

Summary

Although the incidence of gastric cancer is decreasing, worldwide it is still the second most frequent cause of cancer death. Survival, as shown in surgical series from Europe and North-America, is significantly lower than in Asian countries. Therefore, several clinical trials have been performed to improve outcome. Studies that have evaluated these strategies will be shortly mentioned below, but are discussed in more detail in **chapter 1**. In this chapter the etiology, pathology, epidemiology, prevention, diagnosis and surgical treatment amongst other things are discussed too. From this chapter it emerges that postoperative chemoradiotherapy, as explored by the South-West Oncology group/Intergroup in a randomized phase III study, is a strategy that effects overall survival and disease-free survival beneficially. In an attempt to implement postoperative chemoradiotherapy based on the SWOG/Intergroup results in our own setting, we started a series of studies which combined radiotherapy with more intensive concurrent chemotherapy. It was hypothesized that the results of the SWOG/Intergroup study could be further improved using a more effective, intensified and convenient chemotherapy schedule. In **chapter 2**, a phase I-II trial is presented that was performed at the Netherlands Cancer Institute together with two centers from the UK. In this dose escalation study, the maximal tolerated dose (MTD) and toxicity profile of postoperative radiotherapy combined with concurrent capecitabine, an oral drug which mimics continuous 5-FU infusion, was determined. In this study, patients received capecitabine only for the first 2 weeks (1000 mg/m² bid) and then continued treatment with capecitabine (650-1000 mg/m² orally bid, 5 days/week) in a dose-escalation schedule combined with radiotherapy during weekdays for 5 weeks. 64 patients completed treatment as was planned. During chemoradiotherapy only 4 patients developed 4 items of grade III dose-limiting toxicity. The predefined highest dose of capecitabine 1000 mg/m² bid orally was tolerated well and therefore

considered safe for further clinical evaluation. At the same time in another study, the same radiotherapy regimen (45 Gy in 25 fractions) was combined concurrently with escalating daily doses of cisplatin (i.v.) and capecitabine (oral) in patients that had undergone curative surgery for gastric cancer (**chapter 3**). Patients started treatment with capecitabine (1000 mg/m² bid) only for two weeks. Subsequently, during radiotherapy, patients received capecitabine and cisplatin on a daily basis, according to an alternating dose-escalation schedule. In this study, 31 patients completed treatment and during chemoradiotherapy 8 patients developed 9 items of grade III and one episode of grade IV (mainly hematological) toxicity. The maximal tolerable dose (MTD) was 650 mg/m² capecitabine bid and 5 mg/m² cisplatin daily.

Because daily administration of cisplatin (i.v.) is logistically cumbersome for patients and institutions, the weekly application of cisplatin together with daily radiotherapy and capecitabine was also explored (**chapter 4**). In this study, after a capecitabine (1000 mg/m² bid) only period of 2 weeks, patients received capecitabine (575-650 mg/m² orally bid, 5 days/week) and cisplatin (20-25 mg/m² i.v., once weekly) according to a predefined dose-escalation schedule concurrent with radiation. Thirty-one patients were eligible and started treatment. During chemoradiotherapy 7 patients developed 10 items of grade III and one episode of grade IV (mainly hematological) toxicity. The maximum tolerable dose (MTD) was determined to be 20 mg/m² i.v. weekly for cisplatin and 575 mg/m² bid orally for capecitabine.

This dose regimen has subsequently been integrated in the experimental arm of the currently accruing phase III multicenter study (CRITICS; Clinicaltrials.gov NCT 00407186) that is initiated from several institutes in the Netherlands.

Although postoperative chemoradiotherapy seems to reduce local recurrence rates and improve survival of gastric cancer, several issues deserve further study, in particular data on late toxicity. Radiation-induced kidney damage has been recognized as one of the most important dose-limiting factors in upper abdominal radiotherapy. We and others have previously shown in gastric lymphoma that radiation induces a dose- and volume-dependent decrease in renal function which continues to decline over time and is associated with an enhanced risk of developing (renovascular) hypertension. In **chapter 5**, a prospective study, that included 44 patients who underwent postoperative chemoradiotherapy for gastric cancer, is presented, which demonstrates a progressive decrease in left renal function of 11% ($p=0.012$) after 6 months up to 52% ($p<0.001$) after >18 months. Although only one of the patients developed clinically manifest renal dysfunction, these findings illustrate the need for more sophisticated and precise radiotherapy techniques (e.g. 3D-conformal, IMRT, IGRT) in order to minimize renal toxicity.

