover general cancer specific aspects of the patient's QoL. The first 28 questions are answered according to the following scale:

1. Not at all
2. A little
3. Significantly
4. Very much

The last two questions addressing the global perception of the patients' state of health and QoL, respectively, are answered on a seven point scale, with score of 1 representing a very poor and score of 7 an excellent status.

Furthermore, the patients were asked to answer two additional questions after completing all treatment courses:

1. Which of the two treatments did you find most effective?
2. Which of the two treatments did you find most toxic?

The latter added questions were answered before the patient received the results of the last radiological evaluation, by specifying the treatment given before and after the prescheduled switch. The aim of these questions was to add an element of self-reported evaluation.

The QLQ-C30 is composed of five functional scales, three symptom scales, a global health status / QoL scale, and six single items. The scales are addressed by more than one question in the questionnaire. All results are presented according to the EORTC QLQ-C30 Scoring Manual. This procedure results in all scales and single items in measures ranging from 0 to 100, where the higher score represents better level of functioning in all functional scales and the global scale, but, contrary, in the symptom scales and the single items, where it represents a higher level of symptoms.

The scoring procedure if items I_1, I_2, \dots, I_n are included in a score, is as follows:

The Raw Score, an estimate of the average of the items that contribute to the scale is first calculated:

$$RawScore = RS = (I_1 + I_2 + \dots + I_n)/n$$

Further the linear transformation to 0-100 is applied to obtain the score S :

For functional scales:

$$S = \left\{ 1 - \frac{(RS - 1)}{range} \right\} \times 100$$

For symptom scales/items and global health/QoL:

$$S = \{(RS - 1)/range\} \times 100$$

Where, range is the difference between the maximum possible value of RS and the minimum possible value. The QLQ-C30 has been designed so that all items in any scale take the same range of values. Therefore, the range of RS equals the range of the item values. Most items are scored 1 to 4, giving range = 3. The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with range = 6, and the initial yes/no items on the earlier versions of the QLQ-C30 which have range = 1.

In order to evaluate whether there was a positive or negative development of the patients' perception of their QoL we looked at the direction of the change (viz. positive or negative), and at the change in mean scores for all 15 scales in the questionnaire. A clinically significant shift was defined as a difference of over 10 points on a 100-point scale, thus corresponding to a moderate or large change in accordance to EORTC recommendations[177].

5.4 RADIOTHERAPY

Target delineation in Paper IV and V was performed in accordance with the CRITICS protocol and its attached delineation atlas. All CTVs included the gastric bed/gastric remnant, the anastomoses, and lymph node stations in accordance with the Maruyama data. The liver, both kidneys, the heart, the spinal cord, bone marrow, and the bowel outside the PTV were delineated as OARs. The latter included both the large and small bowel from the diaphragm to 1.5 cm below the PTV. In female patients, the breast tissue, and in all patients the lungs, esophagus, bone, and skin were delineated for the purpose of calculation of secondary cancer risk. A PTV margin of 1 cm was added to the CTV. All delineations were reviewed by the weekly gastrointestinal target discussion panel at the Department of Radiotherapy, Karolinska Hospital, consisting of oncologists experienced in target definition for gastrointestinal malignancies.

Planning for both modalities was performed in Eclipse (Varian Medical Systems, Palo Alto, CA, USA). For the photon plans, a Varian accelerator was used and for the proton plans an IBA machine. All photon plans were generated with volume modulated arc therapy (VMAT) technique, using two full arcs and an energy of 6 MV.

5.4.1 Photon planning

The photon treatment planning in Paper IV and V was performed with Rapid Arc, the Varian approach of VMAT. In VMAT, the dose is delivered during continuous gantry rotation and collimator motion[178]. The dose distribution can be optimized based on dose-volume objectives. The MLC openings and monitor units (MU) weights are optimization parameters. With VMAT the gantry rotation, MLC motion, and dose rate modulation are coordinated simultaneously.

The optimization process in Rapid Arc is based on the Progressive Resolution Optimizer (PRO) algorithm[179], in which the entire gantry rotation is described as a sequence of 177 control points equally spaced by roughly 2° . For each control point, the gantry angle, dose rate, and MLC leaves opening shapes are specified. The optimization process proceeds through five multi-resolution levels. The first resolution level has 10 control points and it has an initial distribution of the MLC shapes; the dose rate and gantry speed are then set to their maximum allowed values[180]. During each multi-resolution level, the MLC shapes, dose rate, and gantry speed are simultaneously optimized for a fixed number of iterations. The process is repeated by doubling the number of control points at each level until the final number of 177 (360° arc) control points is reached. The Varian Eclipse TPS for photon beam therapy uses the Analytical Anisotropic Algorithm (AAA) as dose calculation model.

