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Radiation induced spleen changes

Radiation-induced dose-dependent changes of the spleen following postoperative chemoradiotherapy for gastric cancer

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ABSTRACT

Background and purpose: Abdominal (chemo-)radiotherapy is associated with dose-limiting toxicity of various normal structures. The purpose of this retrospective study was to investigate radiation-induced changes of the spleen and their clinical consequences.

Patients and methods: In gastric cancer patients treated with postoperative chemoradiotherapy, the spleen size and its functions were assessed at follow-up by spleen volume on CT-scan, serum leucocytes/thrombocytes, and the occurrence of infectious events consisting of pneumonia and fatal sepsis. To evaluate the effect of radiation dose, mixed effects and Cox regression models were used.

Results: Forty-six out of 90 consecutive patients treated from 2006 to 2011 were evaluable. All patients received 45 Gy in 25 fractions with concurrent capecitabine ($n = 8$), and capecitabine/cisplatin ($n = 38$). Median Dmean to the spleen was 40 Gy (range 32–46). Mean relative spleen volume reduced to 37% (95% CI 32–42%) at 4-year follow-up, which was most strongly associated to the V44 ($p < 0.001$). Median follow-up time was 67 (95% CI 57–78) months. Eleven patients had 13 pneumonias and 3 fatal sepsis. No association with dosimetric parameters was observed.

Conclusions: In postoperative chemoradiotherapy for gastric cancer, the spleen received a high radiation dose. This resulted in a progressive, radiation dose-dependent reduction of spleen volume. Pneumonia and fatal sepsis occurred frequently, possibly as a result of functional hyposplenia.

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Since 2001, postoperative chemoradiotherapy (CRT) is an evidence-based treatment option in patients with gastric cancer who have undergone a potentially curative resection [1,2]. In postoperative CRT for gastric cancer, the clinical target volume (CTV) encompasses the preoperative tumour extension, gastric bed/remnant, draining lymph node stations, and anastomoses [3]. This leads to large treatment volumes of the upper abdomen with external beam radiation therapy (EBRT). Consequently, surrounding organs receive irradiation as well that could potentially result in toxicity. In order to prevent or minimize toxicity, radiation dose constraints to the organ(s) at risk (OAR), such as the kidneys and liver, are applied [4,5]. The spleen, a hematopoietic organ, has not been acknowledged as OAR and consequently usually no radiation dose constraint is applied (Supplement). Nowadays, the importance of unique immunological and haematological functions of the spleen is better understood and therefore, the spleen should be reconsidered as OAR.

The major immunological and haematological functions of the spleen are: recognition and clearance of poorly opsonized encapsulated bacteria, and filtration of the blood to remove aged or damaged erythrocytes, respectively [6,7]. Although a reduced haematological function has been associated with an increase in vascular adverse events [7], this is beyond the scope of this study. Following surgical splenectomy or in case of functional hypo- or asplenia, patients are at an increased risk for overwhelming postsplenectomy infection (OPSI) by encapsulated bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitides* [6,8,9], but other bacterial and non-bacterial pathogens have been reported in this context as well [10]. Although the incidence of OPSI has been estimated around 2–5 per 1000 asplenic patients per year and the lifetime risk for OPSI is approximately 5% with the highest incidence within 2 years, the mortality rates are up to 50–70% [6,8,9]. Guidelines regarding prevention of fatal infection after surgical splenectomy or hypo- and asplenia have been implemented in clinical practice, and are effective in reducing the incidence and mortality of OPSI. These guidelines entail patient education, immunization against *S. pneumoniae*, *H. influenzae* type b, and *N. meningitides*,

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prophylactic antimicrobial therapy during the initial 2 years after splenectomy, and lifelong on-demand antimicrobial therapy [6,8,9].

Although it has been suggested that hyposplenia may occur after radiation of the spleen as well, it is actually largely unknown whether and to what extent the functions of the spleen are affected by irradiation [11–14]. The aim of our retrospective study was to investigate radiation-induced changes of the spleen as OAR, and its clinical consequences in gastric cancer patients treated with postoperative CRT.

Patients and methods

Patient selection and inclusion

For this retrospective study we selected all patients who were treated with postoperative CRT for gastric cancer in our institute between 2006 and 2011. Since 2006 intensity modulated radiation therapy (IMRT) has been standard practice at our institute. Adjuvant CRT was given within clinical trials [15–17]. Furthermore, this treatment has been advised for patients at increased risk of locoregional recurrence and for patients who had not been treated with preoperative chemotherapy. Patients were included if they had completed radiotherapy (RT) and at least one diagnostic CT-scan at follow-up. Patients were excluded if they had undergone surgical splenectomy, comorbidity associated with hyposplenia, or received vaccinations for encapsulated bacteria at any time.

Data collection

Data were collected from patient files and follow-up was completed until June 2014. Data collection at follow-up was discontinued when the patient developed a gastric cancer recurrence or any other type of malignancy, with the exception of scoring of infectious events. For this purpose, data collection was until the last visit or death.

