

# The Effect of Local Regional Therapy on Post-transplantation Survival Rate in Patients with Hepatocellular Carcinoma

Wei Chen<sup>1</sup>, Xiaoli Yang<sup>2</sup>, Yakun Wu<sup>3,\*</sup>

<sup>1</sup>Department of General Surgery, Hospital of traditional Chinese medicine of Yubei, Chongqing, 400010, China

<sup>2</sup>Department of Hepatobiliary Surgery, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, China

<sup>3</sup>Department of Hepatobiliary Surgery, Suining Central Hospital, Suining 629000, China

\*Corresponding author: 353827514@qq.com

**Abstract Background and Objective:** This study aims to use meta-analysis to evaluate whether pre-transplantation local regional therapy (LRT) can improve the survival of patients with hepatocellular carcinoma who accepted liver transplantation. **Methods:** Relevant studies were identified by searching PUBMED, EMBASE and Web of Science Databases up to May 2015. Endpoints were 1 year, 3 years, and 5 years survival rate after liver transplantation. **Results:** Analysis of nine retrospective studies including 1097 patients did not reveal significant difference in 1 year, 3 years and 5 years survival rate between the patients who got LRT or not. Analysis of four retrospective studies including 504 patients showed patients with complete response to LRT have higher 5 years survival rate. **Conclusions:** The results of this meta-analysis suggest that the patients with complete response to LRT have higher post-transplantation survival rate. But LRT before liver transplantation can't improve the overall survival rate.

**Keywords:** liver transplantation, hepatocellular carcinoma, local regional therapy, meta-analysis

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## 1. Introduction

Liver cancer is the fifth most commonly diagnosed cancer and the second most frequent cause of cancer death in men worldwide [1]. During the current treatments for HCC, liver transplantation is considered as the best one [2]. However, due to an increased waiting period caused by the limited availability of suitable donors, more and more transplantation centers adopt pre-transplantation local regional therapy (LRT) to control tumor progression, reduce dropout or down stage the tumors beyond Milan<sup>1</sup> or BCLC criteria [3]. LRT mainly includes radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and percutaneous ethanol injection (PEI), which can induce tumor necrosis and control progression. But if LRT before liver transplantation can improve survival rate in patient with hepatocellular is still disputed. Sourianarayanan's research showed LRT followed by liver transplantation in HCC appears not to have an impact on post-transplant outcome [4]. Kim et al. showed that Pre-transplant LRT did not affect post-transplant outcomes in patients meeting Milan criteria but did result in lower 3 years HCC recurrence and better three-year survival in patients meeting R4T3 criteria [5]. Bharat et al.

also indicated that the LRT group had better 5-year survival [6]. In addition, some studies indicated that the patients with complete response (CR) to LRT have higher 5 years survival rate [7,8,9,10], but their samples were small. So, we use meta-analysis to compare if the patients accepted LRT before liver transplantation have higher post-operation survival rate and if the patients achieving complete response (CR) to LRT have higher survival rate.

## 2. Method

### 2.1. Study Selection

A literature search was performed using Embase, Medline and Web of Science Databases up to May 2015. The following terms were used: "liver transplantation", "local regional therapy(LRT)", "bridge therapy", "bridging therapy", "transarterial chemoembolization (TACE)", "Radio-frequency ablation (RFA)" and "Percutaneous ethanol injection (PEI)". All abstracts, studies, and citations scanned were reviewed.

### 2.2. Data Extraction

Two reviewers independently selected studies, accessed quality and extracted data. Discrepancies were resolved by consensus.

<sup>1</sup> Milan criteria: one lesion smaller than 5 cm, up to 3 lesions smaller than 3 cm, no extrahepatic manifestations, no vascular invasion

**2.3. Inclusion Criteria**

To enter our analysis, studies had to:

Take the liver cancer patients accepting liver transplantation as object of the research. Compare the patients who accepted LRT before liver transplantation and the patients who didn't. Or observe the response to LRT using RECIST/EASL criteria [11,12]. Report the 1 year, 3 years, 5 years survival rate post liver transplantation. When 2 studies were reported by the same institution, our analysis included either the one of better quality, or the most recent publication.

**2.4. Exclusion Criteria**

Object of study, intervention measures, observed indexes didn't meet the inclusion criteria or data was not complete.

**2.5. Outcomes**

The outcome was 1 year, 3 years, 5 years survival rate after liver transplantation.

