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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Treatment of metastatic gastric adenocarcinoma with image-guided high-dose rate, interstitial brachytherapy as second-line or salvage therapy

Jazan Omari
Ralph Drewes
Max Othmer
Peter Hass
Maciej Pech
Maciej Powerski

PURPOSE
We aimed to evaluate the safety and effectiveness of image-guided high-dose rate interstitial brachytherapy (iBT) for the treatment of patients with hepatic, lymphatic, and pancreatic metastases originating from gastric cancer, an entity rarely surgically treatable with curative intent.

METHODS
Twelve patients with a cumulative number of 36 metastases (29 liver, 2 pancreatic, 5 lymph node) from histologically proven gastric adenocarcinoma received iBT between 2010 and 2016 and were retrospectively analyzed. Every patient underwent palliative chemotherapy prior to iBT. The iBT procedure employs a temporarily, intratumorally placed iridium-192 source in a single fraction with the goal of tumor cell eradication. Effectiveness was assessed clinically and by radiologic imaging every three months.

RESULTS
Local tumor control was achieved in 32 of all treated metastases (89%). Four lesions showed a local recurrence after 7 months. Lesion sizes varied from 9 to 102 mm with a median of 20 mm. The median progression-free survival was 6.6 months (range, 1.8–46.8 months). The median overall survival was 11.4 months (range, 5–47 months). One patient suffered a major complication following iBT, hepatic hematoma and abscess (Common Terminology Criteria for Adverse Events grade 3), successfully dealt with by transcutaneous drainage.

CONCLUSION
iBT is an overall safe procedure, which facilitates high rates of local tumor control in treatment of metastatic gastric adenocarcinoma. Compared with surgical metastasectomy, similar overall survival rates could be achieved in our patient collective after iBT application.

Although a constant decline of general gastric cancer incidence has been observed in the past decades, which is assumed to be the result of higher standards in hygiene, nutrition, and *Helicobacter pylori* eradication, this disease still remains the second cause of cancer-related death of all malignancies worldwide (1, 2). The incidence of advanced stage diagnoses has risen in the past 20 years and gastric cancer detected at a stage >T1N0 has a poor prognosis; about two-thirds of all patients already have an advanced primary tumor or even present with metastases at the time of diagnosis (2). During the course of the disease the incidence of hepatic metastases varies between 30% and 50% in Western Europe (3, 4). At the time of diagnosis 4%–14% of patients have metastatic liver manifestations and evidence of distant metastases in general is found in 35% of patients (5, 6). Metachronous metastases after execution of curative gastrectomy are observed in up to 25%–30% of patients, 80% of which emerge within the first two postoperative years. Surgical resection with D2 lymphadenectomy remains the gold standard in gastric cancer therapy with curative intention (7). Median survival in cases of metastatic gastric cancer without treatment is reported to be around 3–5 months (8). Palliative chemotherapy can improve survival to about 11 months, with application of anti HER2 treatment and second-line chemotherapy up to 13 months (9).

Surgical treatment is rarely performed in metastatic disease due to lack of evidence of increased survival time; randomized prospective studies such as the Renaissance / FLOT 5

From the Department of Radiology and Nuclear Medicine (J.O., R.D. ✉ *ralph.drewes@med.ovgu.de*, M.O., P.H., M.Pech, M.Powerski), Otto-von-Guericke University School of Medicine, Magdeburg, Germany; Department of Radiology (M.Pech) Gdansk University School of Medicine, Gdansk, Poland.

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study and the GASTRIPEC study will have to demonstrate the value of aggressive surgical therapy. The AIO-FLOT3 study, although not randomized, as well as several retrospective studies already indicated improved survival in surgically treated oligometastatic gastric cancer (10). A recently published systematic review and meta-analysis of 39 studies and 991 patients by Markar et al. (11) also concluded a significantly prolonged survival in surgically treated liver metastasis. The European Society for Medical Oncology (ESMO) guidelines currently do not recommend resection in a metastatic disease stage (12).

Very few studies evaluate the significance of local-ablative measures like radiofrequency ablation (RFA) or iBT concerning liver metastasis of gastric adenocarcinoma (13–15). Retrospective studies suggest similar improvements in median survival comparing RFA and surgical treatment (13, 14). One study by Geisel et al. examines the use of iBT for treatment of hepatic metastases from gastric or gastroesophageal adenocarcinoma in 8 patients (16). The main limitation of those studies is the low number of patients.