5.4.2 Proton planning

Several attempts were made to find a field configuration that provided optimal robustness for the proton plans. In esophageal cancers and retroperitoneal targets, a posterior approach with two oblique fields is most commonly used. For centrally located abdominal tumors, i.e. pancreas and the stomach, variations of lateral, posterior, and anterior field settings have been applied. The CTV/PTV in patients with gastric cancer is encompassed by structures with variable air content, i.e. lungs/diaphragm, gastric remnant, and the large and small bowel, which resulted in uncertainties regardless of the chosen field configuration. We therefore decided on the optimal field setup of proton planning, which provided the best target coverage and OAR sparing for these large and complex target volumes.

Proton plans were based on two beams, one left lateral at 90 degrees and one oblique frontal at 345 degrees (Figure 5). Both beams were optimized with single field uniform dose (SFUD) in order to increase robustness. The proton beam was of the spot scanning type, with an energy range of 70-235 MeV.

Proton planning was performed using beam data from the University of Pennsylvania proton machine (IBA proton therapy system), since the beam data from the Swedish Skandion Clinic

were not yet available. Since these machines are quite similar and from the same manufacturer, it was considered to be an acceptable approach for estimating the future treatment possibilities at the new Swedish center.

The relative biologic effectiveness (RBE) of 1.1 is widely used for protons[181]. As this fact has an implication for prescription rather than for comparison, physical doses were compared in Papers IV and V.

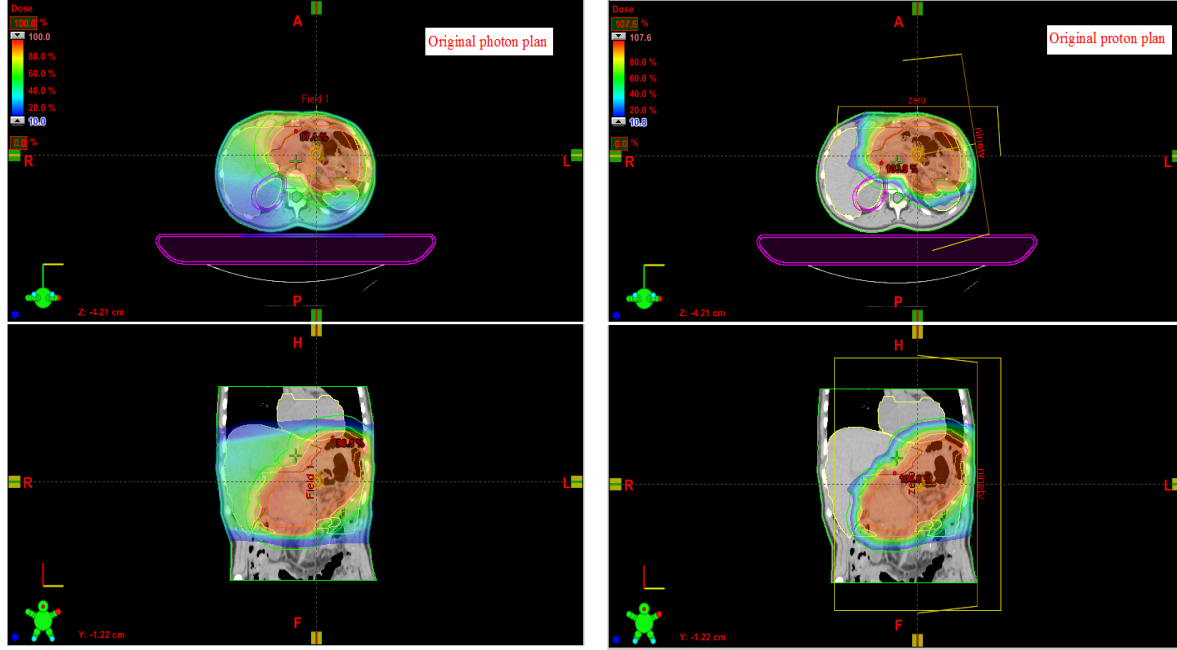


Figure 5. Dose distribution and beam arrangement. For photon therapy (left side), and for proton therapy (right side).

5.4.3 NTCP calculation

A biological evaluation of the dual treatment plans was performed by calculation of normal tissue complication probability (NTCP). To compute the NTCP, the Lyman-Kutcher-Burman (LKB) model was implemented in a computer program (MatLab R2012a)[182]. This model is based on a four-parameter equation (Eq. 1), and makes use of the Emami data[166, 183].

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^t e^{-\frac{t^2}{2}} dt \quad (\text{Eq. 1})$$

where

$$t = \frac{D_{max} - TD_{50}(v)}{m \cdot TD_{50}(v)} \quad (\text{Eq. 2})$$

and

$$TD_{50}(v) = TD_{50}(1) \cdot v^{-n} \quad (\text{Eq. 3})$$

$TD_{50}(v)$ is the tolerance dose which leads to 50% complication probability for uniform irradiation of the fractional volume v of the organ at risk (OAR); when the whole organ is

irradiated $v = 1$ and the tolerance dose is $TD_{50}(1)$. The parameters n and m are, respectively, the volume factor, which describes the volume dependence of the NTCP, and the slope of the NTCP vs. dose curve.

