CLINICAL STUDY

# Combined Effects of Yttrium-90 Transarterial Radioembolization around Immunotherapy for Hepatic Metastases from Uveal Melanoma: A Preliminary Retrospective Case Series

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## ABSTRACT

**Purpose:** To evaluate the safety and efficacy of yttrium-90 ($^{90}$Y) transarterial radioembolization (TARE) around immunotherapy in patients with unresectable hepatic metastases from uveal melanoma (UM).

**Materials and Methods:** From March 2013 to December 2017, 11 patients with unresectable hepatic metastases from UM were treated with TARE around immunotherapy. Two patients received TARE as a first-line treatment followed by immunotherapy. Nine patients received immunotherapy before TARE, and 6 of these patients received additional immunotherapy after TARE. Retrospective review of the clinical data was performed to assess hepatic progression-free survival (hPFS), overall survival (OS), treatment response, and toxicities. The median follow-up period from TARE was 10.5 months (range 1–35.5 months).

**Results:** The median OS from diagnosis of hepatic metastases was 35.5 months (95% confidence interval [CI] 10.0–55.0 months). The median hPFS and OS from the start of TARE were 15.0 months (95% CI 5.9–24.1 months) and 17.0 months (95% CI 1.8–32.2 months), respectively. Complete response was observed in 1 patient (9.1%), partial response in 2 (18.2%), stable disease in 4 (36.4%), and progressive disease in 4 (36.4%). Ten patients had grade 1 or 2 clinical toxicities, and 1 had grade 3 with a peptic ulcer. Six patients had grade 1 or 2 biochemical toxicities and 1 had grade 3, which was related to tumor progression.

**Conclusions:** The present results suggest that TARE around immunotherapy is safe and effective. The combined treatment may improve hPFS and OS in patients with hepatic metastases from UM.


## ABBREVIATIONS

hPFS = hepatic progression-free survival, TARE = transarterial radioembolization, UM = uveal melanoma, $^{90}$Y = yttrium-90

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults, with a yearly incidence of 5–6 cases per million in the United States (1). Approximately 50% of patients develop distant metastases, with the liver as the first site of involvement in up to 90% of patients with metastatic UM (2–5). To date, no effective systemic treatment can improve the overall survival (OS) of patients with UM, and metastatic UM is often refractory to traditional chemotherapy (1,6,7). Recently, immune checkpoint antibodies, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1, were explored for patients with metastatic UM that demonstrated poor response (8–10). Previous studies indicated that there was a strong link between the OS and hepatic tumor control (2,11), so locoregional therapies are paramount for patients with hepatic metastases from

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**Table.** Clinical Characteristics of the Patients

| Patient/Sex/Age (y) | ECOG | Liver metastases number | Liver metastases diameter range (mm) | Extrahepatic disease | Immunotherapy before TARE | Immunotherapy after TARE |
|---|---|---|---|---|---|---|
| 1/F/73 | 0 | >10 | 4–15 | None | Pembrolizumab | Ipilimumab, pembrolizumab |
| 2/M/84 | 0 | 7 | 8–43 | Lung, bone | Ipilimumab, pembrolizumab | Pembrolizumab |
| 3/F/65 | 1 | innumerable | 2–74 | Lung, bone, soft tissue | Ipilimumab, nivolumab | Pembrolizumab |
| 4/M/68 | 1 | 10 | 6–24 | Bone, lymph nodes | Pembrolizumab | Pembrolizumab |
| 5/F/46 | 0 | 10 | 5–14 | None | Ipilimumab, pembrolizumab | Nivolumab |
| 6/F/65 | 0 | innumerable | 2–59 | Bone, lymph nodes | Ipilimumab, nivolumab | Ipilimumab, nivolumab |
| 7/M/64 | 2 | innumerable | 3–46 | None | Ipilimumab | None |
| 8/F/45 | 1 | >10 | 6–31 | None | Pembrolizumab, tremelimumab | None |
| 9/F/80 | 1 | >10 | 3–52 | None | Ipilimumab, pembrolizumab | None |
| 10/F/69 | 0 | >10 | 3–46 | None | None | Pembrolizumab |
| 11/M/65 | 1 | 4 | 11–120 | None | None | Ipilimumab |

ECOG = Eastern Cooperative Oncology Group; F = female; M = male; TARE = transarterial radioembolization.

UM. Common locoregional modalities include surgical resection, thermal ablation, and transarterial therapy (hepatic perfusion, chemoembolization and immunoembolization, et cetera) However, surgical resection and thermal ablation are often not feasible owing to the number of lesions or their location. As a result, transarterial therapies are frequently performed (11,12).

In recent years, transarterial radioembolization (TARE) with the use of yttrium-90 ($^{90}$Y)–labeled microspheres has gained increasing acceptance for primary and secondary liver malignancies, which can improve OS of patients with a favorable tolerability profile (13–16). Because radiotherapy can often achieve excellent local control for primary UM (17), TARE can be a promising option for patients with hepatic metastases from UM. Several studies have shown that TARE is safe and effective salvage therapy for patients with hepatic metastases from UM (18–22). However, these cohorts were treated in the era before the introduction of immune checkpoint antibodies for the metastatic UM population. As a result, there have been no reports that describe combined effects of TARE and concurrent immunotherapy. The purpose of the present study was to evaluate the safety and efficacy of TARE around immunotherapy in patients with unresectable hepatic metastases from UM.

## MATERIALS AND METHODS

### Patients

This retrospective study was approved by the Institutional Review Board with waiver of informed consent and was compliant with the Health Insurance Portability and Accountability Act. From March 2013 to December 2017, 11 patients (4 men and 7 women) with histologically proven unresectable hepatic metastases from UM were treated with TARE around immunotherapy. Four patients had extrahepatic metastases that were not considered to be life threatening. The mean age was 65.8 ± 11.9 years (range 45–84 years; Table). Two patients received TARE as a first-line treatment, followed by CTLA-4 or PD-1 antibody therapy. Nine patients initially received CTLA-4 and/or PD-1 antibody therapy and were referred for TARE after documentation of disease progression. Six of these patients received additional immunotherapy after TARE. The treatment process with immunotherapy and TARE is shown in Figure 1. All patients were classified as Child-Pugh A and Eastern Cooperative Oncology Group performance status 0–2 before TARE (Table). The median intervals from diagnosis of hepatic metastases to the start of immunotherapy and to the start of TARE were 1 month (range 3 days to 18.8 months) and 9.0 months (range 2.0–37.5 months), respectively. Before TARE, all patients presented with hepatic metastases of both lobes with a tumor burden of < 25% in 8 (72.7%) and 26%–50% in 3 (27.3%) patients. Eight patients had >10 intrahepatic lesions and three had 4, 7, and 10 lesions, respectively (Table).

### Radioembolization Procedure

TARE was performed according to previously published guidelines (23,24). First, mapping angiography was performed to identify the tumor-feeding vessels and anatomic variants and to embolize extrahepatic vessels (gastroduodenal artery, right gastric artery, et cetera) as deemed to be necessary by the interventional radiologist performing the procedure. Thereafter, technetium-99m macroaggregated albumin was injected into the targeted hepatic arteries to access the hepatopulmonary shunt fraction. The median lung fraction was 4.2% (range 1.7%–16.0%) in the present study. TARE was performed with the use of $^{90}$Y resin microspheres (SIR-spheres; Sirtex, Wilmington, Massachusetts) a median of 11 days (range 0–18 days) after mapping angiography. For