The effectiveness of iBT has been demonstrated for different carcinoma entities or types of primary and secondary liver malignancies by several investigators (17–20). A major advantage of iBT is its wide range of applicability in almost every imaginable site/organ like pancreas, lymph nodes, adrenal glands, lungs and so on, as demonstrated by researchers like Mohnike et al. and Wieners et al. (21, 22). One or several catheters are placed into the target lesion and an iridium-192 source is installed for the single fraction irradiation. During iBT, a method which has fewer restrictions than thermal ablation measures like RFA, the typical high tumor enclosing reference dose of 20 Gy is applied at the tumor margin and even higher doses at the tumor center to destruct vital tumor cells.

The purpose of this retrospective study was to evaluate the safety and effectiveness of iBT concerning treatment of metastases from advanced stage gastric cancer.

Main points

- Overall survival of metastatic gastric adenocarcinoma is poor and treatment is challenging.
- No treatment consensus has been reached for metastatic gastric cancer.
- Both gastrectomy and metastasectomy are considered experimental in metastatic disease from gastric cancer, as prospective, randomized data are still lacking.
- Interstitial, image-guided brachytherapy (iBT) presents an alternative, overall safe treatment option to inactivate metastatic tumor cells by DNA and RNA damage.
- In selected patients, iBT enables high rates of local tumor control and facilitates prolonged survival in second-line and salvage treatment settings.

Methods

Study design and eligibility criteria

The primary endpoint of this retrospective study was local tumor control; the secondary endpoint was the overall safety of the local ablation method iBT. An interdisciplinary consensus comprised of oncologists, visceral surgeons and interventional radiologists established the indication for iBT in each individual case. The inclusion criteria were determined to be as follows: 1) resection deemed unfavorable due to accessibility, risk/invasiveness, comorbidities and the corresponding ramifications concerning preservation of liver function and tissue due to security margins; 2) adequate coagulation (thrombocytes >50000/nL, prothrombin >50%, partial thromboplastin time <50 s) and liver (bilirubin <30 µmol/L) parameters; 3) oligometastatic disease (≤5 metastases upon initial presentation) and no disseminated metastases; 4) lack of patient consent for surgery. Exclusion criteria were an extensive and uncontrollable tumor spread and peritoneal carcinomatosis in particular. All patients have given their informed consent to participate in the study. The study has been approved by the local ethics committee.

Interventional technique and irradiation

Prior to the scheduled intervention with iBT, a whole-body contrast-enhanced computed tomography (CT) examination and in case of liver metastases an additional gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gb-EOB-DTPA) enhanced magnetic resonance imaging (MRI) was acquired for planning and re-staging purposes. Furthermore, every patient had to pass a thorough clinical check-up and a physical examination; current laboratory parameters were needed as well, before the go-ahead was ultimately given.

Following local anesthesia (lidocaine), peri-interventional sedation (midazolam) and analgesia (fentanyl) adapted to individual discomfort or pain level each patient had to endure during the intervention, one or several percutaneous catheters were implanted intratumorally into the target lesion. Puncture of the lesions was performed using an 18-gauge needle under CT-fluoroscopic guidance (Toshiba). Afterwards, the puncture needle was exchanged for an angiographic sheath of 6 F diameter (Radiofocus, Terumo), inserted over a stiff angiographic guidewire (Amplatz, Boston Scientific). Ultimately, 6 F brachytherapy catheters (Afterloadingkatheter, Primed Medizintechnik Gmbh) were placed in the sheaths – fixation was achieved by transient cutaneous sutures.

For further treatment planning purposes as well as for verification of correct catheter positioning, a contrast-enhanced CT in breath-holding technique or MRI scan was required and obtained. The executing interventional radiologist highlighted the target volume and lesion at risk on the newly acquired images. The HDR afterloading system (Nucletron, Elekta Ab) applied an iridium-192 source with an activity of 10 ci, installed as a single fraction irradiation.

Irradiation design and dosimetric analysis

The detailed treatment strategy was devised using the corresponding software system Oncentra (Nucletron, Elekta AB), which is an integral part of the HDR-afterloading system. After the target volume had been labeled by the interventional radiologist in every CT/MRI slice, the three-dimensional coordinates (x, y, z) of each catheter, i.e., the tip and exit at the tumor margin, were determined and transferred into the planning system. Each boundary of the target lesion was established individually for every installed catheter by specification of the distance to the reference points. The lesion/tumor enclosing reference dose, based on empiric data from prior studies, was 20 Gy installed in a single fraction and enabling a safety margin of 5 mm, i.e., the clinical target volume (Fig. 1). The specified set of reference points was used in the anatomic optimization routine of the planning software. Empiric dose limitations were taken into consideration concerning treatment of lesions in close proximity of organs at risk such as the proximal gastrointestinal system (<14 Gy/mL) (23).

