Locoregional ablative treatment of melanoma metastases

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ABSTRACT
Standard treatment of melanoma has been evolving rapidly over the last decade, with novel treatment approaches improving therapeutic outcome not only in early-stage disease but also in advanced stage metastatic patients. Despite the improvement of systemic therapy outcomes, the current treatment guidelines reflect the fact that locoregional treatment approaches can be beneficial in patients suffering from oligometastatic disease. Minimally invasive ablation techniques have been established as a therapeutic cornerstone in the management of liver tumors, representing a local curative, relatively low-risk procedure. Depending on the size and location of metastatic disease, and on the applied ablation and guidance technique, ablative treatment approaches are effective to treat metastases in solid organs such as the liver or lungs, effectively covering the entire tumor with the ablation zone including a safety margin (A0 ablation in analogy to R0 resection). However, only retrospective data and case reports on locoregional treatment of melanoma metastases are available up to now, and prospective evaluation of this therapeutic approach is warranted to evaluate the beneficial role in the treatment of metastatic melanoma patients.

Introduction
Melanoma has become one of the major public health concerns of the last decades. Despite the fact that only 2% of all skin cancers are melanoma, these tumor entity amounts to 75% of skin cancer-related deaths, and incidence rates in Europe have increased four-fold for women and seven-fold for men over the last 30 years [1].

The worldwide increasing incidence of melanoma has led to the development of novel treatment approaches also for advanced-stage disease. Nearly 20% of patients will develop metastases after surgical resection of the primary, and the median survival of untreated patients reaches less than 12 months [1]. In 10% of melanoma patients, liver metastases are present and the median survival in this cohort varies between 2 and 8 months according to the treatment applied [2].

Treatment options in metastatic melanoma and recurrent disease include excision, lymph node dissection, amputation, immunotherapy, radiotherapy, ablation techniques and chemotherapy. Dacarbazine has been the standard cytotoxic chemotherapy with a 15% objective response rate, while chemotherapy. Dacarbazine has been the standard cytotoxic chemotherapy. However, improvement of 5-year survival after local treatment of metastases has been reported in selected cases [7].

Rare forms of the disease include uveal melanoma. It is the most common form of intraocular tumors in adults and amounts to 4% of all melanoma cases [1,3]. The clinical course and treatment results of uveal melanoma differ from cutaneous melanoma, with the liver being the predominant site of metastatic spread [4–6].

Even though immunotherapy has improved the treatment outcome of metastatic melanoma significantly, the long-term efficacy is still under debate. Generally, patients with advanced-stage melanoma have a poor prognosis, with an estimated 5-year survival of 5–10% in stage IV patients. However, improvement of 5-year survival after local treatment of metastases has been reported in selected cases [7].

The surgical approach is of relevance if complete resection of the tumor is feasible. Prolonged survival after local tumor treatment was confirmed in a study evaluating metastatic melanoma patients with a survival period of more than 2 years [8].

According to the EORTC consensus-based interdisciplinary guideline update 2016, the local treatment of distant metastases in oligometastatic disease is the therapy of choice [9]. Accordingly, the ESMO guidelines state that surgery of visceral metastases may be considered in selected cases with good clinical performance and oligometastatic disease [10].

The aim of this review is to present an overview of ablative techniques for locoregional treatment of melanoma metastases. A variety of minimally invasive interventional techniques is available, and the treatment approaches differ
widely according to the technique applied. The results published so far are summarized, indicating a potentially beneficial role of local ablative treatment in metastatic melanoma.

**Interventional techniques**

Various ablation techniques are available in clinical settings, and the ablation devices are based on different physical principles.

**Radiofrequency ablation**

Radiofrequency ablation (RFA) is based on the principle of heat induction by application of alternating current (375–480 kHz), resulting in tumor heating according to tissue impedance. The friction of the ions surrounding the tip of the otherwise isolated ablation probe results in coagulation necrosis. The current is applied between the ablation probe and a skin electrode. Unipolar or multipolar probes are available. RFA has been investigated in large patient cohorts and has resulted as reliable and feasible technique [11].

