Original paper

Efficacy and safety of image-guided interstitial single fraction high-dose-rate brachytherapy in the management of metastatic malignant melanoma

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Abstract

Purpose: Computed tomography (CT) or magnetic resonance imaging (MRI) guided brachytherapy provides high tumor control rates in hepatocellular carcinoma (HCC) and colorectal liver metastases. In contrast to thermal ablation methods such as radiofrequency ablation (RFA), much less restrictions apply with respect to tumor location or size. In this study, we determined the efficacy and safety of CT- or MRI-guided brachytherapy in metastatic melanoma.

Material and methods: Fifty-two metastases of malignant melanoma in 14 patients were included in this retrospective study. Local tumor control and safety were evaluated as primary and secondary endpoints. Furthermore, we evaluated overall survival and progression free survival. Tumor locations were liver (n = 31), lung (n = 15), adrenal (n = 3), lymph nodes (n = 2), and kidney (n = 1). Treatment planning was performed using three-dimensional CT or MRI data acquired after percutaneous applicator positioning under CT or open MRI guidance. Subsequently, single fraction high-dose-rate (HDR) brachytherapy was applied using a ^{192}Iridium source. Clinical and cross-sectional follow-up were performed every 3 months post intervention.

Results: The median diameter of treated lesions was 1.5 cm (range: 0.7-10 cm). Doses between 15 and 20 Gy were applied (median dose: 19.9 Gy). The mean irradiation time ranged between 7-45 minutes. After treatment, there was one patient with a cholangitis. After a median follow up of five months, the median local tumor control was 90%. The median overall survival of the patients was 8 months. The median progression free survival of the patients was 6 months.

Conclusion: Image-guided HDR brachytherapy is a safe and effective treatment procedure in metastatic malignant melanoma.

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Key words: brachytherapy, CT- and MRI-guided intervention, high-dose-rate, malignant melanoma, metastases.

Purpose

Patients with distant unresectable metastases of malignant melanoma have an impaired prognosis despite treatment strategies using combined chemotherapies or targeted drugs [1,2]. With distant metastases, median survival is 6-8 months with a 5-year survival rate of approximately 10% [2]. An important role in the treatment of advanced, unresectable metastases of malignant melanoma should be the reduction of clinical symptoms by reduction of the tumour volume, and therefore the improvement of quality of life. Due to the limited efficacy of systemic treatments, visceral, lung, or lymph node metastases may quickly become symptomatic despite being locally confined. At present, local treatment options such as surgery, or local tumour ablation do not play an important role because the evidence on their prognostic impact is rare. These treatment options currently are limited to highly selected patients. Patients with visceral metastases are considered to be less qualified for local treatments than patients displaying lung metastases only or in combination with metastatic lymph nodes [3-5]. Regarding local ablation techniques, thermal ablation such as radiofrequency ablation (RFA) is limited by a size restriction of 3-5 cm and a close proximity to risk organs [6,7]. Furthermore, a location near blood vessels decreases the effectivity of thermal ablation due to consecutive heat sink effects [6,7]. Beside percutaneous treatments like RFA, also transarterial chemoembolization (TACE) was analyzed in the treatment of liver metastases of melanoma [8].

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Recently, computed tomography (CT)-guided brachytherapy has been introduced, which may overcome some of the aforementioned limitations. Whereas local tumour control in hepatocellular carcinoma (HCC) and colorectal carcinoma is > 90% after 1 year despite tumour sizes up to 15 cm, cooling effects or proximity to risk organs play no or just a minor role [9]. However, no data has been published evaluating the efficacy of high-dose-rate (HDR) brachytherapy on visceral or other malignant melanoma metastases. In this study described herein, we assessed safety and efficacy of image-guided HDR brachytherapy in patients with metastases of malignant melanoma.

Material and methods

Patient characteristics

Between February 2007 and April 2012, 14 patients with malignant melanoma with an overall amount of 52 unresectable metastases were included in this retrospective study. There were 37 visceral metastases, including 31 hepatic metastases, 4 lesions located in the adrenal gland and kidney, and 2 lymph node metastases. In addition, 15 pulmonary metastases were treated. No patient with pulmonary lesions had a history of previous lung surgery. All the patients who underwent lung treatments had a clinically fully compensated lung function. The patient population comprised 12 men and 2 women; the median age was 66 years (range: 50-81 years) (Table 1). All patients had been pretreated with systemic chemotherapy or chemo-immunological treatment. In detail, eight patients were pretreated with interferon alpha. After treatment with interferon alpha, six patients showed a progressive disease. Furthermore, one patient who was pretreated with interferon alpha finished the therapy because of side effects. Four patients were treated with Dacarbazine and three patients received Fotemustine. All patients displayed tumor progression at the time of referral to our institution for local treatment.