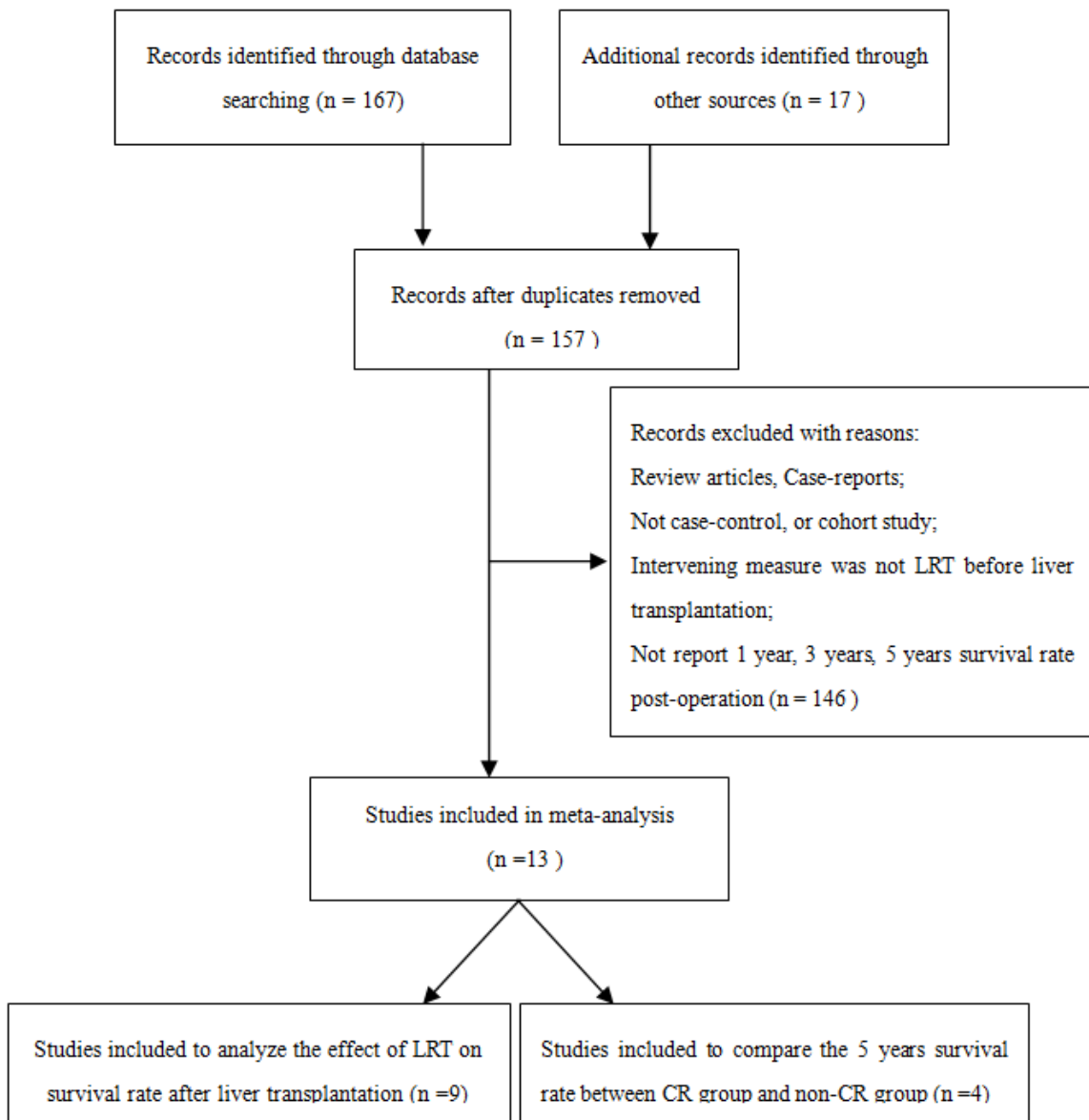
**2.6. Statistical Analysis**

Analysis was conducted by using Review Manager Version 5.2. Statistical analysis for generic inverse variance was carried out using the hazard ratio (HR) as the summary statistic.

**3. Results**

**3.1. Characteristics of Included Studies**

We identified 184 articles during the initial search. With strict screening, 13 case control studies were ultimately included in this meta-analysis (Figure 1). Nine retrospective studies [4,10,13-19] contained 1097 patients published from 2005 to 2012 were included to analyze the effect of LRT on survival rate after liver transplantation. In total, 579 patients accepted LRT before liver transplantation and 518 patients didn't. The characteristics are shown in Table 1. Four retrospective studies [7,8,9,10] contained 504 patients were included to compare if CR-group have higher survival rate after liver transplantation. Among them 176 patients have CR to LRT and 328 have non-CR to LRT. The characteristics are shown in Table 2.