The NTCP equation is applicable under conditions of homogeneous irradiation of the OAR. In order to accommodate the clinical data, which are for inhomogeneous irradiation, the current non-uniform DVHs have to be transformed to uniform. For this purpose, the effective volume method[165] was used. Additionally the linear quadratic (LQ) model was used in order to correct the physical DVHs for fractionation effects by conversion of the delivered total dose D to the 2 Gy equivalent dose per fraction through the equation (Eq. 4)[184].

$$LQED_2 = D \frac{(\alpha/\beta + d)}{(\alpha/\beta + 2)} \quad (\text{Eq. 4})$$

Where $LQED_2$ is the linear-quadratic equivalent dose for 2 Gy per fraction. The data used for calculation are shown in Table 6. Due to the high inhomogeneity in dose distribution in the heart and the spinal cord, the NTCP was not calculated for these organs, as the reliability of the calculation model would be questionable.

Organ	α/β	TD50 (Gy)	N	m
Kidney	3	28	0.7	0.1
Liver	2	40	0.32	0.15
Bowel	3.9	55	0.15	0.16

Table 6. Variables used for calculation of NTCP.

5.4.4 Estimates of risk of treatment induced neoplasms

Presently, there is no single “gold standard” for the estimation of risk of treatment-induced malignancies and there is, furthermore, an ongoing debate as to the shape of the dose-response curve for radiation-induced tumors. It has been discussed in several publications that the traditional linear-quadratic model is insufficient in describing this relationship[173]. Clinical investigations have shown that the dose response relationship for cancer induction following radiotherapy has either of two main characteristics: an increase of the risk with dose to a maximum effect followed by a decrease or an increase followed by a leveling-off of the risk[173, 185, 186].

The induction of secondary cancer following external beam radiotherapy can be estimated using a model by Dasu, which takes into account both the heterogeneity of the dose distribution in the irradiated organs and the fractionation schedule of the radiotherapy delivery[173]. This model, which was applied in Paper IV, is based on the LQ model and makes use of a general equation (Eq. 5) proposed by UNSCEAR[172]. It takes into

consideration both the probability for therapy-induced DNA mutations and the probability for survival of the irradiated cells.

The risk model adopted for calculating the risk of secondary cancer is the following (Eq. 5):

$$Effect(D) = \left(a_1 D + \frac{b_1 D^2}{n}\right) \cdot \exp \left[-\left(a_2 D + \frac{b_2 D^2}{n}\right)\right] \quad (\text{Eq. 5})$$

Where, a_1 and b_1 are the parameters describing the induction of DNA mutations and a_2 and b_2 are the radiobiological parameters of the LQ model for cell survival, n is the number of fractions of the treatment protocol and D is the prescribed total dose.

The risk for induction of secondary cancer is then estimated by the use of Eq. 6 which was proposed by Dasu [173]. The risk for each OAR is calculated by means of this competition model in all the bins of a DVH and the total risk per organ is finally obtained by summation:

$$Total\ effect = \frac{\sum_i v_i \cdot Effect(D_i)}{\sum_i v_i} \quad (\text{Eq. 6})$$

For the estimation of the risk of radiation-induced secondary cancers, Dasu made certain assumptions. In Eq. 5 it was assumed that both the probabilities for induction of DNA mutation and the probability of cell survival have the same α/β parameter. Furthermore, for low doses, the quadratic term for induction of DNA mutations is negligible and the same assumption of low doses was made for calculations in Paper IV. The parameter a_1 is the linear coefficient, which describes the relative probability of cancer risk in different organs for the nominal world population and is listed in the ICRP 60[171]. For every patient included in this study, the risk of developing secondary malignancies was determined for the most important OARs for the two treatment modalities.

5.5 STATISTICAL ANALYSIS

All statistical analyses were performed using the IBM SPSS computer program (version 18.0).

In the GATAC trial (Papers I and II), the primary aims were to explore the efficacy, i.e. objective response rate. Secondary aims included toxicity, overall and progression-free survivals of the planned sequential administration of the two drug combinations. If no complete or partial response (CR+PR) were seen in the nine first patients in each treatment arm, indicating that the response rate would be less than 30%, the trial would be closed for that treatment arm (Gehan's Method Phase II Trials, Step 1). If three or more responses were seen among the first fourteen cases an additional nine patients were to be added (Gehan's Method Phase II Trials, Step 2). It would then be possible to estimate the response rate with a

standard error of 10%. Several responses were seen in both arms in the first nine patients. Taking in account anticipated ineligibility, inevaluability, and the second part of the study, the estimated number of patients to be enrolled per treatment arm was forty. OS and PFS were calculated from the date of randomization and presented according to the Kaplan-Meier method. To test for statistical significance in Paper I, the t-test, χ^2 -test, and log-rank test were used. A p-value of <0.05 was considered statistically significant. In Paper II, the Fisher's Exact Test was used for statistical comparison between the treatment arms. A p-value of <0.05 (Exact Sign. (two-sided)) was considered statistically significant. The Mann-Whitney U-test was used to analyze the correlation between radiological response and the shift in global QoL scores. The statistical analysis in Paper II was performed in collaboration with the Unit of Medical Statistics at the Karolinska Institute (LIME/MedStat).