Study design and eligibility criteria

In this retrospective study, primary endpoint was the local tumor control and secondary endpoint was the safety of CT- or magnetic resonance imaging (MRI)-guided HDR brachytherapy. The indication for the HDR brachytherapy was determined for all patients in an interdisciplinary consensus of dermatologists, oncologists, visceral surgeons, and interventional radiologists. The inclusion criteria for performing image-guided brachytherapy were technically unresectable tumor due to its location or due to e.g. reduced liver function or low residual tissue, medical contraindication for resection or comorbidities, and denial of operation. In case of pulmonary lesions, we performed pulmonary function tests before the treatment to secure sufficient lung capacity. A Karnofsky Index ≥ 70% as well as appropriate coagulation parameters (thrombocytes > 100,000/nl, prothrombin > 50%, partial thromboplastin time < 50 s), and liver parameters (bilirubin < 30 µmol/l) qualified for the treatment. The administration of anticoagulants like coumarin derivatives and inhibitors of platelet aggregation were discontinued 7 days prior to intervention and changed to low-dose heparin if necessary. The exclusion criteria for performing brachytherapy were a diffuse uncontrollable tumor spread.

Interventional technique and irradiation

The detailed methodology of CT-guided brachytherapy has been described elsewhere [10]. In brief, placement of the brachytherapy applicators was performed under guidance of a Fluoroscopy-CT (Toshiba, Japan) (for metastasis with a diameter > 20 mm) or an open MRI at 1.0 T (Panorama HFO, Philips Healthcare, Best, The Netherlands) for smaller liver lesions (Fig. 1A-D). Thirty lesions were treated under CT guidance, twenty-two metastases under open MRI guidance. After adequate patient positioning, puncture of the lesion was performed employing an 18-gauge needle. An angiography sheath of 6 F diameter (Radiofocus, Terumo^{TM}, Tokyo, Japan) was inserted over a stiff angiography guide wire (Amplatz, Boston Scientific, Boston, USA). Finally, 16-gauge brachythera-

Table 1. Patient characteristics

	Value
Total number of patients	14
Sex	
Men	12
Women	2
Age (years)	
Median	66
Range	50-81
Metastases (*n*)	52
Hepatic	31
Pulmonary	15
Adrenal	3
Retroperitoneal lymph nodes	2
Kidney	1
Type of metastases (*n*)	
Synchronous	–
Metachronous	14
Tumor size (cm)	
Median	1.5
Range	0.7-10
Previous treatment	
Interferon alpha	7
Dacarbazin	4
Fotemustine	3
Median follow-up (month)	5

