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Review

A systematic review of yttrium-90 radioembolization for unresectable liver metastases of melanoma

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ABSTRACT

Purpose: To assess the effectiveness of yttrium-90 (^{90}Y) radioembolization in the treatment of unresectable liver metastases of melanoma.

Methods: PubMed and EMBASE were systemically searched for all English language studies related to ^{90}Y radioembolization for unresectable liver metastases of melanoma, including clinical trials, observational studies, and abstracts from conferences, published between January 1991 and March 2016.

Results: A total of 12 reports (7 observational studies and 5 abstracts from conferences) involving 255 patients were included in the analysis. The primary sites of melanoma were cutaneous (n = 22; 8.6%), ocular (n = 197; 77.3%), rectal (n = 3; 1.2%), and unknown (n = 33; 12.9%). The median disease control rate at 3 months was 73.6% (range, 58.3%–88.9%). Among the 207 patients for whom tumor response at 3 months was reported, complete response was seen in 1.0% (2/207), partial response was seen in 19.3% (40/207), stable disease was seen in 46.9% (97/207), and progressive disease was seen in 32.9% (68/207). The median survival was 10 months (range, 7–13.4 months), and the median 1-year survival rate was 34.6% (range, 23%–80%). Complications of ^{90}Y radioembolization were reported in 13 cases. The most common side effects were fatigue (median, 36.1%), abdominal pain (median, 17.8%), and nausea (median, 15.0%).

Conclusions: ^{90}Y radioembolization is a promising alternative therapy for the treatment of unresectable liver metastases of melanoma, with encouraging effects on disease control and survival. Some complications can occur, and side effects are frequent but mild.

1. Introduction

Melanoma is a malignant tumor arising from melanocytes, with the primary tumor most commonly occurring in the eye and skin [1]. Even when the primary tumor is treated, half of affected patients will develop systemic metastasis [2]; the liver is the predominant organ of metastatic involvement. Without aggressive treatment, patient survival after the discovery of liver metastases ranges from 3 to 12 months [3–5]. Unfortunately, mortality rates have not changed significantly over the past 3 decades [3–5]. Although surgical treatment offers the best chance of curing localized liver metastasis, the median survival with this treatment is only 11 months, with a 5-year survival rate of just 7% [6]. Additionally, most patients with melanoma present with multiple lesions and are no longer candidates for surgery. Systemic chemotherapy in this scenario has a poor response rate [4], and interferon alpha is of no benefit in patients with melanoma liver metastasis [7]. Thus, the management of this condition is a clinical challenge.

Locoregional treatments are generally recommended for patients with unresectable melanoma liver metastasis. These treatments may include percutaneous ablation [8], external irradiation [9], percutaneous ethanol injection (PEI) [8], transcatheter arterial embolization (TAE) [8,10], transcatheter arterial chemoembolization (TACE) [8,10], and yttrium-90 (^{90}Y) radioembolization [12]. Percutaneous ablation, external irradiation, and PEI are less applicable and more difficult to perform because of the diffuse nature of melanoma liver metastasis. TAE and TACE are associated with a higher incidence of side effects that may require medication intervention [11].

^{90}Y radioembolization is a form of intra-arterial brachytherapy that has emerged as a promising treatment option for unresectable liver metastases of melanoma [12–14]. However, there is still a need to systematically evaluate the outcomes of ^{90}Y radioembolization in these patients. The purpose of this study was to comprehensively review the effectiveness of ^{90}Y radioembolization for the treatment of unresectable liver metastasis of melanoma.

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2. Methods

2.1. Search strategy

PubMed and EMBASE were searched for English language studies describing ^{90}Y in the treatment of melanoma liver metastasis published between January 1, 1991 (introduction of first commercially available ^{90}Y product) and March 15, 2016. The search was conducted using the keywords "melanoma," "yttrium-90," "^{90}Y," "Y^{90}," "TheraSphere," and "SIR-Spheres." Potentially relevant articles were retrieved; and their reference lists were reviewed to identify any missed studies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) clinical trials, clinical studies, or abstracts from conferences; 2) reports that described ^{90}Y in the treatment of melanoma liver metastasis; and 3) studies that included at least overall survival or 1-year survival rate (with overall survival calculated from the date of first ^{90}Y treatment to the date of death or last follow-up). Additionally, when centers published studies with accumulating numbers of patients or increased lengths of follow-up, only the most recent and complete reports were included for qualitative appraisal and efficacy assessment. Exclusion criteria were as follows: 1) review articles, animal studies, laboratory investigations, case series, and case reports; and 2) any duplicated clinical studies.

2.3. Data extraction

A standardized data extraction database was created by tabulating the following information for each study: title, journal, first author, study design (prospective or retrospective), quality criteria, patient characteristics, primary sites of melanoma, follow-up time, disease control rate, tumor response, overall survival, 1-year survival rate, complications, and side effects/toxicity. Two members of the research team conducted the literature search independently to verify data accuracy and completeness, with a third resolving any uncertainties. Studies were classified by their level of evidence as follows: level I, randomized controlled trials (RCTs); level II, non-RCTs or well-designed cohort studies; and level III, observational studies as described by the US Preventive Services Task Force.

