Treatment of Hepatic Metastases from Gastric or Gastroesophageal Adenocarcinoma with Computed Tomography-guided High-dose-rate Brachytherapy (CT-HDRBT)

DOMINIK GEISEL1, TIMM DENECKE1, FEDERICO COLLETTINI1, CHRISTIAN GRIESER1, PETER WUST2, PETER THUSS-PATIENCE3, BERND HAMM1 and BERNHARD GEBAUER1

Departments of 1Diagnostic and Interventional Radiology, 2Radiation Oncology and 3Hematology, Oncology and Tumorimmunology, Charité, Campus Virchow-Klinikum, Berlin, Germany

Abstract. Background: This retrospective analysis was performed to evaluate the clinical outcome of patients with hepatic metastases from gastric or gastroesophageal adenocarcinoma who were treated with computed tomography-guided high-dose-rate brachytherapy (CT-HDRBT). Patients and Methods: Eight patients with a total number of 12 isolated hepatic metastases from histologically-proven adenocarcinoma of the lower oesophagus or stomach, were treated with CT-HDRBT. Gadoteric acid-enhanced magnetic resonance imaging (MRI) was performed 6 and 12 weeks after CT-HDRBT and then every 3 months to evaluate treatment efficacy. Results: The median follow-up time was 6.1±6.8 months. Lesion size ranged from 14 to 68 mm in diameter with a median of 46±21 mm. No patient developed a local recurrence. Five patients developed systemic progression after a median time of 3.7±3.6 months (three in the liver, one in liver and bone and one in liver and resection margin from gastrectomy). One patient died 3.4 months after CT-HDRBR because of liver progression with cholestasis. No major complications associated with the treatment occurred. Conclusion: CT-HDRBT might be a feasible alternative to surgical resection of liver metastases from gastric or gastroesophageal adenocarcinoma in selected patients and seems to have similar outcome rates as surgical resection in our small collective.

Gastric cancer is the fourth most frequent cancer worldwide and the second most common cause of cancer-related mortality, with approximately 737,000 deaths per year. Esophageal cancer ranks eighth in worldwide incidence and sixth in mortality with 407,000 deaths per year (1, 2). Adenocarcinoma of the lower esophagus is often subsumed with gastric adenocarcinoma because of several similarities (3). About two thirds of all patients with this disease have locally-advanced primary tumour or metastases at the time of diagnosis and even after potentially curative resection the majority of patients develop recurrent locoregional or distant metastatic disease (2, 4). Liver metastases are seen in 3.7 to 11% of patients with gastric cancer (5-7). Without treatment, the survival of patients with metastatic gastric cancer is extremely poor with a median survival of three to five months (8). Palliative chemotherapy is primarily used in inoperable patients and prolongs the median survival time to approximately eleven months, which may be further improved by anti-HER-2-directed treatment and second-line chemotherapy (9, 10). Surgery is a possible chance of cure in patients with metastases from gastrointestinal cancers and liver resection (11). In contrast to the broad use of liver resection in the treatment of hepatic metastases from colorectal cancer, treatment of liver metastases from gastric cancer is rarely performed. There are only a few studies concerning this issue, most of them from Japan (5, 6, 12-14). The results of these studies differ and therefore, the value of surgical treatment of metastatic gastroesophageal cancer remains controversial. For local-ablative treatments, the available number of studies is even smaller. To our knowledge, there is only one study which examined the effect of local ablation (radiofrequency ablation, RFA) of liver metastasis from gastric adenocarcinomas in four patients (15).

Local-ablative techniques such as radiofrequency ablation (RFA) are an emerging part of a multimodal tumour therapy for liver malignancies such as hepatocellular carcinoma,
Cholangiocarcinoma and colorectal liver metastases (16-18). Computed tomography (CT)-guided high-dose-rate brachytherapy (CT-HDRBT) is a new therapy option that has been shown to be an effective treatment for different types of primary and secondary liver malignancies (19-25). It uses an iridium-192 source that is introduced into the tumour during the irradiation using a catheter which is placed using CT guidance. With this method, high tumor-enclosing doses, typically 20 Gy at the tumour margin with much higher doses in the center, can be applied to the tumour in one session. CT-HDRBT is not affected by local cooling effects and thus allows the more intense irradiation of lesions next to vessels or bile ducts.

The purpose of this study was to retrospectively analyze safety and outcome for all patients who underwent CT-HDRBT for liver metastases from gastric or gastroesophageal adenocarcinoma in our departments.

Patients and Methods

In this retrospective analysis, we included all consecutive patients with liver metastasis from histologically-proven gastric or gastroesophageal adenocarcinoma treated by CT-HDRBT between January 2008 and December 2011 at our institution. Following our standards, all patients were presented and discussed in an interdisciplinary tumour conference where the indication for local ablation was discussed. Other criteria for performing the procedure were liver function status of Child-Pugh A or B, bilirubin <2 mg/dl, platelet count >50,000/µl, Quick value (prothrombin time) >50%, and partial thromboplastin time <50 s. If indicated, haemostatic function was improved (e.g. platelet transfusion) (26).