In Papers IV and V, the differences between treatment modalities (Paper IV) and the dose to target organs and OARs changes (Paper V) were analyzed with pairwise Wilcoxon signed-rank test. This test is performed when subjects are tested under two different circumstances. The level of statistical significance was set at $p \leq 0.05$.

5.6 ETHICAL CONSIDERATIONS

The GATAC study protocol (Papers I and II) was approved by the Ethics Committee at the University of Uppsala and by Regional Ethics Committees of the participating hospitals. All patients were required to give written informed consent.

Patients included in Papers IV and V participated in the CRITICS study, which was approved by the Ethics Committee of the Stockholm Region. The patients were informed about the trials and left written consent before participation.

6 RESULTS AND DISCUSSION

6.1 PAPER I - SEQUENTIAL CHEMOTHERAPY IN ADVANCED GASTRIC CANCER

This is the first randomized comparison of prescheduled sequential combination treatment in gastric cancer. In addition, it allows a head-to-head comparison of early response rates and toxicity of the two drugs docetaxel (arm T) and irinotecan (arm C), combined with 5-Fu. In this trial, the primary aim was to study the efficacy, i.e. objective response rate, and secondary aims included the toxicity profile, overall survival, and progression-free survival (PFS) of the planned sequential administration of the two drug combinations.

Of the 81 patients randomized, 78 proceeded to treatment, i.e. 39 in each arm (Figure 4). Patient characteristics were very similar in both treatment arms, with the exception of gender, i.e. 33% females in arm C compared to 13% in arm T. The most common reasons for dropout during the duration of the trial were either death (six patients) or tumor progression (six patients). None of the deaths during the trial was attributed to toxicity.

The response rates in all patients were 44% and 43% after 8 and 16 weeks of treatment, respectively. At the end of the treatment, two patients had a complete response. Median PFS was 4.9 months for the entire patient population and 4.9 vs. 5.0 months for arms C and T, respectively. Forty patients (51%) did not have progressive disease while on study drug. The median PFS for this subgroup was 8.1 months (range 4 – 29). No difference in objective response rates between treatment arms was seen. Median follow-up time was 11 months.

Median OS was 11.5 and 10.6 months in arms T and C, respectively, a statistically non-significant difference ($p=0.33$). Due to the uneven distribution of gender in the treatment arms, we calculated the median OS according to gender. We found no difference in survival between males and females. A small group of ten long-term survivors was identified, which was evenly spread between the treatment arms. The survival times for these patients varied between 17 and 37 months. Five of these patients (6% of the total patient population) underwent surgery with curative intent after completion of chemotherapy; four had a gastrectomy and one a deperitonealisation. Notably, four of these patients had no distant metastases at inclusion. One patient died 37 months after randomization and 21 months after surgery in recurrent gastric cancer.

No significant differences in toxicity were found between the two treatment arms. One hundred and twenty-eight Grade 3 and nine Grade 4 toxicities were registered in both arms combined. One patient underwent acute surgery due to intestinal obstruction. The most common adverse event was hematological toxicity (20%). Anorexia, fatigue, or infections were reported in 15% of patients, respectively. It can be argued whether dysphagia, which appeared in eight patients, was related to the treatment or to the tumor itself or to previous surgery. The vast majority of SAEs occurred during the first four treatment cycles. This could be partly explained by the fact that most events (58%) occurred in patients who did not

complete the whole treatment and partly by dose reductions when toxicity was observed during the first treatment cycles. In almost half of the patients (43% of those having completed all 8 cycles), no Grade 3 or 4 SAEs were observed.

In conclusion, no differences favoring either arm T or C were found with respect to response rates or toxicity after 16 weeks of therapy. Furthermore, no differences in survival outcome could be detected whether treatment was initiated with either irinotecan or docetaxel. This shows that both combinations are effective in the treatment of locally advanced and / or metastatic gastric cancer and that they can be safely administered in random order.

The main interest of our results is, however, that an objective response rate of 41% and a median OS of 11 months were reached in a multicenter trial and a population consisting of 87% patients with distant metastatic disease. These results are at least comparable to recently reported efficacy of combinations including cisplatin or combinations of three cytostatic agents.

In general, combinations of irinotecan or docetaxel with 5-Fu have been better tolerated than combinations of cisplatin and 5-Fu, but have resulted in more gastrointestinal toxicity[95]. Neutropenia is a major problem for combinations of either irinotecan or docetaxel with cisplatin[95, 101], and is especially problematic for the TCF (docetaxel, cisplatin, 5-Fu) combination. The relatively low toxicity seen in this trial is probably a result of “switching” the drug combination after 4 cycles and thus reducing the typical toxicity of each of the study drugs, i.e. hematological for docetaxel and gastrointestinal for irinotecan.