3. Results

The initial search yielded 193 English reports from January 1, 1991, to March 15, 2016. Of the 193 reports, a total of 181 reports were excluded because they did not contain overall survival or 1-year survival rate (n = 169) or were review articles (n = 8) or case reports (n = 4). Ultimately, a total of 12 retrospective reports (7 observational studies and 5 abstracts from conferences) were included in the analysis (Fig. 1). The quality of evidence for the included 12 reports was level III.

Table 1 summarizes the patient demographics for each included study. A total of 255 patients were included in the final analysis. The median percentage of male patients was 44.7% (range, 0%–50.0%), and the median patient age was 56.5 years (range, 48.8–63 years). The primary sites of melanoma were cutaneous (n = 22; 8.6%), ocular (n = 197; 77.3%), rectal (n = 3; 1.2%), and unknown (n = 33; 12.9%). Extrahepatic metastases were present in a median of 63.0% of patients (range, 12.5%–92.0%). The median number of ^{90}Y procedures was 1.7 per case (322/195).

Table 2 summarizes the effectiveness of ^{90}Y radioembolization with respect to tumor response and survival. Only 4 studies reported the median length of follow-up after ^{90}Y radioembolization (range, 9.9–39.6 months). The median disease control rate was 73.6% (range, 58.3%–88.9%). The tumor response at 3 months was reported for 207 patients, with complete response reported in 1.0% (2/207), partial response in 19.3% (40/207), stable disease in 46.9% (97/207), and progressive disease in 32.9% (68/207). The median survival of 91.7% (11/12) studies was 10 months (range, 7.0–13.4 months); among patients with Child-Pugh disease class reported, the median overall survival was 12.7 months, 1.9 months, and 0.9 months for patients with class A (n = 44), class B (n = 5), and class C (n = 3) disease, respectively. The median 1-year survival rate was 34.6% (range, 23.0%–80.0%).

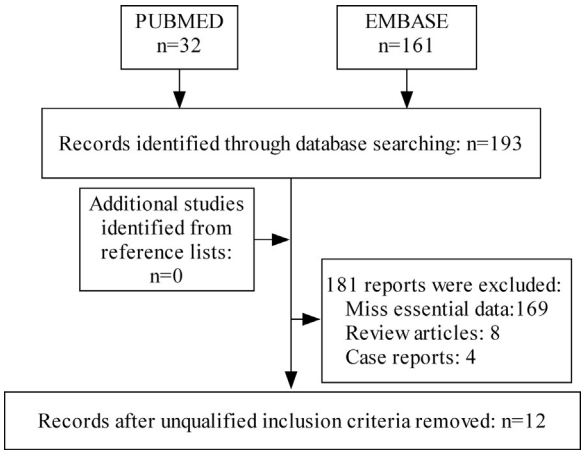

Fig. 1. Screening and selection of the literature.

The complications of ^{90}Y radioembolization included bilirubin toxicity (n = 4), liver failure (n = 3), gastric ulceration (n = 2), absolute lymphocytopenia (n = 2), elevation in aspartate aminotransferase level (n = 1), and cholangitis (n = 1). Table 3 presents a thorough overview of the side effects associated with ^{90}Y radioembolization. The most common side effects were fatigue (median, 36.1%; range, 14.3%–44%), abdominal pain (median, 17.8%; range, 7%–38%), and nausea (median, 15%; range, 0%–23%).

4. Discussion

This study demonstrated that ^{90}Y radioembolization therapy was associated with a disease control rate of 73.6% in patients who had unresectable liver metastases of melanoma, with a median survival of 10 months and a 1-year survival rate of 34.6%. Complications were reported in 13 patients, and side effects were frequent but mild.

Surgical resection is the only curative option for melanoma liver metastasis [24,25]. Unfortunately, most patients with this condition present with multiple hepatic metastatic lesions, making these patients ineligible for surgery. The role of liver transplant in this disease remains controversial [26]. The management of unresectable liver metastases of melanoma is therefore a clinical dilemma, especially for patients in whom a variety of systemic and locoregional treatments have failed.

^{90}Y radioembolization is a form of intra-arterial brachytherapy that was originally found to be effective for the treatment of advanced hepatocellular carcinoma and liver metastases of colorectal cancer [27,28]. However, the application of ^{90}Y microspheres in metastatic melanoma has not been approved by the US Food and Drug Administration (FDA), and the value of ^{90}Y microspheres in the treatment of unresectable liver metastasis of melanoma had not previously been systematically evaluated.

Other therapies for unresectable liver metastases of melanoma have demonstrated varying effects on survival. In one study of patients with metastatic uveal melanoma, the median overall survival with bevacizumab plus temozolomide as first-line systemic chemotherapy was 10 months [29]. In a study of patients with advanced melanoma, the median overall survival with ipilimumab monotherapy was 8.7 months [30]. In another study of patients with melanoma liver metastases, the median overall survival with percutaneous hepatic perfusion was 10.6