During catheter removal, gelfoam or fibrin tissue glue was injected through each brachytherapy sheath to prevent post-interventional bleeding.

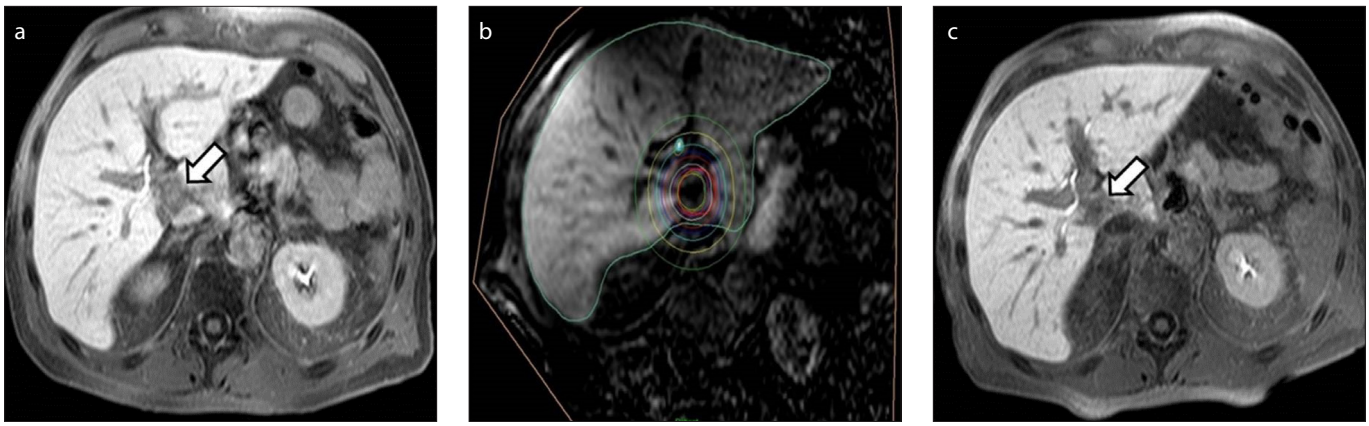

Figure 1. a–c. Local tumor control in a patient with metastatic gastric adenocarcinoma. Axial Gd-EOB-DTPA enhanced T1-weighted image **(a)** shows metastasis from gastric adenocarcinoma prior to treatment with iBT *(white arrow)*; axial Gd-EOB-DTPA enhanced T1-weighted image **(b)** shows treatment planning with marked target lesion *(red line)*, isodose lines (indicates 20 Gy) and the brachytherapy catheter *(white arrow)*; axial Gd-EOB-DTPA enhanced T1-weighted image **(c)** at 3-month follow-up shows local control of treated lesion with new Gd-EOB-DTPA enhancement defect *(white arrow)*.

Table. Patient characteristics

Total number of patients, n	12
Men	10
Women	2
Age at time of diagnosis (years)	
Median	63
Min–max	51–71
Metastases (cumulative), n	36
Liver	29
Pancreatic	5
Lymph node	2
Type of metastatic spread	
Synchronous	4
Metachronous	8
Lesion size (cm)	
Median (Q_1–Q_3)	2 (1.4–3.6)
Min–max	1–10.2
Irradiation dose iBT (Gy)	
Median (Q_1–Q_3)	19.9 (12.9–.3)
Min–max	5.4–22.5
Irradiation time iBT (min)	
Median (Q_1–Q_3)	23.6 (16.1–.4)
Min–max	4-73
Number of catheters / lesion	
Median	2
Min–max	1–8
Local tumor control	32 (89%)
Progression-free survival (months)	
Median (Q_1–Q_3)	6.6±1.63 (3.4–10)
Min–max	1.8–46.8
95% CI	1.7–11.3
Mean	9.5±3.52

Follow-up

Whole body CT and MRI of the liver as well as clinical assessments were performed every 3 months after brachytherapy. Every patient with hepatic tumor involvement received a Gd-EOB-DTPA (Primovist) liver MRI. Changes in size and enhancement defects were correlated in a dynamic T1-weighted gradient echo sequence, diffusion-weighted imaging (DWI), post-Gd-EOB-DTPA and a T2-weighted sequence. Tumor edema was visualized in a T2-weighted sequence, vital tumor tissue in DWI and late enhancement (post-radiation) defects in the post-Gd-EOB-DTPA sequence and the dynamic sequence. Recurrence or local tumor control measurements were ultimately made in the DWI to account for vital tumor tissue and to differentiate from late enhancement defects.