6.2 PAPER II - QOL IN PALLIATIVE GASTRIC CANCER TREATMENT

There are limited data reporting on the effect of palliative chemotherapy on QoL in patients with gastric cancer, and none in a sequential setting. This is, however, a crucial parameter that has to be considered in the process of clinical decision making, as to which or whether palliative chemotherapy should be recommended for these patients. Therefore, the component of QoL-assessment was included in the GATAC trial. The primary objective was to explore whether there was any difference in QoL depending on which regimen was given first. Secondary aims included the evaluation of changes in the QoL scores during treatment vs. baseline and an evaluation of whether they were correlated to or independent of the radiological response of the tumor.

A total of 191 completed QoL questionnaires were collected. The compliance rate in answering questionnaires was 96% at baseline, 85% after 4 courses, and 64% after 8 courses of treatment, which is comparable to other trials assessing QoL. In only nine cases the missing questionnaires were not rendered by disease progression, toxicity, or death. Forty-seven patients completed all three assessments and in those cases the changes in QoL could be evaluated for both treatments. Furthermore, 110 treatment periods of eight weeks could be assessed separately, with completed questionnaire at the start and end of the period, in order to evaluate the dependency of QoL on radiological response.

No statistically significant differences were detected between the two treatment arms at baseline or during the 16 weeks of treatment in all scales of QoL (p values ranging from $p=0.076$ to $p=0.946$), with the exception of insomnia. Patients in arm T had less often a negative change between baseline and the evaluation at 8 weeks than in arm C (8% vs. 32% of patients reporting increased insomnia, $p=0.025$).

The majority (55%) of all patients reported a clinically moderate or large improvement (>10 points) in global health status/QoL during the duration of the treatment. Only 19% reported a moderate or large deterioration. There was no statistically significant change ($p=0.797$) during treatment in the patients' scoring of their global health status/QoL. There was, however, a trend for rising mean and median scores during the treatment period compared to baseline for both treatment arms. This trend was present in other functional scales, with the exception of cognitive and social functioning. Similarly, the scores for most single items, with the exception of dyspnea and diarrhea, showed a trend towards decrease, thus less pronounced symptoms. Both fatigue and loss of appetite were the highest scored symptoms at baseline, and fatigue remained as the highest scored after completing the treatment.

In order to connect the radiological evaluation to the QoL change, which was reported to be dependent of one another in several previous trials in gastric cancer, patients were divided into those who had a radiological response (CR or PR) and those who did not (SD or PD). We then compared the proportion of patients reporting a clinically significant positive, a negative or no shift in the global QoL scores during the entire treatment and during the first and second treatment period. During the first treatment period (first 8 weeks) there was a trend for improved scores for the radiologically responding patients, however, the difference was statistically not significant ($p=0.168$). During the second treatment period (last 8 weeks), however, there was a statistically significant difference ($p=0.007$), i.e. 82% of responding patients reported a positive change or unchanged global QoL score compared to 50% among those with no response. No significant correlation for the other scales or single items was found between the change in scores and radiological response except for nausea and vomiting. In the non-responding group, 34% experienced aggravated symptoms compared to 22% among responders ($p=0.035$).

Although the population consisted of 87% of patients with distant metastatic disease, many of these in several sites, the patient population reported good QoL and relatively few symptoms at baseline. Therefore, the fact that good QoL can be sustained during sequential treatment emphasizes the role of palliative cytotoxic treatment in this patient group. It also stresses the importance of choosing an effective palliative treatment with minimal toxicity. As in most trials addressing QoL, some caution should be taken in interpretation of the results, due to potential skewness of data as a result of missing evaluations. These missing data may represent deterioration of patients' QoL. Methods, such as reporting by proxy or self-reported QoL, are being established in clinical studies, and might increase the validity and generalizability of QoL-data. This uncertainty makes it important to establish reliable early predictors of treatment response.

6.3 PAPER III - ATLAS BASED CTV DELINEATION IN GASTRIC CANCER

The protocol for the CRITICS trial included a CT-based atlas with guidelines for CTV delineation in proximal, middle, and distal gastric cancer. A consensus discussion among the responsible oncologists and two experienced radiologists, specializing in abdominal diagnostics, verified the anatomical accuracy of the atlas. Furthermore, instructions for the PTV construction were defined in the protocol. In this study, after implementation of a delineation protocol, inter physician variability was tested by comparing target volume delineations and treatment plans from 10 different institutes on 1 example case. The primary aim of this study was to quantify the variations in delineated CTV and PTV volumes. The secondary aim was to evaluate the effect of the registered variation on PTV coverage and doses to the OARs.