**Figure 1.** Flow diagram of selection and disposition of studies

**Table 1. Basic characteristics of included studie**

Author	year	Group	Patients	1y SR	3y SR	5y SR	LRT	mean age	female	candidate criteria	mean wait time(days)	mean follow up(days)	mean size(cm)	mean no. of nodule	T1/2/3/4*
Achuthan [4]	2012	study	93	93.5	84.4	64.9	RFA/TACE	58.6	20	Milan	86.1	900	1.6	2.8	N
		Control	132	92.9	81.4	76.2		57.2	25		99.1	1080	1.3	2.2	N
Eswaran SL [13]	2012	study	28	92.80%	78.50%	71.40%	TACE	60	9	N	308	N	4.04	N	N
		Control	7	100%	100%	71.40%		54	0		95	N	3.8	N	N
DuBay DA [14]	2011	study	77	94.10%	52.90%	17.60%	RFA	56	11	Milan	285	N	2.5	1.33	N
		Control	93	94.70%	64.40%	30.30%		55	18		150	N	2.4	1.35	N
Heckman JT [15]	2008	study	50	81%	81%	81%	TACE/ 90Y/ RFA/resection	60.6	N	Milan	N	N	N	N	5/38/4/3
		Control	73	81%	71%	71%		56.4	N		Milan	N	N	N	N
Maluf DG [16]	2007	study	35	100%	100%	76%	Multimodality ablation	53.5	3	N	N	N	N	N	11/22/2/0
		Control	16	93%	93%	93%		51.7	2		N	N	N	N	N
Stockland AH [17]	2007	study	132	82%	64%	48.50%	TACE	59	32	Milan	N	846	3.7	2.55	N
		Control	18	69%	61%	41%		59	5		Milan	N	574	3	3.2
Pérez SB [18]	2005	study	18	83.30%	60.50%	60.50%	TACE	53.44	4	N	N	N	N	N	N
		Control	28	77.20%	58.70%	38.10%		54.61	6		N	N	N	N	N
Ankit6	2006	Study	46	N	N	82.4%	TACE/RFA/PEI	54.2	6	N	N	600	N	N	8/27/9/2
		Control	51	N	N	51.8%		55.9	10		N	N	450	N	N
Decaens T [19]	2005	study	100	N	N	59.40%	TACE	54	6	Mazzaferro's criteria(74)	N	1491	N	N	5/61/20/14
		Control	100	N	N	59.30%		52	10		Mazzaferro's criteria(68)	N	1611	N	N

N means not report; SR means survival rate. \*American Liver Tumor Study Group Modified Tumor-Node-Metastasis (TNM) Staging Classification [23].

**Table 2. Basic characteristics of CR and non-CR group**

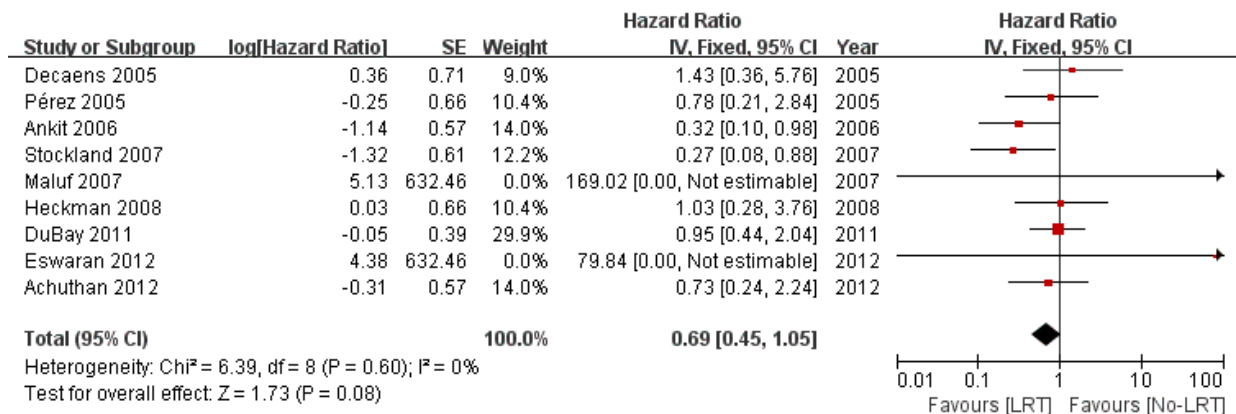
	Year	Group	Patients	5y SR
Allard MA [10]	2015	CR	37	84%
		Non-CR	152	65%
Cucchetti A [7]	2011	CR	88	66.4%
		non-CR	88	45.0%
Bargellini I [8]	2010	CR	18	94.4%
		non-CR	15	46.6%
Millonig G [9]	2007	CR	33	85.7%
		non-CR	73	65.8%

SR means survival rate.