Adverse events associated with the local therapy were defined according to the "Common Terminology for Adverse Events" (CTCAE) version 4.03 and the guidelines of the Society of Interventional Radiology (24). Indicators and prognostic factors of radiation induced liver disease (RILD) were the occurrence of ascites and elevated alkaline phosphatase levels or a serum bilirubin level ≥3 mg/dL in the absence of bile duct obstruction and tumor progression (25).

Definitions of remission criteria and local tumor control rates (primary endpoint)

The Response Evaluation Criteria in Solid Tumors Criteria (RECIST 1.1) categories of stable disease, partial remission, and complete remission of the treated lesions were defined as local tumor control after iBT. Progressive disease was determined as an increase in diameter >20% of any metastatic lesion.

Table. Patient characteristics (cont'd)	
Overall survival after iBT (months)	
Median	11.4±3.37(%95 CI)
Min–max (Q_1–Q_3)	4.3–47 (6.9–22.5)
95% CI	2.7–17.1
Mean	15.3±3.47(%95 CI)
Overall survival from time of diagnosis (month)	
Median	33.5
Min–max	14–86 (21.5–55.3)
Previous treatment (before iBT), n (%)	
Palliative chemotherapy	12 (100)
Resection	9 (75)
Immunotherapy	3 (25)
Selective internal radiotherapy	1
iBT image guidance	
CT	24
MRI	12
Time of hospitalization (days)	
Median	4
Min–max	3–6

Q_1–Q_3, interquartile range; 95% CI, 95% confidence interval; iBT, image guided, high-dose-rate, interstitial brachytherapy; CT, computed tomography; MRI, magnetic resonance imaging.

Statistical analysis

The primary objectives of the retrospective, single arm study were local tumor control as well as the overall safety of the iBT procedure. Overall survival and the progression-free survival were secondary objectives. Local tumor control, progression-free survival and overall survival were evaluated by employment of the Kaplan-Meier method with SPSS version 22 (SPSS, version 22.0; IBM Corp.).

Results

Between 2010 and 2016 twelve patients with histologically proven gastric adenocarcinoma, having a cumulative overall amount of 36 metastases (29 liver, 2 pancreatic, 5 lymph node) from gastric adenocarcinoma treated with iBT in our department, were included in this retrospective study (Table). At the time of referral to our institution, the metastatic gastric cancer of every patient was deemed to be in an advanced and progressive stage in the last routine follow-up staging CT. The indication for iBT, discussed in an interdisciplinary tumor board, was progressive disease, i.e., metastases showing size progression under systemic chemotherapy. The quantity of metastases upon initial referral to our institution varied from 1 to 5. The iBT procedure was in some cases applied repeatedly in separate sessions either to treat several existing lesions or newly developed metastases elsewhere.

The median patient age was 63 years (range, 51–71 years). Eleven patients had hepatic iBT treatment: 7 patients had metachronous, 4 patients had synchronous liver metastases. One patient had 2 pancreatic metastases, and another had simultaneous liver and 5 lymph node metastases, treated with iBT respectively. Prior to local ablation therapy every patient underwent palliative first-line chemotherapy with doublet or triplet regimens based on cisplatin and 5-FU. The time interval between the last chemotherapy and the iBT treatment (following the tumor board indication) was 4 weeks.

Nine patients had gastric surgery before local tumor ablation. Anti-HER-2 directed treatment was administered in 3 cases. Selective internal radiotherapy (SIRT) was performed in one case.

Five patients received additional treatment after local therapy before disease progress: three cases had another cycle of chemotherapy, one case had primary resection, and one case had immunotherapy.