**Microwave ablation**

Microwave ablation (MWA) uses heat induction by means of an electromagnetic field surrounding a needle-like antenna. The emitted energy causes tissue heating by excitation of water molecules, resulting in coagulation necrosis. The heating of the tissue is achieved faster and with larger diameters in comparison to RFA [12,13]. However, up to now, RFA and MWA achieved similar results in clinical studies [14].

**Cryoablation**

The creation of a defined ice ball using dedicated probes is based on the application of argon or helium gas. The freezing results in dehydration of tumor cells and irreversible cell damage. The ice ball can be directly monitored under imaging. Compared to thermal ablation techniques, cryoablation has resulted in a higher rate of adverse events in the initial studies available [15,16].

**Irreversible electroporation**

Irreversible electroporation (IRE) is a non-thermal technique. Apoptosis of tumor cells is induced by the application of short electric high-frequency pulses of high voltage using special electrodes, resulting in cell membrane disruption. General anesthesia, muscular blockade and synchronization with the heartbeat are required in order to perform this procedure.

**Endovascular techniques**

Tumors showing a high grade of vascularization can be treated by selective catheterization of tumor supplying vessels followed by the administration of therapeutic substances into target vessels, leading to tumor ischemia and local effects of applied chemotherapeutics.

Transarterial mechanical embolization (TAME) is performed by administration of particular embolization materials into hepatic arteries. If Lipiodol is used as a carrier for chemotherapeutic agents, the therapy is called conventional transarterial chemoembolization TACE (cTACE). When drug-eluting beads are used (DEB-TACE), chemotherapeutic agents such as doxorubicin or irinotecan are applied to treat melanoma metastases [17]. In addition, first reports indicate a potential role of selective internal radiation therapy (SIRT) using yttrium-90 microspheres for transarterial radioembolization of melanoma liver metastases [18]. Thereby, high radiation doses can be delivered directly to liver tumors, depending on the local blood supply, which has to be evaluated pretherapeutically.

**Beneficial role of interventional techniques**

Ablation techniques may be performed percutaneously, laparoscopically or during open surgical procedures. The percutaneous approach represents a minimally invasive procedure, and different imaging procedures such as ultrasound (US), computed tomography (CT) or magnetic resonance imaging (MRI) are available for guidance. CT imaging offers an excellent visibility of the target structures and the devices used during the procedure.

In order to create overlapping ablation zones in larger or anatomically more complex tumor formations, stereotactic guidance allows for three-dimensional treatment planning, giving an overview of ablation zones and ablation margins. The use of stereotactic navigation systems and aiming devices improves the outcome of ablation procedures, which are performed under general anesthesia and muscle relaxation [19]. Disconnection from the tracheal tube facilitates respiratory triggering during the planning phase, needle advancement and CT control scan. Image fusion of control CT scans with the planning phase allow for precise evaluation of effective treatment and coverage of the tumor by the treatment zone [20–23].

In comparison to surgical procedures, the ablation techniques offer a parenchyma sparing, safe and feasible alternative, with a low rate of adverse events and a reduction of postinterventional costs. The technique is only limited in case of restricted tumor visibility and the correct interpretation of tumor extent and stage, depending on the technique applied.

The potential role of endovascular techniques in the palliative setting has been reported in case reports and small retrospective cohort studies. So far, long-term outcomes are missing. First results of SIRT in melanoma liver metastases are promising and showed prolonged survival in small patient cohorts with low rates of toxicity. However, the potential role of SIRT as treatment alternative still needs to be investigated.
Available literature

Despite a vast armamentarium of systemic treatment approaches and novel immunomodulatory therapeutic agents, the role of locoregional treatment in advanced-stage melanoma patients has been investigated only in small case-control studies, retrospective evaluations and case reports. Treatment approaches include surgical resection, TACE and SIRT as well as ablation techniques such as RFA.

According to treatment guidelines for melanoma published by the EORTC and ESMO, local treatment can be an effective strategy in oligometastatic disease. Yet, large prospective trials are missing to support this statement. However, results from surgical resection of melanoma metastases indicate a benefit of local treatment [24–28].