### 3.2. Survival Rate after Liver Transplantation

Nine studies [4,6,14-19] compared the 1 year, 3 years, 5 years survival rate of study group and control group. The pooled HR for 1 year survival rate in the included studies calculated using the IV models model was 0.69 (95% CI 0.45–1.05, p=0.08; I<sup>2</sup>=0%, P=0.60) (Figure 2). The pooled

HR for 3 years survival rate in the included studies calculated using the IV models model was 0.86 (95% CI 0.63–1.18, p=0.35; I<sup>2</sup>=0%, P=0.53) (Figure 3). The pooled HR for 5 years survival rate in the included studies calculated using the IV models model was 1.06 (95% CI 0.78–1.44, p=0.71; I<sup>2</sup>=0%, P=0.73) (Figure 4).



**Figure 2.** Comparison of 1y survival rate between LRT group and control group

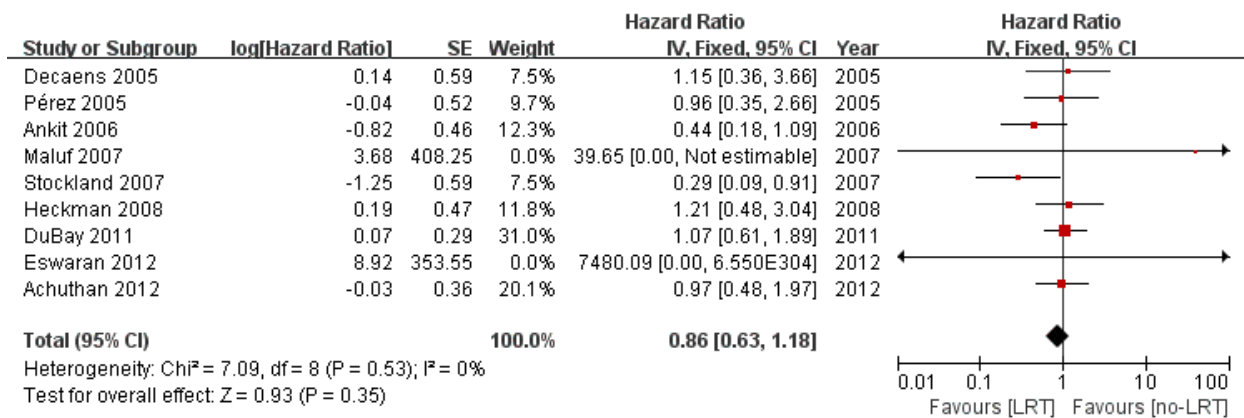


Figure 3. Comparison of 3y survival rate between LRT group and control group

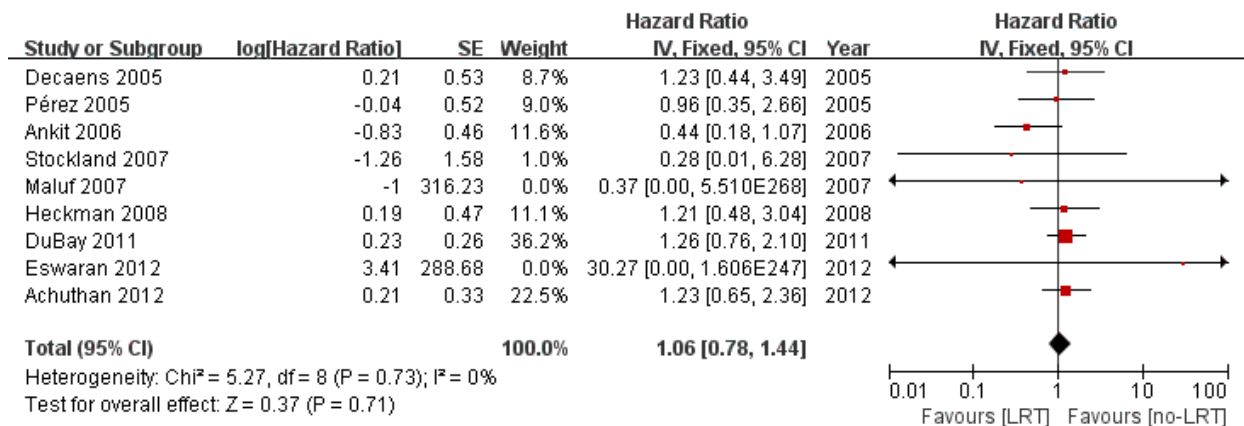


Figure 4. Comparison of 5y survival rate between LRT group and control group

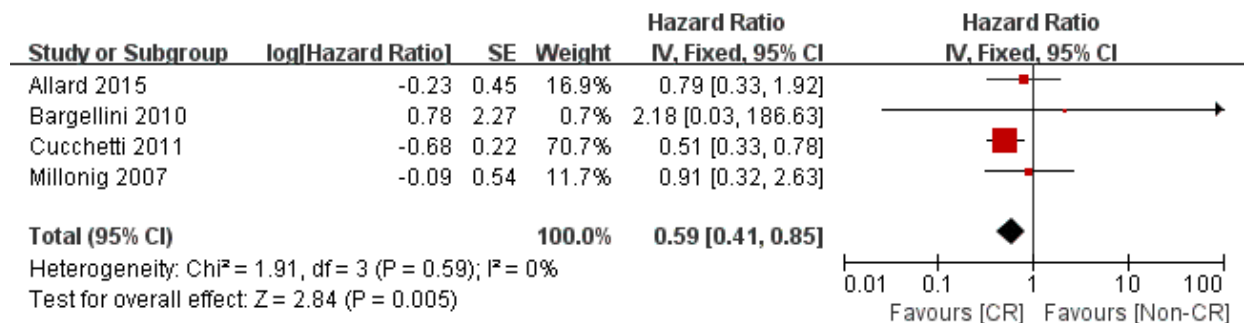


Figure 5. Comparison of 5y survival rate between CR group and non-CR group

### 3.3. Years Survival Rate between CR Group and Non-CR Group

Four studies [7,8,9,10] were also used to compare the 5 years survival rate between CR group and non-CR group. The pooled HR for 5 years survival rate in the included studies calculated using the IV models model was 0.59 (95% CI 0.41–0.85, p=0.005; I<sup>2</sup>=0%, P=0.59) (Figure 5).

## 4. Discussion

To the best of our knowledge, this is the first meta-analysis to assess the long-term outcomes of liver transplantation followed by LRT and transplantation alone in HCC patients. The present meta-analysis provided a relatively high level of evidence showing that HCC patients treated with liver transplantation followed by

LRT exhibited a equal 1 year survival rate (HR=0.69, 95% CI 0.45–1.05, p=0.08; I<sup>2</sup>=0%, P=0.60), 3 years survival rate (HR=0.86, 95% CI 0.63–1.18, p=0.35; I<sup>2</sup>=0%, P=0.53) and 5 years survival rate (HR=1.06, 95% CI 0.78–1.44, p=0.71; I<sup>2</sup>=0%, P=0.73) with those treated with liver transplantation alone. But patients with CR to LRT showed higher 5 years survival rate (HR=0.59, 95% CI 0.41–0.85, p=0.005; I<sup>2</sup>=0%, P=0.59).