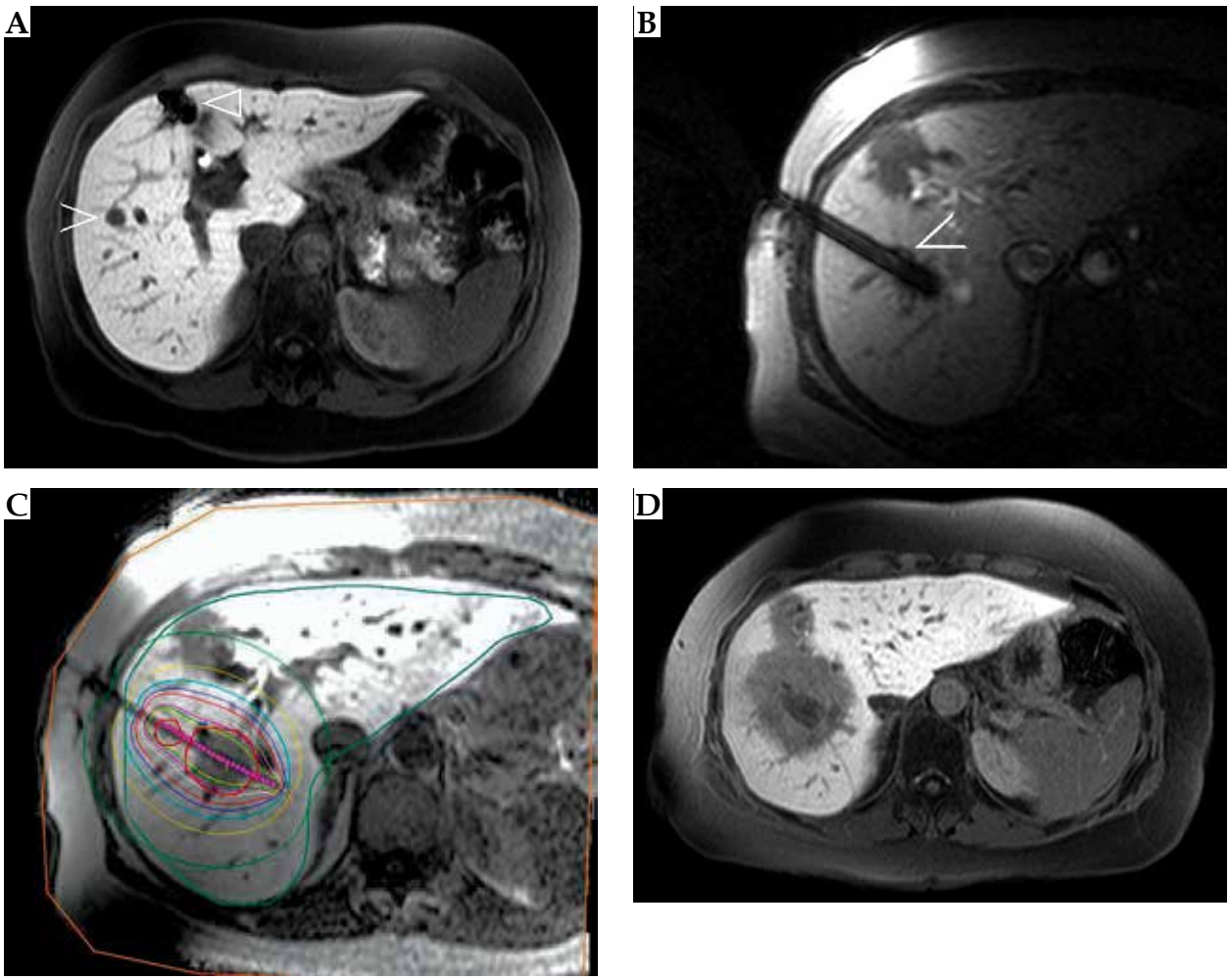

Fig. 1. Local tumor control in a 58-year-old female patient with histological proven malignant melanoma metastases. **A)** Preoperative axial contrast-enhanced liver magnetic resonance imaging (MRI) (liver specific contrast agent Gd-EOB-DTPA) shows two metastases in segment V in the right liver lobe (open arrow), former partial resection of the liver segment IV (outlined arrow). **B)** Both metastases were treated by open MRI high-dose-rate brachytherapy using one catheter. **C)** Treatment planning and dosimetric analysis, tumor encircling isodoses (red line indicates 20 Gy). **D)** Follow-up contrast-enhanced liver MRI at 3 months shows the shrinking ablation zone with local control of the treated lesions

py catheters (Nucletron, Elekta AB, Stockholm, Sweden) were placed in the sheaths. For treatment planning purposes, a contrast-enhanced CT in breathhold technique was acquired after placement of the catheters. The HDR afterloading system (Nucletron, Elekta AB, Stockholm, Sweden) used a ^{192}Iridium source of 10 Ci. The source diameter was < 1 mm. In mean 2 applicators were inserted (range 1-5).

Treatment planning and dosimetric analysis

Treatment planning was performed using the software system Oncentra (Nucletron, Elekta AB, Stockholm, Sweden) integrated in the HDR-afterloading system. Firstly, a careful delineation of the target volume was performed in every CT/MRI slice with the afterloading catheters in place. Secondly, the relative coordinates (x, y, z) of the catheters were determined, considering the tip and the exit at the margin of the tumor, and transferred into the planning system. The given boundary of the target was individually addressed for every catheter by specifying the distance to the reference point. A reference dose of 15-20 Gy was prescribed in our patients, which was by definition identical to the minimum dose enclosing the lesion, and applied as a single dose. The anatomic optimization routine of the planning software was employed with the specified set of reference points. Isodose lines relative to the target contours were controlled and matched slice by slice by varying input parameters of the planning system. We considered dose limitations in treatment planning for treated tumors adjacent to organs at risk (OAR), such as the gastric wall or duodenum for tumors in the left liver lobe (< 15 Gy/ml), or the spinal canal (10 Gy/ml) for treated retroperitoneal lymph node metastases, adrenal gland, or kidney.

