

# Comparison of the survival and tolerability of radioembolization in elderly vs. younger patients with unresectable hepatocellular carcinoma

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**Background & Aims:** The European Network on Radioembolization with Yttrium-90 resin microspheres study group (ENRY) conducted a retrospective study to evaluate the outcomes among elderly ( $\geq 70$  years) and younger patients ( $< 70$  years) with unresectable hepatocellular carcinoma (HCC) who received radioembolization at 8 European centers.

**Methods:** Patients with confirmed diagnosis of unresectable HCC who either progressed following resection or locoregional treatment and/or who were considered poor candidates for chemoembolization were evaluated by a multidisciplinary team for radioembolization with <sup>90</sup>Y-resin microspheres (SIR-Spheres; Sirtex Medical). The survival outcome and all adverse events were compared between the two age groups.

**Results:** Between 2003 and 2009, 128 elderly and 197 younger patients received radioembolization. Patients in both groups had similar demographic characteristics. Many elderly and younger patients alike had multinodular, BCLC stage C disease, invading both lobes ( $p = 0.648$ ). Elderly patients had a lower tumor burden, a smaller median target liver volume ( $p = 0.016$ ) and appeared more likely to receive segmental treatment ( $p = 0.054$ ). Radioembolization was equally well tolerated in both cohorts and common procedure-related adverse events were predominantly grade 1–2 and of short duration. No significant differences in survival between the groups were found ( $p = 0.942$ ) with similar median survival in patients with early, intermediate or advanced BCLC stage disease.

**Conclusions:** Radioembolization appears to be as well-tolerated and effective for the elderly as it is for younger patients with unresectable HCC. Age alone should not be a discriminating factor for the management of HCC patients.

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**Keywords:** Elderly patients; Hepatocellular carcinoma; HCC; Radioembolization; SIRT; Safety; Tolerability; Survival.

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**Abbreviations:** HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; AEs, adverse events; INR, International Normalized Ratio; MELD, Model for End-Stage Liver Disease; SIRT, selective internal radiation therapy; <sup>90</sup>Y, Yttrium-90; ENRY, European Network on Radioembolization with Yttrium-90; EASL, European Association for the Study of the Liver; CT, computed tomography; AFP, alpha fetoprotein; ECOG, European Cooperative Oncology Group; <sup>99m</sup>Tc-MAA, Technetium-99m macroaggregated albumin; CTCAE, common toxicity criteria adverse events; GI, gastrointestinal; ANOVA, analysis of variance; SD, standard deviation; ALT, alanine transaminase; GBq, gigabecquerel; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; REILD, radioembolization-induced liver disease; GGTP, gamma-glutamyl transpeptidase.



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# Research Article

## Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and its incidence is increasing [1,2] particularly in the elderly population, defined in this paper as those over the age of 70 years [3–5]. As the life expectancy improves within the general population, discussions on the best way to manage ageing HCC patients have become increasingly relevant. The elderly tend to be considered clinically ‘fragile’ due to comorbidities and a poorer performance status, which make them less amenable and/or tolerant to resection, transarterial or systemic treatment [6–8]. In the past, the elderly have been considered poor candidates for major surgery and non-surgical treatments such as radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), and transarterial chemoembolization (TACE). This assumption has been challenged by recent evidence, which suggests that the outcome of radical and/or other effective HCC treatments is not influenced by age, when the correct selection of patients is adopted [5,6]. However, since the majority of these data come from undifferentiated groups, not distinguished by prognostic factors [1,6], these results remain controversial and the impact of old age *per se*, as an independent factor affecting outcome, has yet to be clarified. After major hepatectomy for HCC, there is a trend towards higher morbidity and mortality rates in the elderly compared with the young [9], but these differences tend not to be statistically significant [9–11].

TACE is widely used as a non-surgical treatment and is considered to be effective in prolonging survival in patients with HCC and may be an acceptable alternative to surgery for high-risk elderly patients. The literature, however, reflects the divergent experience with TACE with equivalent outcomes in the young and old subjects in some studies [6,9,12,13], and poorer outcomes in the elderly in other studies [14,15].

RFA and PEI are radical therapies, which are recommended for very early stage HCC by the most recent amendment to the Barcelona Clinic Liver Cancer (BCLC) staging system [16]. Although the published data in the elderly are limited, a large series from Japan [17,18] has recently suggested that RFA might be as safe and as effective in elderly and non-elderly patients alike, and that both should be treated in the same manner.