Interventional technique. Percutaneous intratumoural catheter implantation was performed under local anaesthesia (lidocaine), sedation (midazolam) and analgesia (fentanyl). A recent (<4 weeks) gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced MRI was used for planning the intervention. Under CT-fluoroscopic guidance, a 17-G trocar puncture needle was placed into the metastasis and exchanged for a flexible 6-F catheter sheath (Radiofocus, Terumo™, Tokyo, Japan) over a stiff angiographic guide wire (Amplatz, Boston Scientific, Boston, MA, USA) using the Seldinger’s technique. Subsequently, the angiographic guide wire was removed and a closed-end 6-F afterloading catheter (Primed™, Halberstadt Medizintechnik GmbH Halberstadt, Germany) was introduced into the sheath. Depending on tumour size and location, multiple afterloading catheters per target lesion were placed. Upon completion of catheter placement, non-enhanced or contrast-enhanced CT of the liver was acquired to verify the correct catheter positioning within the tumour and to acquire images for exact 3-D treatment planning. Computer-based 3D treatment planning was performed using the afterloading planning software BrachyVision™ (Gammamed™; Varian, Palo Alto, CA, USA). The clinical target volume (CTV) and all potential risk structures were marked by an experienced radiologist. Source dwell points and times for the iridium-192 source inside the afterloading catheters were calculated semi-automatically to ensure full coverage of the target volume while at the same time sparing out risk structures (Figure 1). Irradiations were performed as single-fraction irradiations using an iridium-192 source. The minimum dose to cover the CTV was 15 Gy. Maximum doses >50 Gy were allowed in the tumour centre. After irradiation, the afterloading catheters were carefully removed and the puncture tracts were sealed with resorbable, thrombogenic material (Gelfoam, Pfizer Inc., NY, USA) to prevent post-interventional bleeding.

Follow-up. Gd-EOB-DTPA (Primovist®/Eovist®, Bayer Pharma, Leverkusen, Germany)-enhanced MRI was performed twice within 6-8 weeks and after that every three months after treatment to evaluate treatment efficacy (Figure 2). Irradiation with more than 10 Gy leads to a reduced uptake of the hepatocyte-specific contrast agent by the hepatocytes; this effect was used to assess complete enclosure of the tumour, which was considered reached when gadoxetic acid-enhanced MRI showed a hypointense rim around the treated tumour. An increase in size or enhancement, as well as any new nodular growth within the ablation area was considered as local progression. In cases with local tumour progression eligible for repetitive local ablation, patients underwent repetitive brachytherapy to provide assisted local tumour control. Distant progression was defined as any tumour progression and/or any newly-occurring tumour manifestation beyond the liver or within the liver at sites other than the ablation zone (27).

Statistical analysis. Statistical analysis was performed using PASW Statistics 20 (IBM, Armonk, NY, USA). Influence on patient survival by complicating factors was compared using the Chi-square test. All quantitative data are expressed as the mean±standard deviation, unless otherwise indicated. Univariate survival analysis was performed using the Kaplan Meier method.

Results

Patients. During the interval from January 2008 to December 2011, eight patients with a total number of 12 isolated hepatic metastases from histologically-proven gastric or gastroesophageal adenocarcinoma (six gastric, two gastroesophageal) were treated with CT-HDRBT at our Institution for minimally-invasive local tumour-ablation. A total of 10 treatment sessions was necessary to treat all lesions. Six patients were completely treated after one session. In two patients, the ablation was split into two sessions within four to six weeks to preserve good liver function because of large tumour volume in relation to the remaining liver tissue.

The median patient age was 68±9 years (range 60-82 years). Five patients underwent gastrectomy or resection of the lower esophagus before CT-HDRBT. The mean time between the primary operation and CT-HDRBT was 95±86.3 months (range 6-212 months). Two patients had synchronous liver metastases, the others had metachronous metastases. Three patients still had their primary tumour which was considered as less life-limiting than their hepatic metastasis. No patient had been previously treated with other local-ablative methods such as RFA. All patients had undergone palliative chemotherapy before CT-HDRBT (Table I).

Treatment parameters. The median diameter of the metastases was 46±21 mm (range 14-68 mm). An average of 2.3±1.3 (range 1-5) ablation catheters were used during one session.
The target dose was 20 Gy for the tumour volume in five patients and 15 Gy in three patients. For the patients with 20 Gy target dose an average of 99.9\(\pm\)0.1\% of the tumour volume was irradiated with this dose, in patients with 15 Gy target dose these values were 91.8\(\pm\)8.3 percent. No adjacent structures were irradiated in excess of the critical values. One patient developed a perihepatic haematoma which was detected by ultrasound follow-up the next day. The haematoma required no further treatment and did not cause any symptoms. Post-interventional pain was sufficiently treated with ibuprofen or metamizole in all patients. No treatment-related infections were noted. The median hospital stay was 3.1\(\pm\)0.4 days.