All procedures were performed under local anesthesia. Midazolam and fentanyl *i.v.* were given for sedation and analgesia according to the individual discomfort level of each patient during the intervention. For catheter re-

trieval, gelfoam or fibrin tissue glue was injected through each brachytherapy sheath during removal.

Follow up and safety assessment

Clinical visits, supplemented by CT or MRI, were performed after 6 weeks and then every 3 months after treatment. We included standard laboratory tests. Therapy-related adverse events were defined according to the guidelines of the Society of Interventional Radiology (SIR) [11]. Liver toxicity after CT/MRI-guided HDR brachytherapy was assessed according to the definition of radiation-induced liver disease (RILD), characterized by the occurrence of ascites accompanied by elevated alkaline phosphatase levels or by a serum bilirubin level of ≥ 3 mg/dl, and ascites 1-2 months after HDR brachytherapy with an absence of tumor progression or bile duct obstruction [12]. There was no need for lung tests in the follow up period because no clinical symptoms were shown.

Definitions of remission criteria and local control rates

Local tumor control after CT or MRT-guided brachytherapy was defined according to RECIST 1.1 response criteria and classified either as stable disease (SD), partial (PR), or complete remission (CR) of the treated lesion. Any increase > 20% in diameter of a singular lesion was interpreted as progressive disease (PD). However, restrictions apply for lung and liver follow up. Since in both, lung and liver tissue adjacent to the target volume, focal radiation pneumonitis or radiation hepatitis may mimic tumor growth. For liver tumors, we therefore limited tumor measurements to hepatobiliary phase imaging > 20 min. post *i.v.* application of gadoxetic acid (Primovist®). For lung tumors, we measured tumor response not in comparison to the baseline, but to the first follow up examination in order to compensate for lung tissue alterations adjacent to the clinical target volume.

Statistical methods

All results were analyzed in a non-randomized and retrospective approach. To evaluate the local tumor control, the overall survival and the progression free survival statistical analysis was performed employing the Kaplan-Meier method with SPSS version 19 (SPSS, version 19.0; SPSS, Chicago, Illinois). The secondary endpoint safety was evaluated descriptively.

Results

Treatment characteristics

The median diameter of the metastases was 1.5 cm (range: 0.7-10 cm). There were 5 lesions with a maximum tumor diameter between 5 and 10 cm, which were treated with 5 or 6 catheters. Metastases with a maximum tumor diameter of 2 to 5 cm received 1 or 2 catheters depending on the geometrical position of the first catheter implanted, or depending on specifics of adjacent critical organs. Patients with tumor < 2 cm received a single applicator per lesion only. All lesions were treated once by a single fraction HDR brachytherapy. The prescribed minimal tumor dose (D_{100}) was 20 Gy. However, in some patients, the minimal dose had to be lowered to spare adjacent risk structures. The applied minimal doses inside the clinical target volume (CTV) ranged from 15 to 20 Gy (median dose D_{100}: 19.9 Gy). A complete coverage of the tumor with 20 Gy was applied in 15 pulmonary and 21 hepatic lesions. In the adrenal gland and in the retroperitoneum, a dose of 15 Gy was given. Total irradiation time ranged between 7 and 45 min. The mean hospital stay of the patients was 4 days (range: 3-13).

Adverse events

Three of fourteen patients (21%) showed slight side effects like sickness and emesis. One of the three patients had an allergic reaction, which was treated successfully with Fenestil® and Tagamet®. Five of fourteen patients (35%) described unspecific abdominal pain after the image-guided brachytherapy, in the ultrasound control no associated reasons could be found. The symptoms regressed spontaneously. We encountered no intraoperative bleeding complications. Two small pneumothoraces regressed spontaneously after the treatment of pulmonary metastases. One patient with a central liver metastasis developed cholangitis 3 weeks after HDR brachytherapy as well as abdominal pain in the right epigastrium and an increase of liver parameters. He was successfully treated with endoscopically guided stent implantation and *i.v.* antibiosis.

