



Review

Yttrium-90 radioembolization for unresectable metastatic neuroendocrine liver tumor: A systematic review

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ABSTRACT

Objective: To evaluate the value of yttrium-90 (⁹⁰Y) microspheres in the management of unresectable liver metastases secondary to neuroendocrine tumors (NETs).

Materials and methods: PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and the “gray” literature (Google Scholar) were searched for all studies related to ⁹⁰Y therapy for unresectable liver metastases of NETs.

Results: A total of 11 studies and 7 abstracts involving 870 patients were included in the final analysis. In 11 of these studies, 19.8% (77/388) of patients had undergone transarterial bland embolization (TABE) or transarterial chemoembolization (TACE) before ⁹⁰Y therapy. The median disease control rate among all patients was 86% at 3 months after ⁹⁰Y therapy. The median survival was 28 months, with 1-, 2-, and 3-year survival rates of 72.5%, 57%, and 45%, respectively. The median survival values for patients who received resin- and glass-based ⁹⁰Y treatment were 27.6 and 31.7 months, respectively. The survival values for patients with carcinoid, pancreatic, and unclassified origin of NETs were 56, 31, and 28 months, respectively; the survival values for patients with grade I, II, and III NETs were 71, 56, and 28 months, respectively. Carcinoid syndrome was reported in 52.4% (55/105) of patients, and 69.1% of those with clinical symptoms demonstrated improvement in symptoms after ⁹⁰Y radioembolization. Complications were reported in 9 studies, including radiation gastritis (n = 4), duodenal ulcer (n = 2), death due to liver failure (n = 1), and radiation cholecystitis (n = 1). The most common side effects were abdominal pain (median, 32.6%), nausea/vomiting (median, 32.5%), and fatigue (median, 30.4%).

Conclusions: ⁹⁰Y radioembolization can be used as an alternative therapy for unresectable liver metastases of NETs, with an improved survival rate and tumor response. This treatment is also effective for patients who have undergone unsuccessful TABE/TACE therapy and for the relief of symptoms in patients with carcinoid syndrome.

1. Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms that are thought to arise from neuroendocrine cells and their precursors located throughout the body [1]. The overall incidence of these tumors is reported to be 5.25 per 100,000 people [2]. The tumors are characterized by variable but most often indolent biologic behavior; therefore, NETs are often asymptomatic until liver metastases occur, which is the leading cause of death for patients with this disease [2–4]. In some patients, the tumors are able to secrete peptides that result in a distinctive hormonal syndrome known as the carcinoid syndrome.

Systemic treatment options for metastatic NETs are limited to therapies that control tumor growth and/or symptoms of hormone hypersecretion from gastroenteropancreatic NETs and therapies that

treat poorly-differentiated neuroendocrine carcinomas. Local treatment options play an important role in treating patients with well-differentiated metastatic gastroenteropancreatic NETs. For the initial management of hepatic metastases from carcinoid or NETs that are resectable, surgery is considered to offer the best chance for curing localized liver metastasis [5–7]. Unfortunately, most patients present with multifocal disease and are no longer candidates for surgery. The role of ablation (radiofrequency ablation, cryoablation, microwave ablation) in the therapeutic management of small (< 3 cm) neuroendocrine liver metastases, particularly in patients who are eligible for resection, is undefined. Because most patients present with multifocal and bilateral disease, ablation is most often used as an adjunct to surgical resection to allow local treatment of all disease when major hepatectomy alone might compromise residual liver function.