The median tumor diameter was 2 cm (range, 1–10.2 cm). A median of 2 ablation catheters (range, 1–8) were used during one iBT. CT guidance was used in 24 interventions, MRI in 12. The prescribed minimal tumor dose was 20 Gy, which had to be lowered in some cases due to adjacent risk structures; a median irradiation dose of 19.9 Gy (range, 5.4–22 Gy) was applied. The total irradiation time ranged between 4 and 73 min, with a median of 23.6 min. The time of hospitalization varied between a minimum of 3 and a maximum of 6 days. One patient suffered a major complication (grade 3) and developed an infected, hepatic hematoma that was successfully treated with transcutaneous drainage and antibiotics. Three patients received antibiotics before brachytherapy as a precaution due to cholestasis; none of them had any complication.

The localization of the 36 treated metastases from gastric adenocarcinoma was: 29 liver, 2 pancreatic, 5 lymph nodes (retroperitoneal). A cumulative number of 4 local relapses (2 hepatic, 1 lymph node, 1 pancreatic) were observed.

The specifics of the 4 local relapses, which occurred during follow-up are as follows (the given Gy values are the D99,9 tumor enclosing doses): one pancreatic metastasis with a maximum diameter of 4.5 cm was irradiated with only 5.4 Gy (2 catheters used) due to proximity of risk structures (small bowel) – the recurrence occurred 6 months later; one hepatic lesion with a maximum diameter of 5.3 cm showed no local tumor control after an irradiation dose of 16.3 Gy (7 catheters used) and a recurrence was observed after 8 months; another hepatic lesion in a different patient with a maximum diameter of 3.4 cm was irradiated with 19.69 Gy (3 catheters used) and showed a recurrence after 16 months, one lymph node with a maximum diameter of 1.6 cm in the same patient could be irradiated with only 6.46 Gy (1 catheter) and demonstrated a relapse after 12 months. In these cases, the applied dose had to be adapted due to nearby risk structures.

The range of applied doses is found in the Table. The maximum dose rises exponentially towards the irradiation center/center of the tumor but is not exactly known. However, it is much higher than the prescribed enclosing dose (D99.9) of 20 Gy.

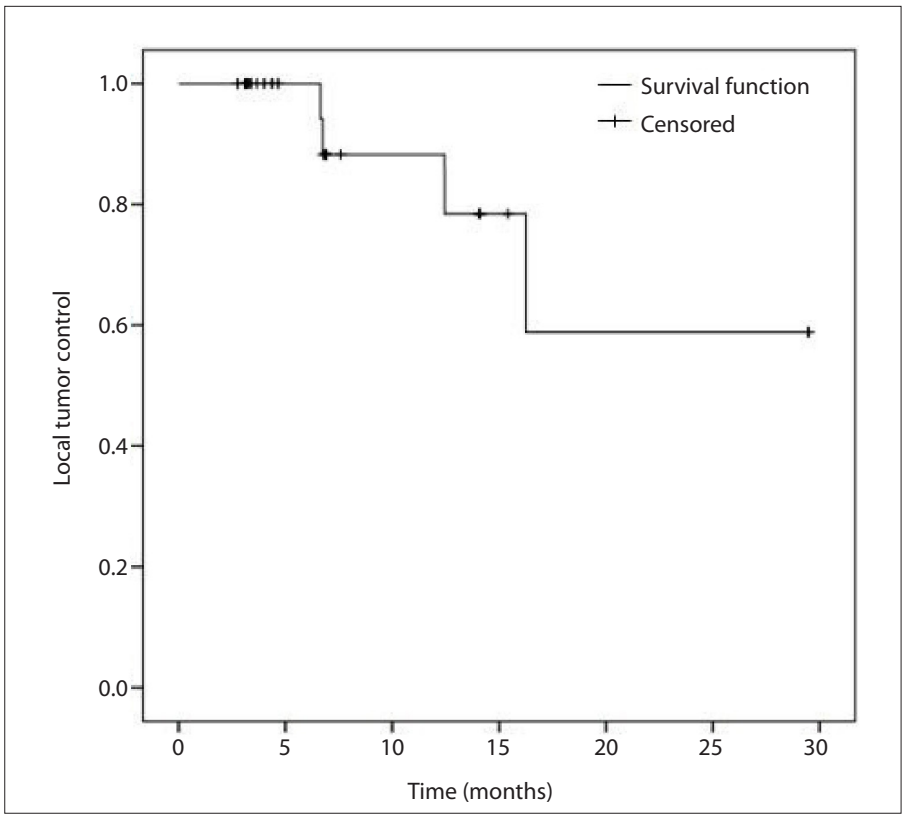

Figure 2. Local tumor control after iBT.