Local tumor control, overall survival, and progression free survival

According to Response Evaluation Criteria in Solid Tumors Criteria (RECIST 1.1), one of the treated lesions exhibited complete remission, 19 partial response, 30 treated metastases showed stable disease, and two progressive disease after a median follow up of five months (1-11 months). Local tumor control was 90% in the Kaplan-Meier analysis (Fig. 2). All patients showed a progressive disease elsewhere during the follow-up period. The median overall survival of the 14 patients with metastatic malignant melanoma after HDR brachytherapy was 8 months (Fig. 3). The median progression free survival (PFS) of the 14 patients was 6 months (Fig. 4).

Discussion

In metastatic malignant melanoma, tumor resection or image-guided ablation must be considered a palliative treatment option, not a curative approach. Due to macroscopically undetectable tumor spreading, progression free survival after these interventions is usually limited [4,5]. The effect of debulking, i.e. the reduction of the unresectable tumor mass, either by surgery or radiation is so far unknown due to the lack of prospective randomized data. However, in a retrospective data, long-term survivors have been described after liver and lung surgery specifically in ocular rather than cutaneous melanoma [3-5]. In pulmonary metastases of malignant melanoma, a number of factors have proven to be predictive for sur-

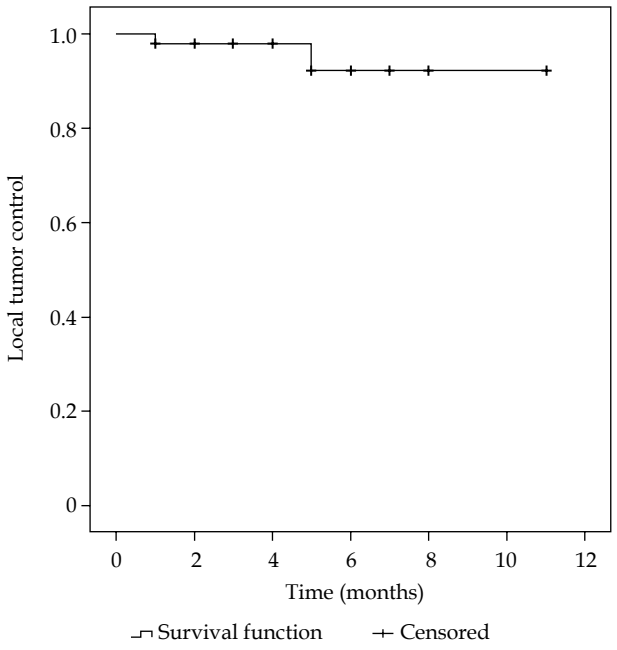

Fig. 2. Graph shows the local tumor control after image-guided high-dose-rate brachytherapy; two patients experienced local tumor progression 1 and 5 months after the treatment

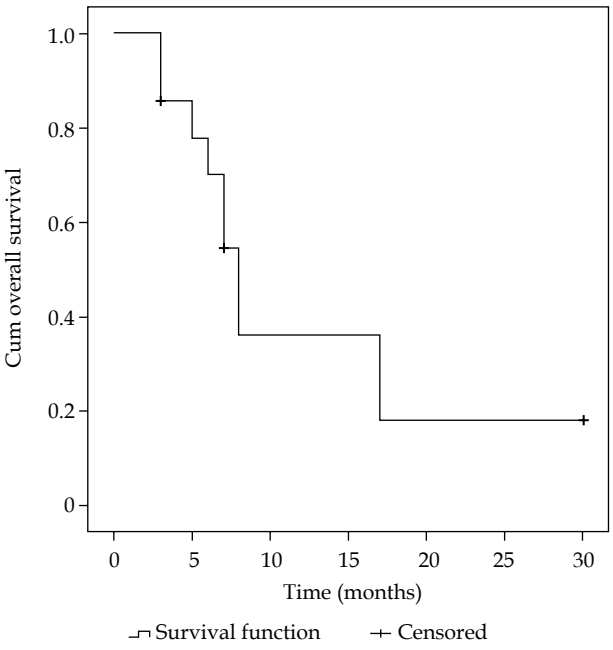

Fig. 3. Overall survival of all patients with metastatic malignant melanoma treated with high-dose-rate brachytherapy