Because of close proximity of critical organs like kidneys and liver to the clinical target volume (CTV) in gastric cancer radiotherapy, and because there is a need for a clear delineation protocol for this CTV in the multicenter phase III trial, we have developed a CT-based delineation atlas. In **chapter 6**, the interobserver variation between 10 institutions in CTV delineation of a single gastric cancer case is analyzed. As is already known from radiotherapy studies in head and neck cancer and prostate cancer, large variability was also demonstrated in the gastric cancer CTV volume, mainly at the caudal part.

In this thesis, three phase I-II studies are presented that have led to an intensified concurrent chemoradiotherapy regimen in postoperative treatment of gastric cancer. The exact benefit of this strategy is currently investigated in a randomized phase III

trial (CRITICS). Results of this study have to be awaited for some years. Meanwhile, in order to obtain an indication how these chemoradiotherapy regimens influence locoregional control and survival, a retrospective analysis of the first 115 patients that completed chemoradiotherapy and had adequate follow up at our institute was performed (**chapter 7**). These patients were compared to patients entered in the Dutch Gastric Cancer group D1 vs. D2 trial, which randomized between D1 (limited lymph node dissection) and D2 (extended lymph node dissection) surgery only. Patients who received postoperative chemoradiotherapy demonstrated a significantly better local control, but had similar survival as those who had been treated with surgery only. Furthermore, in patients who had long local control after chemoradiotherapy, uncommon distant metastatic disease relapses (e.g., brain) were found, which demonstrates that in gastric cancer too, an improved local control can influence the disease progression pattern. Peritoneal carcinomatosis was found more frequently after chemoradiotherapy, which probably reflects more intensive CT-based follow up in this group. Limited patient numbers in the cohort with chemoradiotherapy and short follow up, are probably the main reasons that this improved local control did not (yet) translate in improved overall survival.

CONCLUSIONS AND FUTURE

After publication of both the MAGIC and SWOG/Intergroup gastric cancer studies, which both demonstrated a survival benefit, the important question that needs to be answered is whether postoperative chemoradiotherapy has a role in the optimal treatment of operable gastric cancer. Therefore, accrual in a prospective randomized multicenter phase III trial addressing this question was started. An optimized

chemoradiotherapy schedule with radiosensitizing drugs cisplatin and capecitabine during the entire radiotherapy treatment has been based on the phase I-II studies, which are part of this thesis. In this thesis, late renal toxicity after postoperative gastric irradiation is presented as well, which stresses the need for the use of optimal 3D-conformal, Intensity-Modulated RadioTherapy (IMRT) or Image-Guided RadioTherapy (IGRT) in gastric cancer. Furthermore, continuous evaluation of delineation protocols is needed, because of large interobserver variability in target volume delineation as is demonstrated in this thesis. Studies, like the one presented in chapter 7, which compare recurrence patterns after chemoradiotherapy with those after surgery only, could achieve this. In the future, studies with clear delineation protocols and safe radiotherapy techniques should be evaluated on the effect on disease recurrence patterns. Adaptation of treatment modalities, like in surgical treatment, should only be based on these studies.

To improve patient selection and treatment tailoring, the value of genomics studies, biomarkers and validated prognostic and predictive tests, such as Maruyama Index and Memorial Sloan-Kettering Cancer Center nomogram for gastric cancer, should be explored. Better patient selection for more individualized (i.e. targeted) treatment could possibly be achieved by improved imaging modalities (PET; endosonography; MRI) and by gene signatures of tumor tissue. However, all steps leading to improved treatment outcome have first to be proven in well designed phase III randomized clinical studies.