CT-Guided High-Dose-Rate Brachytherapy of Metachronous Ovarian Cancer Metastasis to the Liver: Initial Experience

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Abstract. Aim: Hepatic resection for hepatic ovarian cancer metastases remains controversial. The purpose of this study was to evaluate the clinical outcome of CT-guided high dose rate brachytherapy (CT-HDRBT) for minimally invasive cytoreduction of isolated metachronous ovarian cancer metastases to the liver. Patients and Methods: Seven patients with 12 isolated ovarian cancer metastases to the liver were treated with CT-HDRBT. To evaluate tumor response a gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA)-enhanced liver MRI was performed before, six weeks after and every third month after treatment. Results: The mean MRI-follow-up period was 15.4 months. Tumors ranged from 13 to 120 mm in diameter. Complete ablation was achieved for all lesions. No complications occurred. No local progression was observed in any of the included patients. Overall survival was 100% after 12 months. Two patients died after 14 and 25 months, respectively. Conclusion: CT-HDRBT is a safe and valid technique for performing minimally invasive cytoreduction of metachronous isolated liver metastases from ovarian cancer.

Epithelial ovarian cancer (EOC) is the leading cause of gynecologic cancer-related death in Europe and the United States (1). Since screening strategies to detect EOC at an early stage have not shown any influence on survival so far, optimizing treatment strategy remains the only way to improve the outcome in patients with EOC (2). While primary cytoreductive surgery is well accepted as the standard treatment for primary EOC, the value of secondary or tertiary aggressive debulking surgery for recurrent ovarian cancer (ROC) remains one of the most debated topics in the gynecologic cancer community. Although some authors have succeeded in demonstrating an advantage of optimal cytoreductive surgery in terms of overall survival (OS) in selected patients (3-7), currently, operative therapy for ROC plays only a minor role in the clinical routine, especially in centers that are not specialized in the treatment of gynecologic tumors (8, 9). The proponents of a medical approach, while acknowledging that tumor debulking may enhance the potential efficacy of adjuvant chemotherapeutic strategies and further relieve disease-related manifestations thereby improving quality of life, believe that the benefits obtained from surgical tumor debulking are not outweighed by the invasiveness of the procedure in patients weakened by previous surgery and medical treatments. Even less agreement was reached for the treatment of metachronous liver metastases from ovarian cancer. Although the principles of cytoreduction suggest that resection of liver metastases would be beneficial, surgery is often avoided in cases of liver metastases and the presence of parenchymal liver metastases is often indicated as a criterion for exclusion when deciding whether a patient is a candidate for optimal cytoreduction (10). In recent decades minimally invasive ablative techniques have shown promising results in the treatment of selected primary and secondary hepatic tumors. Computertomography-guided high dose rate brachytherapy (CT-HDRBT), a local radioablative technique in which an iridium-192 (Ir-192) source is temporarily inserted through afterloading catheters placed into the tumor under CT guidance, is a novel ablative technique which is not influenced by cooling of adjacent large vessels and is not limited by tumor size (11). In recent years CT-HDRBT has proven to be a safe and effective procedure for the local treatment of unresectable primary and secondary liver tumors, demonstrating not only excellent results in terms of local tumor control but also results in terms of time to disease progression (TTP) and even OS (12-14). The purpose of this pilot study was to investigate the safety, feasibility and clinical outcome of minimally invasive ablation of metachronous liver metastases by means of CT-HDRBT in selected patients with isolated recurrent EOC to the liver.

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Key Words: CT-guided high-dose-rate brachytherapy, CT-HDRBT, ovarian cancer, metachronous liver metastasis, ablation of liver metastases.
Patients and Methods

All consecutive patients with hepatic metastases from ovarian cancer treated by CT-HDRBT over the past two years at the Division of Minimally Invasive Tumor Therapy of our institution were included in this retrospective analysis. Related imaging and clinical records were reviewed for all patients.