**Follow-up and clinical outcome.** In the first follow-up Gd-EOB-DTPA-enhanced MRI six weeks after CT-HDRBT, complete enclosure of the tumour was found in all patients. The median follow-up time for the patients was 6.1\(\pm\)6.8 months. Five patients developed systemic progression after a mean time of 3.7\(\pm\)3.6 months (three liver, one liver and bone, one liver and resection margin from gastrectomy) (Figure 3). One patient died during the follow-up period 3.4 months after CT-HDRBT because of distant hepatic progression with obstructive cholestasis (Figure 4). The median progression-free survival was 3.5\(\pm\)6.3 months. Exploratory univariate analysis revealed that neither the appearance of liver metastasis (synchronous vs. metachronous) nor the distribution of liver metastases (unilobar vs. bilobar), the diameter of the metastasis or the primary tumor site (proximal vs. distal) were significant predictive factors regarding overall disease-free survival in our patients.

**Discussion**

Hepatic metastases are one of the most frequent site for metastases of gastric or gastroesophageal adenocarcinoma, the reported percentages range from 3.7\% to 11\% (15, 28-30). Often there are additional factors that worsen the prognosis such as involvement of both liver lobes, peritoneal carcinosis, lymph node metastases or invasion of adjacent organs (30, 31). Consequently the rate of hepatic resection only ranges from 0.5\% to 2.3\% of patients (11, 28, 30, 32-34). Survival rates after hepatic resection vary greatly ranging from 8.8 to 34 months; 5-year survival was 26.5\% in a meta-analysis, but there are several studies which report that patients may benefit from hepatic resection with improved survival (11, 29, 32, 35). Zacherl et al. reported that curative resection might even allow for long-term survival of selected patients (32). Survival for patients with metachronous hepatic metastases is better than that of these with synchronous metastases (74.3 months vs. 13.0 months) (36). One drawback of surgical management is the higher mortality and morbidity of hepatic resection; older studies report up to 26.7\% major complications and 3.5\% in-hospital mortality rate (32, 34).

There are only few studies investigating the use of local ablative techniques for gastric or gastroesophageal adenocarcinoma. For RFA-alone, there are only case-based reports of up to four patients (15, 37), for the combination with arterial chemotherapy there is one study with seven patients and one case report (15, 38). The larger study combining arterial chemotherapy with RFA reported a median survival time of 16.5 months, although they only included patients without extrahepatic metastasis (39).
Our results suggest that CT-HDRBT can lead to a convincing local treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma. No patient experienced local progression 8.4±6.8 months after CT-HDRBT. Distant progression seems to be the limiting factor for survival. It can be hypothesized that treatment of hepatic metastases by CT-HDRBT can improve overall survival of selected patients the same way surgical resection can. Patients without extrahepatic manifestations and metachronous metastasis seem to be ideal candidates. The advantage of CT-HDRBT in contrast to RFA is the ability to treat large tumour masses and its immunity to local cooling effects of vessels, which can lead to incomplete local ablation and consequent local recurrence. Using 3-D planning in CT datasets, radiation exposure to surrounding organs and tissues can be optimally controlled, maximum tolerable doses can be maintained and treatment of large tumour masses can be split into multiple sessions.

In our series of eight patients, we had one minor complication (40). One patient developed a perihepatic haematoma, which required no further treatment and did not cause any symptoms. Treatment-associated morbidity and mortality seems to be far better than that for surgical resection based on our experience for gastric and gastroesophageal metastases. Combined with our experience of other hepatic metastases, the superiority in treatment-related complications is even more obvious (20-22, 25, 41-43). Patients generally tolerate the treatment well and can be discharged 48 h after treatment. The hospital stay is necessary because of the risk of occult intra-abdominal bleeding. Post-interventional pain can be treated with simple analgesics. There were no systemic side-effects of the treatment. This makes CT-HDRBT suitable for patients who are surgically- or medically-irresectable, similar to our published results for hepatic cellular carcinoma or intrahepatic cholangiocarcinoma (20, 21).

Figure 2. Gd-EOB-DTPA-enhanced MRI of a 69-year-old patient with metastasis from esophageal adenocarcinoma of up to 7 cm in diameter before CT-HDRBT (a). The tumour was treated by CT-HDRBT using five brachytherapy catheters with a tumour-surrounding isodose of 20 Gy. Eight weeks after CT-HDRBT, the tumour shows size reduction with a surrounding area of reduced liver function, which can be seen by a lowered Gd-EOB-DTPA enhancement (b). Six months (c) and 12 months (d) after CT-HDRBT, the tumour shows further size reduction, no local recurrence was found.
A limitation of our study is the low number of patients, but as already outlined, surgical or local-ablative treatment of liver metastases from gastric or gastroesophageal carcinoma remains rare and operable patients are generally referred for surgical resection prior to CT-HDRBT.

In our opinion, CT-HDRBT might be a feasible alternative to surgical resection for patients with liver metastases from gastric or gastroesophageal adenocarcinoma. Patients with no extrahepatic manifestations and metachronous metastases seem to have the greatest improvement in survival. A study of these selected patients comparing the survival following CT-HDRBT with hepatic resection should be conducted.

Acknowledgements

Special thanks to Mrs. Marianne Geister for patient management.

References