Six centers in the Netherlands and four in Sweden participated in this trial. All centers were provided with the same clinical information about the patient, including the pre- and postoperative CT-scans in addition to the planning scan. According to the guidelines in the atlas, the CTV in the study patient had to consist of the tumor bed with the gastric remnant, the gastrojejunal anastomosis and duodenal stump, and perigastric, suprapyloric, infrapyloric, celiac, splenic hilum, suprapancreatic, porta hepatis, and pancreaticoduodenal lymph nodes. In all centers, the radiation oncologist with most experience in upper abdominal tumors, delineated the CTV. However, with the exception of NKI, the participating centers had no or little experience in irradiation of gastric cancer. Furthermore, all centers were asked to provide clinically acceptable treatment plans in accordance with the study protocol, and based on their own delineations.

The ten CTV and PTV delineations were compared by means of the volume and overlap between institutions. Subsequently, a 3D median PTV was constructed out of the delineated PTVs, defined as the volume included by at least 50% of the observers. Target coverage was compared by the application of the planned dose to the median PTV. Furthermore, the doses to OARs were analyzed for the liver and both kidneys. For the liver the mean dose was calculated, whereas for the kidneys the relative volume receiving more than 20 Gy was calculated for each separate kidney.

Large inter observer variation was found in the analysis of CTV and PTV volumes. The CTV volume ranged between 240 cm³ and 821 cm³ (average = 392, 1SD = 176). On average, the CTV overlap between institutions was 72%, whereas for the PTV the average overlap was 78%.

The PTV volume, ranged between 634 cm³ and 1677 cm³ (average = 915, 1SD = 312). The resulting median PTV had a volume of 890 cm³. The minimum observer variation was found at the border of the liver and the left kidney (1–3 mm SD). Maximum observer variation was found at the caudal part of the target volume, ranging up to 19 mm SD. This could be attributed to the difficulty in defining the section of the diaphragm and the extent of

periesophageal nodes included in the CTV. For the remainder of the PTV, observer variation was on average 7 mm SD, ranging between the minimum and maximum.

All participating centers met the preset requirements of PTV coverage in their treatment plans, which resulted in the average V95 of 99.5% (range, 98.4–100%). All institutes also succeeded in minimizing the dose to the OARs. The mean liver dose, which had to be <30 Gy, was on average 24.3 Gy (range, 20.5–27.3 Gy). All institutes sacrificed the left kidney and spared the right one for good target coverage, with an average V20 of 94.2% (range, 65.2–100.0%). The V20 for the right kidney was on average 12.0% (range, 1.6–32.4 %), which was adequately below the constraint of 33%.

Despite the use of the delineation atlas and the contouring workshop, substantial inter physician variation was found in this trial. Although differences in delineation between institutes were in the order of centimeters, because of the size of the total target volume, the effect on coverage of the median PTV was relatively small (approximately 10%). The impact of these variations may, however, become larger as more conformal treatment techniques, such as IMRT and VMAT, are more commonly used. Furthermore, adjuvant CRT in gastric cancer in Europe is today not considered as standard of care and, thus, the relative lack of experience in constructing a complex target in this region may have influenced the large inter physician variation in this trial.

6.4 PAPER IV - PROTON TREATMENT, DOSES TO OARS AND SECONDARY CANCER IN GASTRIC CANCER

The clinical benefits of proton therapy (PT) remain uncertain. There is a need to identify potential groups of patients who may benefit from the different dose distribution patterns offered by PT compared to photons. The normal tissue sparing effect of protons can potentially be greater in large target volumes, such as in gastric cancer, than in the classical proton targets. Furthermore, PT may also lower the risk of therapy-induced secondary neoplasms, which is of importance with increasing survival rates and life expectancy in cancer patients. The aim of this study was to explore, by means of dosimetric comparison, the potential sparing effect on OARs and the risk of therapy-induced secondary tumors of scanned proton beam planning in patients with gastric cancer undergoing postoperative RT compared to photons.

Nine consecutive patients with gastric cancer, included in the CRITICS trial and referred to the Department of Radiation Oncology at the Karolinska University Hospital for postoperative CRT between November 2008 and December 2013 were asked to participate in this study. All patients were previously treated with neoadjuvant chemotherapy followed by R0 total (n=1) or partial gastrectomy (n=8). One patient was excluded due to a prior splenectomy, which resulted in a large disarrangement of the upper abdominal anatomy.

The prescribed dose was 45 Gy in 1.8 Gy fractions. For each of the eight patients one VMAT and one scanned pencil beam (PBS) proton plan was generated. The optimization was performed with the aim of achieving a minimal and maximal dose in the PTV of 95% and

107%, respectively, in all cases. The mean liver dose did not exceed 30 Gy and the allowed maximal dose in the spinal cord was below 45 Gy. In every case, an effort was made to spare one kidney as much as possible, and in no cases did 2/3 of one kidney receive more than a maximum of 40% of the prescribed dose. The VMAT plan was the actual clinical plan.