Patient selection. Patients were referred for CT-HDRBT by their gynecologist who, in collaboration with the interventional radiologist, evaluated all patients to determine each patient’s suitability for the procedure and to ensure that all suitable treatment alternatives had been considered. In particular each patient had previously been evaluated for possible surgical resection of hepatic metastases, and surgery was not thought to be a therapeutic option in any of these patients. Further inclusion criteria for HDRBT comprised: (i) liver function status at Child-Pugh A or B, (ii) Bilirubin < 2 mg/dl, (iii) platelet count >50,000/ml, Quick >50% and (iv) partial thromboplastin time <50 s.

Interventional technique. The technique of CT-HDRBT has been described in detail in previous reports (11). It consists roughly of two major steps: (i) CT-guided catheter placement and subsequent (ii) high dose rate irradiation in afterloading technique. Catheter implantation is completed under CT guidance after intravenous sedation and local anesthesia at the cutaneous puncture site. After having reached the tumor with a 17-G needle, a stiff angiographic guide wire (Amplatz, Boston Scientific, Boston, USA) is inserted through the needle. Afterwards the needle is removed and replaced by a flexible 6-F sheath (Radiofocus, Terumo™, Tokio, Japan). Finally, the angiographic guide wire is removed and a 6-F afterloading catheter (Primed™, Halberstadt Medizintechnik GmbH Halberstadt, Germany) is placed through the sheath into the tumor. Once the placement of catheters is complete, a contrast-enhanced scan of the liver is acquired for documentation of the correct catheter location in relation to the tumor and treatment planning. The computer-based 3D treatment planning was performed on a dedicated workstation using the acquired data set and the software Brachyvision™ (Gammamed™, Varian, Palo Alto, CA, USA). To this end, all afterloading catheters were digitized from the tip to the body exit point. Subsequently, the clinical target volume (CTV) of each tumor and all risk structures (e.g., stomach, bowel, spinal cord, hepatic hilus etc.) were demarcated (Figure 1). Source dwell points and times for the iridium-192 source inside the afterloading catheters were optimized semi-automatically to ensure full coverage of the target volume and contemporary preservation of the at-risk structures. All irradiations were performed as single-fraction irradiations in afterloading technique by means of an iridium-192 radiation source with a nominal activity of 10 Ci. The minimum dose to cover the CTV was 15 Gy (11, 13). Maximum doses >50 Gy were allowed within the tumor center. If exposure of the gastric wall or duodenal mucosa exceeded 10 Gy for every milliliter of the organ at risk, then proton pump inhibitors were prescribed (pantoprazole 40 mg). After irradiation the afterloading catheters were carefully removed and the puncture channels were sealed with absorbable gelatin (Gelfoam®, Pfizer Inc. New York, NY, USA).

Therapeutic response and follow-up. Six weeks after CT-HDRBT, the first Gd-EOB-DTPA-enhanced MRI confirmed that complete tumor enclosure was achieved in all patients after the first CT-HDRBT session, with a technique effectiveness rate of 100%. Furthermore patients were followed up with MRI every 3 months post-intervention. All patients were available for MRI assessment at a mean follow-up of 15.4 months (range: 11-19 months). None of the treated patients developed local progression during the follow-up period. Two patients experienced systemic tumor progression during the follow-up period; they were not amenable to CT-HDRBT due to widespread intrahepatic disease and were scheduled for salvage chemotherapy.
OS was 100% after 12 months. Two patients died after 14 and 25 months, respectively.

Discussion

Hepatic metastasis from ovarian cancer, which can be found at autopsy in about 50% of patients who die of the disease, remain an issue that is covered only by a few studies and where many uncertainties remain (17, 18). Although some authors have proposed liver resection as part of cytoreduction, there is still great reluctance in practicing it, and many patients are declared not liable to cytoreduction precisely because of the presence of parenchymal liver metastases (10). Two factors are most often identified as contraindications to surgery in these patients: The performance status of the patient, who is often deemed medically unfit for major upper abdominal surgery, and the tumor location/configuration precluding their resection with grossly negative surgical margins (19). In recent years there have been many developments in the treatment of liver metastases, particularly those from colorectal carcinoma. One of the most promising approaches are the minimally invasive ablative techniques, such as radiofrequency ablation (RFA), which have received great attention as effective alternatives for the local treatment of liver tumors, including complex, unresectable primary and metastatic tumors (20-
Many authors have published their experience in the treatment of liver metastases by means of RFA, reporting satisfactory results. Gervais et al. first described the use of percutaneous radiofrequency ablation in a series of six consecutively treated patients with ovarian cancer involving the liver, reporting a primary efficacy rate of 80% and showing that minimally invasive ablation techniques may achieve similar cytoreduction without repeated open surgical resection in selected patients with ovarian cancer metastases to the liver (23). In our series we employed CT-HDRBT to attain minimally invasive cytoreduction in seven heavily pretreated EOC patients with metachronous hepatic metastases from ovarian cancer.