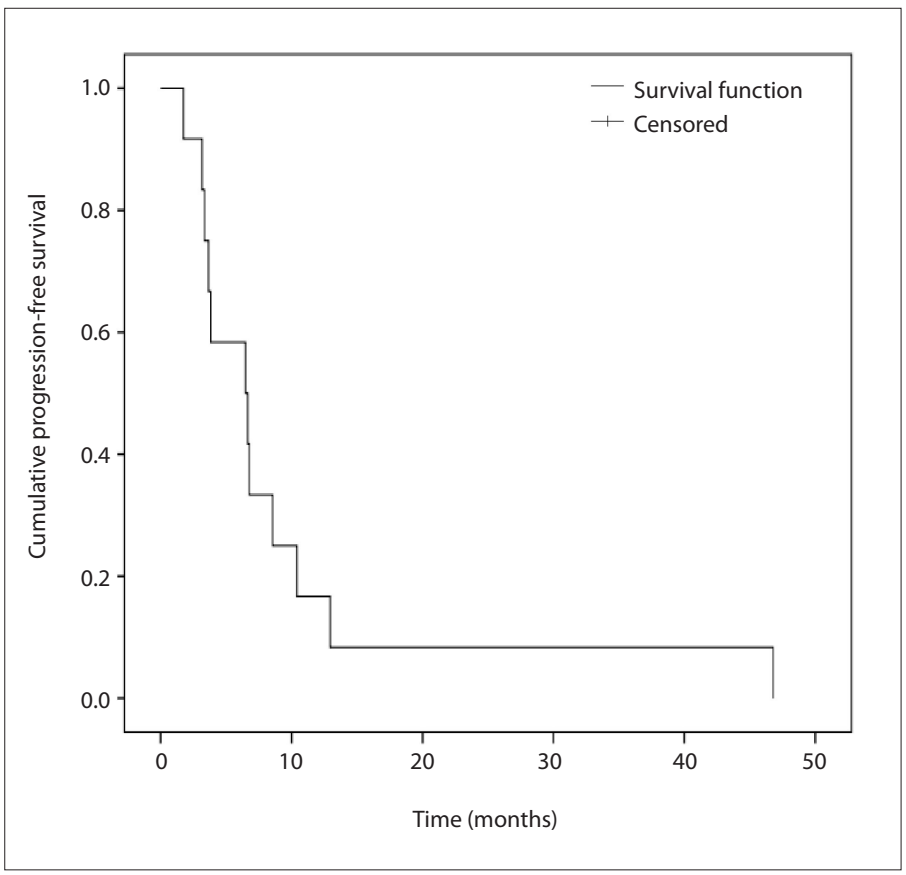

Figure 3. Progression-free survival of all patients with metastatic gastric adenocarcinoma treated with iBT.

The minimal tumor enclosing dose (clinical target volume) of 20 Gy was achieved in 23 of the 36 treated lesions (63.9%). Two doses were under 10 Gy (lymph node and pancreatic relapse); the other 11 irradiated lesions were in the range of 10.5–16.3 Gy.

Local tumor control was achieved in 89% of all lesions in the Kaplan-Meier analysis (Fig. 2). The mean follow-up time was 8.3 months. A cumulative number of 4 local relapses (2 hepatic, 1 lymph node, 1 pancreatic) were observed in 3 patients after 7 months.

The median progression-free survival was 6.5 months (Fig. 3). The median overall survival of the 12 patients with metastatic gastric cancer, calculated after iBT, was 11.4 months (Fig. 4). The overall survival from the time of diagnosis was 33.5 months.

Discussion

Surgical or local treatment of hepatic metastases from gastric adenocarcinoma is still discussed controversially (26). The liver is one of the most frequent metastasis localizations in gastric adenocarcinoma and accounts for up to 11% of metastatic lesions. No consensus about standardized or best therapeutic regimen for metastatic gastric cancer depending on disease extent has been achieved yet (27). ESMO guidelines recommend palliative chemotherapy for limited metastatic disease and reassessment for surgery depending on positive response to chemotherapy (12). Furthermore, the ESMO guidelines state that patients generally do not benefit from metastasis resection. The randomized REGATTA trial demonstrated that not even gastrectomy prolongs survival for patients suffering from limited metastatic disease (28). Therefore both gastrectomy and metastasectomy are currently considered experimental for metastatic gastric cancer patients according to the guidelines.