Recently, embolization techniques have been evaluated as palliative treatment approach in melanoma patients with liver metastases. TACE and SIRT have been investigated in small patient cohorts [29,30]. In a small group of patients suffering from liver metastases from uveal melanoma, the OS in patients undergoing TACE with different chemotherapeutic substances including cisplatin, doxorubicin and carboplatin reached 5.2–11.5 months [31]. Shibayama et al. retrospectively evaluated the results of TACE using cisplatin and gelatin sponge in 29 patients with liver metastases from uveal melanoma [32]. Treatment resulted in an overall response rate of 21%, with a median survival time of 23 months. The 1-, 2- and 5-year survival rates were 72.4, 39.4 and 0%. 34.5% of patients suffered a post embolization syndrome, while long-term efficacy was not proven. Valpione et al. retrospectively assessed the outcome of TACE with CPT-11 charged microbeads in 58 patients with liver metastases from uveal melanoma. These patients were compared to 83 patients receiving other first-line treatments. TACE showed better results, with a median survival of 16.5 vs 12.2 months, while TACE did not result in any high-grade toxicities [33]. Chemoembolization using DEB-TACE in 14 patients with liver metastases from melanoma resulted in an OS of 9.4 months, and major complications including one death were reported in 12 cases [34].

Fiorentini et al. evaluated TACE using irinotecan eluting beads in 10 patients with liver metastases from uveal melanoma. All patients showed a partial response. However, the median follow-up time was only 6.5 months, and 2 patients died earlier after treatment [35].

SIRT was evaluated in a retrospective study including 18 patients with uveal melanoma with liver metastases, of whom 14 underwent SIRT and four had systemic chemotherapy as standard treatment [36]. Treatment results were compared to a historical control group receiving systemic chemotherapy. Patients undergoing SIRT had a median OS of 13.5 months, while the control group had a median OS of 10.5 months. In the SIRT group, no high-grade toxicity was observed. However, embolization techniques are generally considered as palliative treatment approach, while surgery and ablation techniques represent potentially curative therapeutic approaches.

Compared to surgical resection, the ablation techniques offer a more tissue sparing, clinically feasible and cost-saving curative treatment approach, with a low complication rate. The ablation procedures are minimally invasive and allow to access tumors that are surgically not treatable due to their localization.

However, no studies with larger patient cohorts comparing surgical and ablation techniques in melanoma patients are available. A retrospective study including 1078 patients with ocular and cutaneous melanoma liver metastases included 58 cases with local liver treatment including resection and ablation. The median OS was reported to be 8 months, and the 5-year OS was 6.6% in the whole group, while patients undergoing liver resection or ablation had OS rates of 24.8 and 30%, respectively, indicating a survival benefit after locoregional treatment [37].

Derek et al. evaluated eight patients with liver metastases from ocular melanoma after enucleation of the primary tumor. One patient had liver segmentectomy, three had combined liver resection and RFA of liver lesions. One patient was not operable, and one patient had RFA. Median survival was 36 months, and RFA was reported as a valuable treatment option in the surgical management of melanoma patients [38].

The comparison of open and percutaneous RFA in two patients with melanoma out of a group of 37 patients with liver metastases yielded no specific information on the outcome of the two melanoma patients [39]. In each of two studies on laparoscopic ablation techniques, only one patient with liver metastases from melanoma was included, giving no detailed information on the outcome of these patients [40,41]. In a study on RFA reporting results from a larger patient cohort, out of 447 patients, 8.5% of all lesions were metastatic melanoma. In this subgroup, the local recurrence rate was reported to be 10.9%, while in the entire cohort the rate reached 6.7% for open RFA, 9% for laparoscopic RFA and 15.1% for percutaneous RFA [42].

One further study has evaluated surgical and/or ablative treatment in metastatic ocular melanoma, with a total number of eight patients being included [39]. Three underwent combined resection and ablation, one patient received RFA alone and one patient resection only, while the other patients had no local treatment due to multilobar metastases. Patients undergoing resection and/or ablation had a median survival of 46 months. However, seven patients also received adjuvant therapies.