In order to compare plans with different modalities, cumulative dose-volume histograms were calculated for the OARs. For the kidneys, the level of 18 Gy was chosen due to indications of a threshold value for RT-induced renal injury, with a risk of 5% and 50% for whole kidney irradiation with 18 Gy and 28 Gy, respectively[187, 188]. For the liver, the mean organ dose was registered, which is a predictor of the risk of developing radiation-induced liver disease (RILD), as well as the volumes receiving 10 Gy (V10) and 30 Gy (V30)[189]. Organ volumes of the bowel outside the PTV receiving 30 Gy and 40 Gy and the mean dose were registered. The V25 Gy in the heart was evaluated. The maximum dose to the spinal cord was obtained for each plan. Rarely, the CTV encompassed the lower paraesophageal lymph nodes, thus, very limited dose to the base of the lung was found. Thus, the lung doses were not considered clinically significant.

Patient age ranged between 42 and 71 years (median 65.5 years). The CTVs and PTVs varied from 576 to 1032 cm³ (median 767 cm³) and from 1146 to 1836 cm³ (median 1505 cm³), respectively. All sixteen plans met the preset constraints. The coverage of the PTV and the CTV was compared for all pairs of plans and ranged from 97.5% to 99.7% for the PTV. There was no statistical difference in coverage between the two groups (p=0.498).

Doses to OARs and NTCP were reduced in all organs except the bowel outside the PTV and the heart in the proton plans compared with VMAT plans. Protons offered significantly lower doses to the left kidney, liver, and spinal cord (p=0.012). Due to the used planning technique, no gain was seen in the dose to the bowel outside the PTV and the heart. The proton plans resulted in statistically lower risks for all types and malignant secondary neoplasms compared to photon plans (p=0.012 and p=0.011, respectively).

6.5 PAPER V - GAS VARIATIONS IN THE ABDOMEN AND SCANNED PROTON THERAPY

In patients with gastric cancer, proton therapy (PT) can reduce doses to OARs due to the defined range in tissues and advantages in depth dose distribution. In the majority of trials in PT in the abdomen, proton plans were developed with the passive scattering technique. A large amount of skepticism was directed at the prospect of treating targets in the vicinity of bowels with protons, especially with the active scanning technique, due to unpredictable bowel movements and bowel gas in particular. Dose distribution in PT has a high susceptibility to variations in tissue homogeneity, in particular at the proximal and distal end of the intraabdominal PTV, of the beam. These uncertainties have been commented upon in published trials but they have not been quantified. The aim of our study was to quantify the influence of large variations in gastrointestinal gas filling on dose distribution in large upper abdominal targets when using the scanned proton radiation technique.

Eight patients, participating in the CRITICS trial, were included. For each patient, a PBS proton and VMAT photon plan was made in order to deliver 45 Gy in 25 fractions with comparable PTV coverage. For each patient, both plans were created on the original planning CT scan. When the plans were considered acceptable they were applied on two altered planning CT scans representing variations of the gas filling in the abdominal organs, i.e. the bowels and the gastric remnant. The dose distributions for both protons and photons from the original plan were recalculated on the two altered CT scans.

In the first altered scan, we simulated a situation in which no gas would be present in the treatment situation. All gas in the intestines and in the gastric remnant at the axial level of the PTV was delineated and the volume enclosed was set to replicate water, by setting the Hounsfield value (HU) to 0.

In the second CT scan, we simulated a situation in which more gas would be present in the abdomen. The previously delineated bowel gas was expanded with 1 cm in all directions. Areas expanding into the OARs and the thoracic wall were subtracted. The latter procedure was done in order to hinder the interchange of bony structures, i.e. ribs with air. The entire enclosed volume was then defined as gas by setting the HU value to -1000.

The mean gas volume on the planning CT scan and thus the volume of gas changed to water equivalent on the first altered CT was 370 cm³ (range 226-605 cm³) and the mean gas volume after expansion in the second altered CT scan was 743 cm³ (range 394-1051 cm³).

The substitution of air with water equivalent as well as the addition of extra air had only minor impact on the PTV/CTV coverage in VMAT planning. The change was larger when air was substituted with water, with PTV coverage dropping from 99% to 93% and from 99% to 94% in two patients.

However, in the proton plans, the registered shifts in PTV/CTV coverage were larger and clinically probably more significant. Due to the field arrangement and proton plan susceptibility to variation in tissue homogeneity, there was a shift of the high dose areas towards the ventral abdomen when air was substituted with water equivalent resulting in under dosage of the dorsal part of the PTV and higher dose in the bowel outside the PTV. Contrary, when extra air equivalent was added the shift of high dose areas was towards the dorsal/right abdomen resulting in under dosage of the ventral PTV and higher doses to the right kidney and liver. These variations were dependent on the initial volume of the gastrointestinal gas and its location in relation to the proton beams. The median PTV coverage with 95% of the prescribed dose dropped from 99% (range 98-99%) in the original plan to 91% (range 78-97%) when air was substituted with water equivalent and to 86% (range 58-98%) when the extra air equivalent was added. Similarly, the median CTV coverage with 95% of the prescribed dose changed from 100% to 97% (range 80-100%) and 91% (range 54-100%), respectively. However, in all cases, the sparing effect of protons was sustained or the dose to the OARs did not significantly exceed the dose delivered with the

corresponding photon VMAT-plans. The gas variations never resulted in doses exceeding the preset constraints for the OARs.