The 5-year overall survival rate of metastatic gastric cancer ranges from 0% to 10%. However, overall survival may be improved up to 20% after curative hepatectomy in case of liver metastases according to a meta-analysis (29). Overall survival of patients with synchronous hepatic metastases is worse than that of patients with metachronous metastases. Tumor resection or local ablation can usually only serve as a palliative treatment option and is rarely a curative approach in this setting. The rate of resection is reported as 0.5%–2.3% of all patients

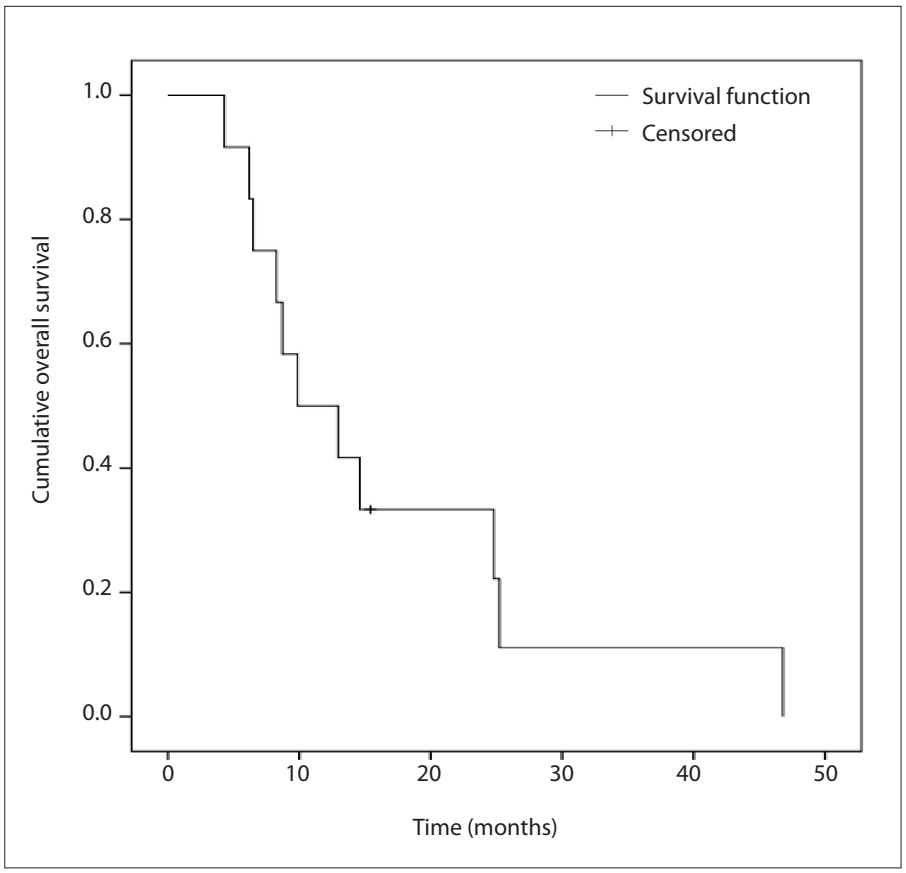

Figure 4. Overall survival of all patients with metastatic gastric adenocarcinoma ablated by iBT.

(6, 30–32). Hepatectomy is indicated in only 0.4%–1% of gastric cancer patients with liver manifestations due to multiple bilateral metastases or advanced disease with extrahepatic (peritoneal or lymphatic) dissemination (14, 33, 34). The obvious downside of surgical procedures is the higher general mortality, which is also often associated with higher patient age and several comorbidities. The few studies presently available are either not randomized, retrospective, or only include a small insignificant number of patients and in consequence the study design implies a relevant bias.

However, the FLOT 3 study, which included patients with fewer than 5 liver metastases and no other simultaneous organ manifestation, demonstrated an impressive overall survival benefit in an oligometastatic setting of 31.3 month in the surgery group versus 15.9 in the no surgery group. Patients with three or fewer liver metastases with a size <5 cm seem to benefit most of all. Limitations were the patient selection and lack of randomization. The most promising studies concerning gastric cancer seem to be the RENAISSANCE /FLOT 5 and the GASTRIPEC study, which will have to evaluate whether an aggressive surgical therapy of metastatic manifestations stemming from gastric cancer is warranted. Furthermore, several smaller retrospective studies also indicate improvement of overall survival comparing resection of gastric liver metastases with palliative chemotherapy (35).