Bale et al. have published the first study reporting results from RFA in a larger patient cohort, including their experience in CT guided multi-probe stereotactic radiofrequency ablation (SRFA) in 20 patients with melanoma metastases to the liver [43]. Six patients had an uveal melanoma, and 14 patients suffered from cutaneous melanoma. SRFA was performed under general anesthesia using a navigation system to treat multiple tumors with multiple probes, resulting in a procedure more time-consuming in comparison to conventional image-guided RFA. In this study, patients with up to 14 liver lesions and with a diameter of up to 14.5 cm were treated by SRFA. Overall, 75 liver lesions were treated. The lesions had a median size of 1.7 cm. The authors report a primary success rate of 89.3%, justifying the additional technical
In three patients, retreatment was performed to eliminate residual tumor tissue. The secondary success rate was reported to reach 93.3%. The local recurrence-free survival rate was reported to be 85% at 1 year and 76% at 3 and 5 years after initial treatment. The local recurrence rate reached 13.3%. Main factors leading to local recurrence were insufficient ablation margin below 1 cm due to tumor vicinity to large vessels and metastatic spread through the diaphragm and the proximity to surrounding hollow organs. One out of six patients with ocular melanoma and eight of 14 patients with cutaneous melanoma developed extrahepatic metastases during follow-up. The median OS reached 19.3 months after SRFA. In the group of patients with ocular melanoma, OS reached 38 months, while in the group with cutaneous melanoma OS was low reaching 11.6 months. The median disease-free survival (DFS) in these 20 patients reached 9.3 months.

The treatment effectiveness was evaluated on a lesion basis defined as the absence of residual tumor in the follow-up CT 1 month after treatment. If tumor recurrence or residual tumor were present, re-ablation was performed, and up to four treatment sessions were performed in individual patients. The authors reported no procedure-related deaths. In overall 34 RFA procedures, three complications were observed that needed further treatment, namely pleural drainage of pleural effusions. The median duration of hospitalization was reported to reach 4.5 days.

For the local ablative treatment of lung metastases of melanoma, various case reports are available in the literature indicating a possible long-term benefit, and most patients received RFA as one treatment approach in a multidisciplinary treatment regimen [44,45]. Steels et al. [46] reported combined surgical resection of the primary tumor and one metachronous liver metastasis in combination with RFA of two lung metastases and one liver metastasis, with the patient showing complete remission over a 3 year follow-up period.

Treatment of melanoma metastases in other solid organs has not yet been evaluated in larger patient cohorts, and only small retrospective studies or case reports are available. In a report of 12 patients with adrenal tumors being treated with RFA, two suffered melanoma metastases to the adrenal gland [47]. All of these 12 patients had progression of disease on follow-up imaging. However, the techniques and imaging guidance devices used for these procedures have been developed and advanced since this report in 2004, and further investigations are needed to evaluate a possible role of ablation techniques in this setting.

In-transit nodal metastases of melanoma at the skin level, caused by lymphatic deposits of melanoma cells in locally advanced disease, seem to be another interesting target for thermal ablation. These in-transit metastases are biologically different from distant cutaneous metastases and pose a significant risk of distant metastatic spread. Various therapeutic approaches are applied, including local excision, laser ablation, cryosurgery, regional chemotherapy, isolated limb perfusion, immunotherapy and gene therapy [48]. The locoregional treatment is especially of interest if surgery is limited because of the cosmetic and functional outcome. MRI guided cryoablation of in-transit metastases from melanoma lead to effective local tumor control in small patient cohorts [49]. Thus, thermal ablation may be an attractive, well-tolerated alternative to surgical resection.

Conclusion

Minimally invasive locoregional ablation techniques represent a potentially curative treatment approach for metastatic melanoma patients in selected cases with oligometastatic disease. The ablation procedures offer a clinically safe and feasible treatment with low mortality and morbidity rates compared to surgery, while showing similar results regarding local recurrence and survival rates. Therefore, ablation techniques may be an attractive alternative to improve treatment outcome in a multidisciplinary treatment regimen. Endovascular therapies including TACE and SIRT have shown promising results in terms of efficacy and feasibility in small patient cohort studies in a palliative treatment setting.

Disclosure statement

Reto Bale is a paid consultant for CASCINATION and Interventional Systems. The other authors have no conflicts of interest to disclose.

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