CT-HDRBT is a relatively new technique that has recently been shown to achieve very good results in the cytoreduction of primary and secondary hepatic tumors (10-14). Hence, we decided, in concordance with the referring gynaecologist, to assess feasibility, safety and results in terms of local control obtained by this technique in this new series of highly complex patients. CT-HDRBT proved to be safe and feasible.

<table>
<thead>
<tr>
<th>Patient No./Age (years)</th>
<th>Previous treatments</th>
<th>No. of lesions</th>
<th>Tumor size (mm)</th>
<th>No. of CT-HDRBT sessions</th>
<th>Minimal tumor enclosing dose (Gy)</th>
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<td>11, 17, 10</td>
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<td>20</td>
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<td>Primary cytoreduction&lt;br&gt;First line chemotherapy&lt;br&gt;First recurrence&lt;br&gt;Secondary cytoreduction&lt;br&gt;Third line chemotherapy&lt;br&gt;Second recurrence: isolated hepatic metastasis</td>
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<td>15</td>
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<td>Primary cytoreduction&lt;br&gt;First line chemotherapy&lt;br&gt;First recurrence&lt;br&gt;Secondary cytoreduction&lt;br&gt;Third recurrence: isolated hepatic metastasis</td>
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<td>62, 22</td>
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<td>1</td>
<td>13</td>
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also in this series of patients; conducting the interventions under conscious sedation also makes this therapy extremely minimally invasive in terms of anesthesiologic risk. In all cases, postprocedural pain was successfully treated by means of simple analgesics, and none of the patients experienced any kind of minor or major complications. Our early clinical results with CT-HDRBT of ovarian cancer metastases to the liver are encouraging, all lesions were successfully treated as suggested, by Gd-EOB-DTPA-enhanced MRI follow-up performed 6 weeks after ablation. On average the treated lesions were not particularly large, but one of the successfully treated lesions was 12 cm in diameter. By applying the CTV as two subvolumes (cranial and caudal) and irradiating the two CTVs in two successive sessions, we were able to completely enclose the lesion, with no need for further re-ablation. This strategy, frequently adopted by our group when treating very large hepatic tumors (>10 cm), allows us to evenly distribute the dose to the two CTVs to be irradiated without delivering too high a dose of radiation to adjacent organs, and thereby obtaining highly satisfactory local control. In fact, the last Gd-EOB-DTPA-enhanced MRI control 21 months after treatment showed persistent LTC for this massive lesion (Figure 2). This also applied to the other treated lesions. After a mean follow-up time of 15.4 months, no local progression had occurred. The conclusions we can draw after this initial experience with the use of CT-HDRBT in the management of metachronous hepatic metastases in EOC patients are encouraging. The technique proved to be feasible, safe and minimally invasive for patients. Although we were dealing with complex patients with poor performance status and repeated abdominal surgery, no minor or major complications occurred. The extremely low number of treated patients only allows us to take note of the fact that this is a safe and feasible technique. However, we believe that this is a very attractive technique for cytoreduction of liver metastases from ovarian cancer and this experience in heavily pretreated patients has really highlighted the tolerability of this technique. CT-HDRBT might not only be a viable alternative for cytoreduction of metachronous liver metastases from ovarian cancer but also a valuable technique for a combined approach of CT-HDRBT and surgical tumor debulking to achieve complete cytoreduction in EOC patients with synchronous or metachronous hepatic metastases.

References


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