Treatment schedules

Postoperatively, capecitabine (1000 mg/m^2 p.o. b.i.d.) monotherapy was administered for 2 weeks prior to the start of postoperative CRT, only if patients had not received preoperative chemotherapy. CRT consisted of EBRT to a total dose of 45 Gy in 25 fractions of 1.8 Gy, 5 times a week, and concurrent capecitabine (575 mg/m^2 p.o. b.i.d.) on all RT-days, with or without cisplatin (20–25 mg/m^2 i.v. weekly) on RT-days 1, 8, 15, 22 and 29. Preoperative chemotherapy consisted of 3 cycles of epirubicin, cisplatin/oxaliplatin, and capecitabine.

Radiotherapy

The CTV encompassed the preoperative tumour extension, gastric bed/remnant, draining lymph node stations, and anastomoses. The planning target volume (PTV) was constructed by expanding the CTV with 1 cm in all directions. Dose distributions were planned according to the International Commission on Radiation Units and Measurements recommendations, using Pinnacle (Philips Medical Systems, the Netherlands). Typical set-up was with 7 beams.

The following dose constraints were applied to OAR. Kidneys: <18 Gy to at least two-thirds of one kidney, liver: mean dose <30 Gy, spinal cord: maximum dose <45 Gy, and heart: <40 Gy to 30% of the cardiac silhouette. No dose constraints were applied to the spleen.

Dosimetric parameters and measurements of the spleen

The spleen was delineated on the RT-planning CT-scan using 5 mm slides (level: 46 HU, window: 300 HU). Subsequently, the corresponding dose distribution was retrieved to compute a dose–volume histogram (DVH) of the spleen. The following dosimetric parameters were derived from the DVH: Vx (relative volume that received $\geqslant x$ Gy in percentage) in steps of 1 Gy from V1–V50, EUD_n (equivalent uniform dose in Gy for n) in steps of 0.05 from $EUD_{0.01}$–EUD_{10}, of which EUD_1 represents Dmean (mean dose in Gy) [18]. The physical radiation dose could not be converted to the EQD_2, because the α/β of the spleen is unknown.

To investigate changes in the organ-size of the spleen (normal volume 100–400 cc) [19–21], the spleen volume was delineated on all available diagnostic CT-scans during follow-up (5 mm slides, level: 46 HU, window: 300 HU). To investigate changes in the function of the spleen, we assessed the number of serum leucocytes and thrombocytes, and the occurrence of infectious events at follow-up. Leucocytes (normal value 4.0–10.5 10^9/l) and thrombocytes (normal value 150–400 10^9/l) were collected before CRT, 6 months and yearly after CRT. An infectious event was defined as the occurrence of any pneumonia and/or fatal sepsis (clinical diagnosis). Measurements were excluded from analysis if another cause of alteration was present at that time.

Statistical analysis

Correlations between dosimetric parameters were assessed using nonparametric Spearman correlation coefficient. The spleen volume on the RT-planning CT-scan, and the leucocytes and thrombocytes before CRT were used as baseline value. The median time from baseline until the last available measurement was calculated. Median follow-up time until the last visit or death was estimated from the end of RT by the Kaplan–Meier method. For the analysis of changes in spleen volume, leucocytes and thrombocytes over time, a model for correlated data had to be applied. Due to unequal spacing of measurements at follow-up as well as substantial drop-out, a mixed effects model was applied. The incidence rate of pneumonia and the mortality rate of sepsis were calculated per 1000 person-years. The Kaplan–Meier method and Cox regression models were used to evaluate the occurrence of infectious events over time. We investigated the association of longitudinal and time to event outcomes in all models with V20–V47 and $EUD_{0.01-10}$. The following confounders were explored in all models: age, cardiovascular comorbidity, preoperative chemotherapy, and dissection of the vasa brevia during gastrectomy. *P*-values below 0.05 were considered statistically significant. The analysis was performed using R software (R version 2.14.2) and SPSS (version 20).

Results

Forty-six out of 90 consecutive patients were evaluable for this study (Fig. 1). All included patients completed RT as planned (Table 1).

Variation in the DVH was present at V20–V47 (Fig. 2). Almost half of the patients (46%) received at least 20 Gy to 100% of the spleen volume. The median Dmean was 40 Gy (range 32–46 Gy). The dosimetric parameters were highly correlated with each other (data not shown).

A median of 5.5 (range 2–10) spleen volume measurements was available per patient for analysis (6 scans were excluded). Median time from baseline to the last measurement was 28 (range 2–91) months. The model-based mean (95% CI) spleen volume decreased from 201 cc (173–234 cc) at baseline to 82 cc (67–102 cc) at 4 years ($p < 0.001$, Fig. 3A), corresponding to a relative spleen volume of 37% (95% CI 32–42%, $p < 0.001$). None of the confounders