7 CONCLUSIONS AND FUTURE PERSPECTIVES

7.1 PAPER I

The results of the GATAC trial indicate that sequential administration of the two presented combinations is feasible and effective with similar median OS as for the commonly used, more toxic, ECF/EOX/TCF-combinations, which suggests that comparable efficacy can be obtained with less toxic regimens if given in a sequential fashion. Another observation is that in a small group of patients, with locally advanced tumors, at diagnosis considered non-resectable, tumor reduction was obtained to such a degree, that the patient could be reconsidered for surgery with a potentially curative intent. Furthermore, despite the generally poor prognosis of patients with metastatic gastric cancer, a subgroup of patients had a considerable gain in the form of durable PFS and overall survival. Our results are encouraging, meaning that sequential chemotherapy is a strategy well worth further investigation in the treatment of gastric cancer and other GI-malignancies. In this context, sequential chemotherapy, with comparable overall survival and low toxicity in comparison to triple drug combinations, is an attractive alternative. Furthermore, the results of the GATAC trial in combination with results of similar trials in other tumor sites, foremost in adjuvant breast cancer treatment, stress the question whether sequential treatment should be further explored as an alternative to intensified up-front treatment in patients with gastric cancer and other patient groups.

7.2 PAPER II

We found no significant change, positive or negative, in the average QoL during the treatment period compared to baseline in the GATAC study. There was, however, a trend for improved mean and median scores for global health and QoL during the treatment. This is of clinical importance as there was no evidence that the cytotoxic treatment had a negative impact on patients QoL for the entire patient population. However, patients with no radiological response had a decline in the global QoL score. This fact further stresses the question of decision making while recommending an appropriate treatment for patients with advanced gastric cancer. While making the choice of treatment regimes over time, consideration should be made to achieve an optimal response rate or longest possible PFS with limited toxicity and sustained QoL. Furthermore, due to the poor prognosis of these patients, many will not be candidates for second line treatment at the time of disease progression. In this context, our opinion is that further exploration of the prescheduled switch of therapy concept is of great interest in this disease.

7.3 PAPER III

Despite the inclusion of a CT-based delineation atlas in a clinical protocol, the inter physician variations were still large. The resulting clinical dose plans did not, however, show large differences in target coverage or doses to OARs. This relationship may perhaps become larger and potentially decisive for the clinical outcome, when new planning techniques, i.e.

VMAT or PT, are used. Increasing experience in delineation of upper abdominal targets, when combined with support by radiologists and well-defined clinical protocols, may hopefully lead to higher conformity between physicians in defining treatment targets for RT in this region. Our conclusion is that delineation atlases are of crucial importance in constructing future clinical study protocols and quality assurance.

7.4 PAPER IV

Our data suggest that scanned proton beam therapy in the upper abdomen has a potential for sparing of OARs, e.g. preserving kidney function, should be further evaluated in prospective controlled trials. The results of our study are comparable to previously reported data in comparisons of the doses to the OARs between photons and protons when large PTVs are treated in the lower thorax and abdomen. Few trials have reported on the effect of PT on the risk of treatment-induced secondary neoplasms when large PTVs are treated. This late side-effect of RT is, however, of growing significance in the context of increasing cure rates. The influence of RT on the risk of secondary tumors, alongside the OARs doses, should be considered when choosing the treatment technique. This is of importance foremost in individuals with high-risk of developing treatment-induced neoplasms, i.e. pediatric patients and young adults, but also for patients large irradiated target volumes.

7.5 PAPER V

The uncertainties in dose delivery, due to intestinal gas variations and breathing movement resulting in inhomogeneity, have often been used as an argument against the use of protons in the irradiation of tumors in the thorax and abdomen. As a result, in treatment planning for abdominal targets, the scattered proton technique has been dominating. The scattering technique does not, however, have the same magnitude of normal tissue sparing.

Proton treatment with pencil beam scanning, at this dose level, can be considered feasible from the organ sparing point of view. Nevertheless, the effects of the intestinal gas variations on the PTV and CTV coverage are large, stressing the necessity for an adaptive approach to proton treatment in the upper abdominal region. Today, the image guided (IGRT) based, “plan of the day” approach is applied at some proton centers. Other techniques for adaptive therapy are developing at a fast pace, i.e. online planning on daily imaging CT scans, suggesting that methods of handling these uncertainties can be resolved in the near future.

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