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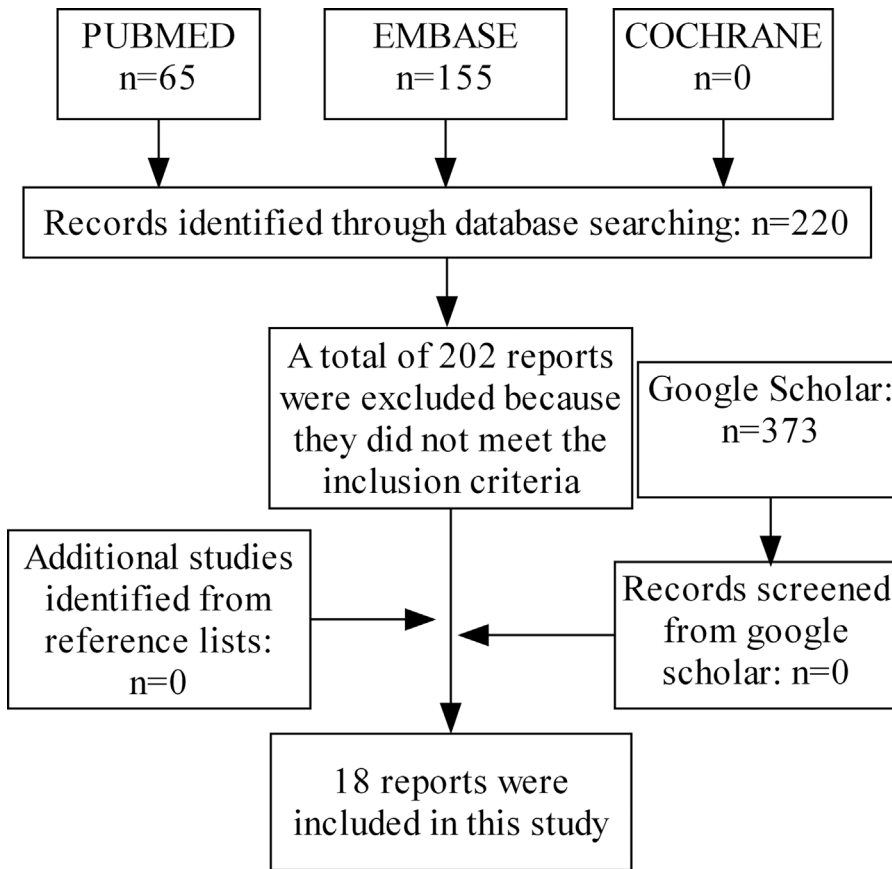


Fig. 1. Screening and selection of the literature.

Therefore, the management of unresectable liver metastases of NETs is often a clinical challenge. Many therapies have been used to treat this condition, but the clinical outcomes with these options remain poor.

Yttrium-90 (^{90}Y) radioembolization is a form of intra-arterial brachytherapy that has emerged as a new option for the treatment of unresectable liver metastases of NETs over the past two decades [8]. The purpose of this study was to comprehensively evaluate the value of ^{90}Y microsphere treatment in the management of unresectable liver metastases of NETs.

2. Methods

2.1. Search strategy

PubMed, EMBASE, the Cochrane Database of Systematic Reviews, and the “gray” literature (Google Scholar) were searched for studies describing ^{90}Y in the treatment of liver metastasis of NETs that were published between January 1, 1991 (first commercially available ^{90}Y product), and February 14, 2016. The keywords used for this search were as follows: neuroendocrine tumor, neuroendocrine cancer, liver metastases, hepatic metastases, yttrium-90, ^{90}Y , TheraSphere, SIR-Spheres, and English language. The references from retrieved articles were cross-searched to identify any studies missed by these electronic search strategies.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) clinical trials, clinical studies, or abstracts from conferences; 2) studies describing ^{90}Y microspheres in the treatment of liver metastasis of NETs; and 3) studies that included at least overall survival as an outcome, which was calculated from the date of first ^{90}Y treatment to the date of death or last follow-up.

Exclusion criteria were as follows: 1) review articles, animal studies, laboratory investigations, case reports, and case series; and 2) any duplicated clinical studies or abstracts. 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; the others were defined as duplicated clinical studies.

2.3. Data extraction

A standardized data extraction database was created by tabulating the following information: title, journal or conference, year of publication, first author and corresponding author, prospective or retrospective design, quality criteria, patient characteristics, primary NETs, NETs grade, presence of carcinoid syndrome, ^{90}Y products used (TheraSphere or SIR-Spheres), follow-up time, disease control rate (percentage of patients who achieved complete response, partial response, or stable disease with ^{90}Y therapy) [9], radiological response and the assessment criteria (Response Evaluation Criteria In Solid Tumors [RECIST], modified RECIST [mRECIST], World Health Organization [WHO] criteria, or European Association for the Study of the Liver [EASL] criteria), overall survival, factors related to survival, complications, and side effects/toxicity. Studies were classified into three levels 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 U.S. Preventive Services Task Force [10].

3. Results

Our initial search returned 220 studies in English published between January 1, 1991, and February 14, 2016. Further search using Google Scholar found no additional relevant articles. Of the 220 reports, a total

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