Radiation therapy with stereotactic body radiation in metastatic gastric cancer is only described in singular case reports and does not seem to be a feasible alternative for wider application.

On the other hand, local ablation shows promising results not only in the treatment of metastatic gastric disease but also in the treatment of other tumor entities. Retrospective data suggests similar or even the same overall survival with local-ablative measures like RFA compared with surgical resection (13). Guner et al. (13) compared liver resection (n=68) and RFA (n=30) in a patient collective of 98 gastric adenocarcinoma patients and observed no significant difference in outcome; median overall survival after resection was 24 months compared with 23 months after RFA. Some smaller studies and case reports support these results and come to the same conclusion.

In contrast to RFA, brachytherapy applies an internal source of gamma radiation that results in tumor cell deactivation via DNA and RNA damage. Excellent rates of local tumor control of around 90% after 12 months are reported by several investigators treating primary and secondary liver malignancies with iBT (18, 20). There are no restrictions to tumor sites and almost every imaginable (extrahepatic) treatment site has been tested by different researchers (21, 22). Coinciding with these figures, the results of our study show a local tumor control of 89% for gastric cancer metastases, a median progression-free survival of 6.6 months and a median overall survival of 11.4 months, despite our patients being in a progressive and advance disease stage (Figs. 2–4, Table). The median overall survival calculated from the time of diagnosis was 33.5 months; at that time, four patients already had synchronous metastases. We report and confirm similar results to Geisel et al. (16) who treated esophageal and gastric cancer and stated a progression-free survival of 3.5 months after the application of iBT (16).

IBT is an overall safe procedure; only one of our patients suffered a major local complication (CTCAE grade 3), which was hepatic hematoma and abscess, successfully dealt with by transcutaneous drainage and antibiotics. Major complications (CTCAE grade 3 and 4) after iBT arise in 3% of cases according to the literature (20). In contrast, studies evaluating gastric cancer metastasis resection report up to 26.7% major complications (26).

No systemic side effects were observed and therefore time of hospitalization was short but remains a necessary safety precaution to monitor possible occult post-interventional abdominal hemorrhage. Patients usually stayed in hospital for at least two nights.

The advantages of brachytherapy over thermal ablative measures and the minimal invasive access compared with surgery are an incentive for wider application of iBT, which can be performed repeatedly in multiple sessions. Restrictions like tumor size, cooling effects /heat sink effect of large vessels do not apply to brachytherapy and therefore do not limit its efficacy. More-

over, iBT has fewer limitations concerning proximity to risk structures or other organs compared with thermal ablation procedures. Empiric observations suggest low treatment-associated morbidity and mortality compared with surgical resection due to the minimal invasive nature of the procedure, especially when iBT is performed by an experienced interventional radiologist. Patients not eligible for surgery for whatever reason should therefore be evaluated for the application of minimally invasive iBT. Another incentive to prefer iBT over extensive surgery is the preservation of liver function due to the low required security margins of 5 mm. The issue of potential needle-track metastasis was addressed specifically by irradiation of the interventional access route as a precaution.

The main indication to apply local tumor ablation in these patients was salvage therapy and, consequently, prolonged survival. Metastatic gastric adenocarcinoma has an overall survival of 11 months under palliative chemotherapy; after iBT our patients had an additional 11.4 months of overall survival (after progressing under palliative chemotherapy); thus, our goal of prolonged survival seems to have been met for the selected patient group in our study. The goal of this retrospective analysis, however, was primarily safety and applicability of the procedure and local tumor control.

The main limitation of our study, comparable to other data concerning this topic, is the low patient number due to lack of available randomized controlled trial data which could supply the needed evidence of benefit in outcome and survival to support the general and wider application of either local-ablative measures or surgical resection of gastric adenocarcinoma metastases. For the time being, any aggressive approach (surgery or local ablation) remains experimental. The current treatment rationale should be to identify appropriate candidates with limited or oligometastatic disease and whenever possible to include them in a prospective clinical study to evaluate the effectiveness of different treatment options in the anti-neoplastic toolbox. Ultimately, the aim should be prolonged survival and in very rare cases even a curative approach as well as improvement of quality of life through palliative treatment of clinical symptoms until further evidence is obtained based on prospective randomized studies.

In conclusion, the results of our study demonstrate that iBT is an overall safe procedure, and excellent local tumor control rates in the treatment of gastric cancer metastases can be achieved.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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