Liver transplantation is the best choice for patients within accepted criteria. LRT can induce tumor necrosis, decrease tumor stage and put off tumor progression. Also, some article showed LRT can reduce dropout rate in the waiting list [20]. So, in the condition of worldwide donor liver shortage, many transplantation centers adopt LRT to expect a higher survival rate after liver transplantation. But published studies got disputed results [4,5,6]. Our meta-analysis showed LRT before liver transplantation can't improve survival rate after liver transplantation. But

it doesn't mean that LRT before liver transplantation is useless. The most widely accepted criteria for liver transplantation is Milan criteria, but many doctors doubt the criteria is too strict to reject many patients who can benefit from liver transplantation. Some researches showed that patients with CR to LRT have higher survival rate and suggested CR to LRT may become one index of the inclusion criteria for liver transplantation [7,8,9,10]. Our meta-analysis also observed that the patients getting CR have a better prognosis. So we can set this as an index of prognosis and we support taking this as one of the inclusion criteria for candidates selection. But it still has obvious shortage. In the included studies, only 34.9% patients got CR. So, indicators to predict CR is essential to avoid unnecessary LRT. Fortunately, Allard MA et al. found a maximal tumor size <30 mm, a single tumor and an preoperative AFP < 100 ng/ml were associated with CPR [10].

Our meta-analysis included relatively less studies and patients. Moreover, all the included studies are retrospective. So, more high-quality, multiple-center, large-sample randomized controlled trials are required.

In conclusion, this meta-analysis revealed the patients with complete response to LRT have higher post-transplantation survival rate. But LRT before liver transplantation can't improve the overall survival rate. Further studies, such as large sample case-controls or cohorts, will be necessary to determine the role of LRT in the patients with hepatocellular carcinoma.

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