There is, however, some evidence from the US National Organ Procurement and Transplantation Network which suggests that age may be a key factor determining prognosis amongst the few elderly transplant recipients [19]. Overall, survival for septuagenarians with liver transplants (compared with younger patients) declined more rapidly with time when they have undergone transplantation (even though elderly transplant recipients tended to be healthier than younger transplant recipients with a lower incidence of diabetes, lower Body Mass Indices, lower International Normalized Ratios [INR], higher serum albumin levels, and a lower Model for End-Stage Liver Disease [MELD] score) [19]. Due to the greater incidence of confounding factors with increasing age, elderly patients are less likely to be eligible for treatment with resection and/or loco-regional therapies, regardless of disease stage, and instead tend to be managed with systemic therapies such as sorafenib [8]. The limited published data on sorafenib in the elderly indicated that increasing age does not appear to impact on the tolerability of sorafenib with a similar frequency of sorafenib-associated adverse events (AEs) and median

treatment duration across the age groups [20,21]. However, Morimoto and colleagues observed that those patients older than 75 years tend to experience more frequent side effects with standard doses of sorafenib [20] and for those at increased risk for thromboembolic and/or bleeding events, therapy interruptions may increase the risk of a rapid disease progression [7].

Radioembolization (also known as selective internal radiation therapy [SIRT]) has been recently confirmed as an effective and well-tolerated therapy in intermediate- and advanced-stage HCC patients [22–26], but the effects of advancing age on the tolerance and clinical outcomes following radioembolization in elderly patients are largely unknown with only one previous published report in a cohort with either primary or metastatic liver tumors [27].

Therefore, a retrospective analysis was conducted by the European Network on Radioembolization with Yttrium-90 (<sup>90</sup>Y) resin microspheres (ENRY) study group to evaluate the clinical outcomes among elderly compared with younger patients based on the database generated by the radioembolization treatment of 325 patients with unresectable HCC performed at eight European centers. This analysis supplements the data, published in *Hepatology* [25], from the primary analyses of this cohort.

## Materials and methods

### Patient enrollment

Local Review Board authorization was received to conduct a retrospective analysis of consecutive elderly and younger patients with unresectable HCC who received radioembolization between 25 September, 2003 and 17 December, 2009.

Prior to treatment, patients were evaluated by multidisciplinary teams for their suitability for radioembolization with <sup>90</sup>Y resin microspheres (SIR-Spheres<sup>®</sup>; Sirtex Medical Limited, Sydney, Australia). All patients in these analyses had a confirmed diagnosis of HCC with liver-only or liver-dominant tumors, which had either progressed following surgical resection or loco-regional treatment and/or who were considered poor candidates for TACE because of presence of portal vein invasion or thrombosis or extensive tumor burden. Diagnosis of HCC was either histologically proven or based on the European Association for the Study of the Liver (EASL) criteria [16,28].

Baseline computed tomography (CT) scans of the abdomen and chest were performed in order to evaluate tumor burden, location, the volume of both the target tumor and liver. Laboratory blood tests, including a complete blood count, prothrombin time, liver function tests, creatinine, and alpha-fetoprotein level (AFP) measurements were obtained. Baseline functional performance status of each patient was determined according to the European Cooperative Oncology Group (ECOG) criteria.

The appropriateness of radioembolization was considered by multidisciplinary teams consisting of hepatologists, oncologists, radiotherapists, physicians, and radiologists. Only patients who met the following inclusion criteria were considered for radioembolization [25]: ECOG performance status of 0–2; an untreated life expectancy of >12 weeks; not amenable to curative therapy (surgical resection, ablation or liver transplantation); uncompromised pulmonary function; adequate hematologic parameters (i.e., granulocyte count  $1.5 \times 10^9/L$ , platelets  $50 \times 10^9/L$ ), renal function (creatinine <2.0 mg/dL), and liver function (i.e. bilirubin  $\leq 2.0$  mg/dL). Patients were excluded from radioembolization if there was: evidence of any uncorrectable flow to the gastrointestinal (GI) tract observed on angiography or Technetium-99m macroaggregated albumin (<sup>99m</sup>Tc-MAA) scan; estimated radiation dose greater than 30 Gy (16.5 mCi) delivered to the lungs in a single administration or 50 Gy on multiple administrations; abnormal organ or bone marrow function (total bilirubin level >2.0 mg/dL in the absence of a reversible cause; serum albumin <3.0 g/dL); limited hepatic reserve; or ascites or other clinical signs of liver failure on physical examination. The radioembolization procedure has previously been described [25].

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