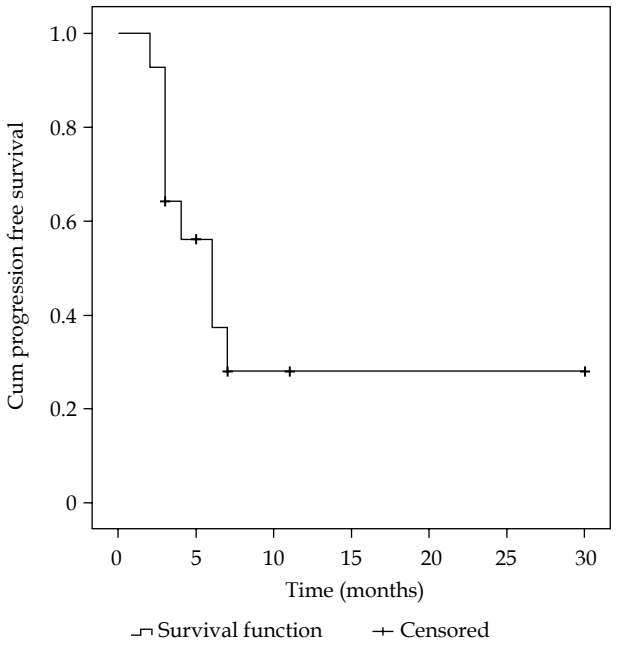

Fig. 4. Progression-free survival of all patients with metastatic malignant melanoma treated with high-dose-rate brachytherapy

vival, including site of primary lesion, histological type, lymph node status, disease-free interval, number of metastases, and the presence of extra-thoracic metastases [4]. Based on these data, surgical resection or local ablation of lung metastases has been adopted in the treatment algorithm in many centers, even in patients displaying minor additional non-visceral tumor implants.

The objective of surgery or local ablation in metastatic melanoma is symptom relief such as pain or organ compression, e.g. jaundice caused by obstruction of the bile duct. Few studies reported the application of image-guided local ablation by radiofrequency ablation (RFA), or laser induced thermotherapy (LITT), with limited efficacy in tumor larger 5 cm and in proximity to critical organs [6,7,13]. That includes bile duct in the liver hilum, large liver vessels that lead to cooling effects, and therefore incomplete ablation, lung hilum, proximity of gut or tubular structures (ureter) and more. Image-guided HDR brachytherapy, a technique that has been so far predominately evaluated in metastatic colorectal as well as hepatocellular carcinoma (HCC) [9,14], renders a new minimally invasive approach unharmed by those restrictions. In contrast to thermal ablation, tumor size, cooling effects of large vessels, or proximity to risk organs such as liver or lung hilum, bile duct or intestines do not limit its efficacy [10,15-17].

In the study described herein, we report only one major complication after MRI-guided brachytherapy of a central localization in the liver with a presentation of cholangitis. Other than this, the treatments were well tolerated with just one minor pneumothorax in another patient, which disappeared without treatment. Even though the applicator sizes are similar in RFA, LITT, and image-guided brachytherapy, mechanical damage, such as pneumothorax, seems to be more frequent in cases, in which thermal ablation techniques are used, with a reported frequency of 30% to 50% [18]. In addition, the instantaneous thermal effect holds, at least theoretically, a higher risk of acute complications and, by formation of necrotic cavities, a higher risk of late adverse effects [18].

Thus, advantages in favor of brachytherapy exist with respect to conformity and control of dose distribution, which becomes especially important when treating adjacent to risk structures [16].

Melanoma is widely believed to be a radio-resistant tumor, a misunderstanding that has led to the limited use of radiotherapy for its treatment [19]. Reason for this relative radiation resistance was the large shoulder referred to the linear-quadratic (LQ) model. Actually malignant melanoma is not radio-resistant, which was shown in local control rates after radiation *in vivo* [20]. A promising local control means, in a few cases, an improvement in the quality of life and, occasionally, an extended overall survival. Regarding visceral metastases, most experiences were collected in the treatment of bone and brain metastases [21]. For a lasting effect, minimal cumulative- and partial dose, or rather biologic equivalent dose (BED) is required. Konefal *et al*. suggested that the increase of dose is useful in treating cutaneous metastases, but in case of side effects, it is dispensable in treating visceral metastases [22]. A randomized study from Overgaard *et al*. showed an increasing efficacy in single doses > 4 Gy [23], analysis from Olivier showed a significantly higher efficacy in high doses > 30 Gy and BEDs > 39 Gy [24].

