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ScienceDirect

EJSO 41 (2015) 120–127

EJSO the Journal of Cancer Surgery

www.ejso.com

Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: A systematic review and pooled analysis

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Accepted 22 September 2014
Available online 7 October 2014

Abstract

Radioembolization with yttrium-90 microspheres offers an alternative treatment option for patients with unresectable intrahepatic cholangiocarcinoma (ICC). However, the rarity and heterogeneity of ICC makes it difficult to draw firm conclusions about treatment efficacy. Therefore, the goal of the current study is to systematically review the existing literature surrounding treatment of unresectable ICCs with yttrium-90 microspheres and provide a comprehensive review of the current experience and clinical outcome of this treatment modality. We performed a comprehensive search of electronic databases for ICC treatment and identified 12 studies with relevant data regarding radioembolization therapy with yttrium-90 microspheres. Based on pooled analysis, the overall weighted median survival was 15.5 months. Tumour response based on radiological studies demonstrated a partial response in 28% and stable disease in 54% of patients at three months. Seven patients were able to be downstaged to surgical resection. The complication profile of radioembolization is similar to that of other intra-arterial treatment modalities. Overall survival of patients with ICC after treatment with yttrium-90 microspheres is higher than historical survival rates and shows similar survival to those patients treated with systemic chemotherapy and/or trans-arterial chemoembolization therapy. Therefore, the use of yttrium-90 microspheres should be considered in the list of available treatment options for ICC. However, future randomized trials comparing systemic chemotherapy, TACE and local radiation will be required to identify the optimal treatment modality for unresectable ICC.

Keywords: Cholangiocarcinoma; Radioembolization; Yttrium-90 microsphere

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a malignant transformation of cholangiocytes within the hepatic parenchyma. The incidence of this primary liver malignancy is increasing,[1,2] and ICC accounts for up to 15% of primary liver cancers.[3] In contrast to the other two locations of cholangiocarcinoma (hilar and distal bile duct), intrahepatic lesions are often asymptomatic and, therefore, present as an incidental mass lesion without jaundice or other stigmata of biliary obstruction.[4] Given the asymptomatic nature of many ICCs, patients often present with locally advanced tumours. Although surgery offers the highest curative potential, many tumours are deemed unresectable at the time of diagnosis.[5] Patients with unresectable ICC have a median survival of less than eight months.[6,7] Systemic chemotherapy with gemcitabine and cisplatin offers an overall survival advantage in patients with advanced biliary cancer[8]; however, given the aggressive nature of

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http://dx.doi.org/10.1016/j.ejso.2014.09.007

cholangiocarcinoma and overall poor prognosis, other treatment modalities are being investigated.[9–11]

Radioembolization with yttrium-90 microspheres offers an alternative radiotherapy option for primary and secondary intrahepatic tumours.[12] In this treatment modality, β-emitting yttrium-90 microspheres are injected into the hepatic artery feeding the tumour, become trapped in the tumour and emit local internal radiation. The advantage of radioembolization is the ability to deliver high dose radiation to the tumour with minimal collateral damage to the normal liver parenchyma or surrounding tissues.[13] In contrast, non-selective external beam radiation has higher rates of radiation-induced liver disease as normal hepatic tissue is radiated in addition to the tumour. Recently, yttrium-90 radioembolization for the treatment of hepatocellular carcinoma showed a longer time-to-progression and fewer side-effects than trans-arterial delivered chemotherapy protocols.[14,15] In addition, high response rates were seen with radioembolization treatment of intrahepatic neuroendocrine tumours.[16,17]

Patients with unresectable cholangiocarcinoma have limited treatment options with only modest survival advantages.[8,11] Local therapy with yttrium-90 microspheres offers the promise of delivering a high dose of radiation directly to the tumour, thereby causing increased tumour destruction. Treatment of ICCs with radioembolization has been attempted; however, only small trials have been performed with this novel treatment. In addition, the relative rarity of ICCs and heterogeneity of this disease makes it difficult to draw firm conclusions about treatment efficacy. The goal of the current study is to systematically review the existing literature surrounding treatment of unresectable ICCs with yttrium-90 microspheres with the aim of providing a comprehensive review of the current experience and clinical outcome of this treatment modality.

Methods

Inclusion criteria for considering studies for this review

Study characteristics

Given the rarity of yttrium-90 radioembolization treatment for unresectable ICC, studies with greater than one patient were included in order to ensure the comprehensive capture of the available clinical experience. This included human case-series (>1 case), randomized controlled trials, non-randomized controlled trials, prospective cohort series.

Participants

The target population consists of adult (>18 years old) male or female patients with unresectable ICC.

Interventions

The intervention under study is radioembolization therapy with yttrium-90 microspheres. The yttrium-90 microsphere treatment may be performed before, synchronously, or after systemic chemotherapy.

Outcome measures

Primary outcomes

The primary outcomes are overall survival and radiological response to radioembolization therapy with yttrium-90 microspheres.

Secondary outcomes

The secondary outcomes of this study are the ability of yttrium-90 treatment to convert unresectable cholangiocarcinoma to resectable, mortality, and morbidity.

Search methods for identification of studies

Electronic searches

Published English-language manuscripts were considered for review with inclusion from 2000 to 2013. A comprehensive search of electronic databases (e.g., MEDLINE, EMBASE, SCOPUS, BIOSIS Previews and the Cochrane Library) using broad search terms was completed. The bibliographies of all included articles were examined to identify additional potentially relevant publications. Search terms included unresectable intrahepatic cholangiocarcinoma, advanced biliary tract cancer, microsphere, SIR-Spheres, Selective Internal Radiation, TheraSphere, yttrium-90, radioembolization and radiation lobectomy.

Data collection and analysis

Selection of studies

All studies involving radioembolization therapy with yttrium-90 microspheres for unresectable ICCs were included. Given the rarity of studies focussing on yttrium-90 microsphere treatment, manuscripts published in abstract form were included. A dedicated search for the full-length manuscripts of published abstracts was also undertaken. A trained librarian conducted the electronic searches (X.S.), and one author (D.A.) conducted a prescreen to identify the articles clearly irrelevant articles by title, abstract and keywords of publication. Following this, three independent reviewers (R.G., S.A. and D.A.) assessed the studies for relevance, inclusion, and methodological quality. Articles were classified as either:

1 Relevant (meeting all specified inclusion criteria);
2 Possibly relevant (meeting some but not all inclusion criteria);
3 Rejected (not relevant to the review).

Three reviewers (R.G., S.A. and D.A.) independently reviewed full-text versions of all studies classified as relevant or possibly relevant. Disagreements were resolved by re-extraction, when necessary. In the cases of numerous