Recently, Stinauer *et al*. reviewed 17 patients with 28 metastatic melanoma lesions, treated with a single body radiation therapy [25]. A higher dose per fraction and higher single fraction equivalent dose (SFED) were significantly correlated with a better local control. The authors concluded that an aggressive stereotactic body radiation therapy with SFED ≥ 45 Gy is effective for controlling metastatic melanoma [25].

However, the use of higher doses shows limitations regarding the radiation tolerance of the adjacent structures (OAR). A possibility to apply such effective BED is the use of stereotactic body radiation therapy (SBRT). Different strategies (e.g. 4D-CT, gating, tracking) provide a reduction of the planning target volume (PTV), resulting in a significant decrease in exposure of normal tissue. Meanwhile SBRT is, due to a connotatively figure of retro- and prospective analyses, a widely used and accepted method for several tumors even in curative intention, e.g. treatment of early-stage non-small-cell-lung-cancer, primary and secondary liver malignancies [26-29]. Several authors considered limitations in case of liver treatment. According to Rusthoven, liver-SBRT requires a well-defined quantity and size of lesions [30]. Although these specifications are arguable, certainly there are constrictions mostly due to adjacent organs and structures. In contrast, interstitial brachytherapy enables treatment of larger tumors due to the steep dose gradients and a constant catheter position, latter enabling a lesser PTV.

In the present study, we achieved a local tumor control of 90% after a median follow up of 5 months. Amersi *et al*. showed local recurrences for tumors larger than 3 cm in 29% of melanoma lesions treated with RFA [25]. Not only the size of the treated lesions, also the number of ablated lesions (> 3, < 3) was related to the appearance of recurrence. However, the diagnosis melanoma was a predictive factor for developing local recurrence in an univariate analysis when compared to other diagnosis such as colorectal, breast or neuroendocrine primary. Most likely the comparatively aggressive tumor biology of melanoma is responsible for earlier and more frequent detection of tumor recurrence [31].

There are also promising results in the literature regarding the treatment of malignant melanoma in the nasal cavity and choroidal melanoma by using brachytherapy [32,33]. In this case report, a patient with choroidal melanoma was successfully treated with brachytherapy, achieving tumor control for 12 years [33].

After the treatment with HDR brachytherapy, we achieved a median overall survival of 8 months. Over the last decades, only two systemic treatments were approved in the therapy of metastatic melanoma until 2010: Dacarbazin and Vindesine. The reached prolongation of median overall survival was limited to 6-10 months [34]. Similar rates of remission or survival were reached with the treatment of interferon-alpha and interleukin-2. With the introduction of new target therapies like Ipilimumab and BRAF-inhibitors Vemurafenib, two new effective options are available. Diverse phase II studies showed a prolongation of overall survival up to 15 months [35]. In the future, the combination of target therapies and local ablative options, such as image-guided HDR brachytherapy, could be a promising strategy. We achieved a median progression-free survival of 6 months, which is comparable to the literature. As mentioned, the introduction of target therapies like BRAF-inhibitors in combination with MEK inhibitors may prolong the progression-free survival [34,35].

Several limitations to our study need to be acknowledged. The first weakness of this study is the retrospective nature and the short follow up period. However, the results of this investigation show that HDR brachytherapy can be safely used for local tumor control in selected patients. To identify appropriate candidates for local ablation with the intention to prolong survival, a prospective comparative trial is needed, i.e. to assess the combination of local ablation plus systemic treatments versus systemic treatment alone. In such a study format, HDR brachytherapy would just be one out of a set of tools for local tumor treatment, supplemented by RFA, SBRT, TACE, Y90 radioembolisation, surgery, and others. A thoughtful, interdisciplinary consideration of local and systemic treatment options will in future be mandatory for optimal treatment success in each patient with metastatic melanoma.

We conclude that for patients in a palliative and non-curable stadium, image-guided single high-dose-rate brachytherapy is a promising alternative and well-tolerated treatment, which can be used in most tumor locations, and may therefore be considered specifically in metastases causing symptoms or metastases at risk to cause complications. Treatment rationale should be the reduction of clinical symptoms by reduction of the tumor volume, and therefore the improvement of quality of life.

Disclosure

Authors report no conflict of interest.

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