CHAPTER 1
INTRODUCTION

1.1 Objective

To assess the efficacy of hepatic resection compared with transarterial chemoembolization in improving the survival rates of early hepatocellular carcinoma patients.

1.2 Introduction

Globally, hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths. Although it is the sixth most prevalent cancer, it takes third place when it comes to cancer-related deaths owing to its poor prognosis. The poor prognosis associated with this cancer further necessitates the need for its early diagnosis and management. One of the notable epidemiological findings of HCC is its association with viral infections and excessive alcohol intake. Hepatitis B virus (HBV) and Hepatitis C virus (HCV) infections account for 80–90% of all HCC cases worldwide. Other factors associated with the increased risk of HCC include male sex, older age, smoking, genetic factors, chemical factors, environmental factors, diabetes, and obesity.[1]

HCC has large variation in incidence according to geographic locations. High-incidence regions include sub-Saharan Africa, East Asia, and South-East Asia (i.e., China, Hong Kong, Taiwan, Korea, and Japan). The distribution of HCV-related HCC also differs among ethnic groups within the same country and among regions within the same country. In contrast, HBV-related HCC is evenly distributed, except in high aflatoxin exposure areas.[2]

According to the National Cancer Registry in Kuala Lumpur for 2008, HCC is the 8th most common cancer amongst Malaysian males. In patients with HCC, 59% are Chinese, 29% Malays and 5% Indians. The male to female ratio is 2.4 to 1. The age-standardized incidence rate is 3.6 per 100 000 persons for men

and 1.6 per 100,000 persons for women. The incidence rates for both men and women start to increase after the age of 50 years.[3]

According to the Singapore Cancer Registry 2002-2005, HCC is the fourth most common cancer in males. According to a study, the age-standardized incidence of HCC in Singapore is decreasing. It feel by 58% (from 17 to 7.1 per 100,000 persons, *P*=0.004) in men and 47% (from 2.8 to 1.5 per 100,000 persons, *P*=0.01) in women from 1968-1972 to 1998-2002. Singapore has Chinese, Malay and Indian populations. The incidence for HCC is the highest in Chinese compared with Malays (*P*=0.048) and Indians (*P*=0.023).[3]

Surgical resection is the standard modality of curative treatment for HCC, but it is applied in only a limited number of patients. Liver transplantation is the optimal therapy for HCC and underlying cirrhosis with good survival and adjusted overall rates. However, the shortage of donors is the main limitation of liver transplantation.[4]

Hepatocellular carcinoma is often associated with liver cirrhosis, and the possibility of hepatic resection depends on both tumor stage and liver functional reserve. Hepatic resection for HCC can be performed without hospital mortality, even in cirrhotic patients, because of advances in surgical techniques and perioperative and postoperative care in recent years. According to the clinicopathologic parameters, several staging systems for HCC have been proposed to predict the prognosis. The Barcelona Clinic Liver Cancer (BCLC) classification has been generally adopted as the treatment algorithm.[4]

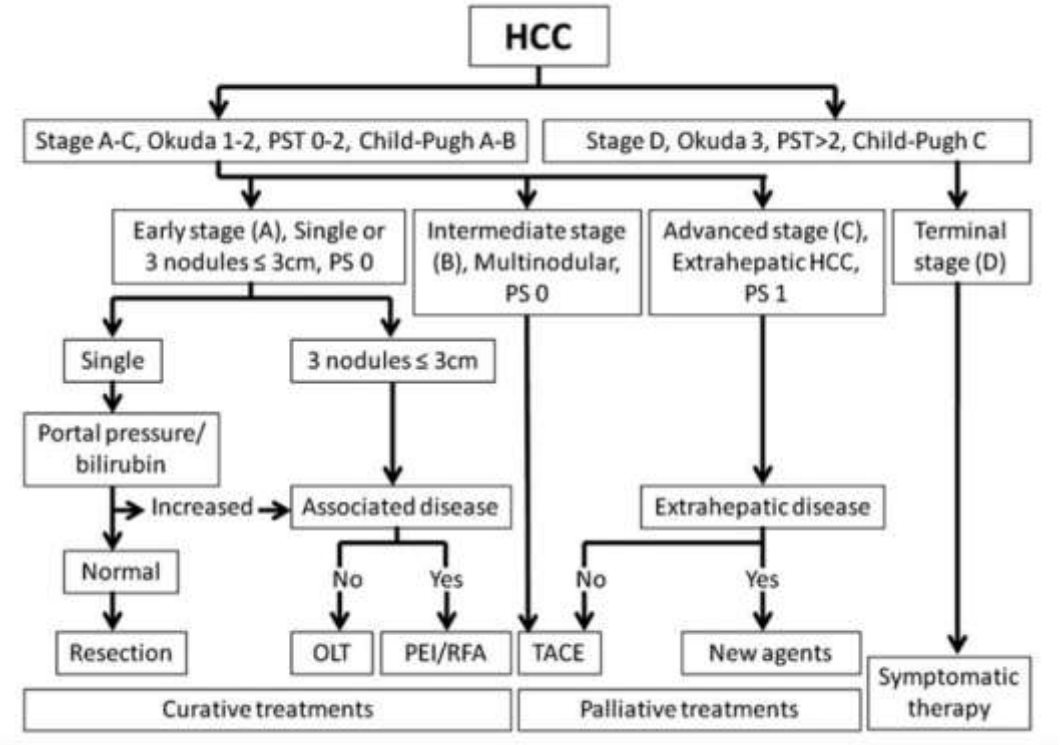

Figure 1. Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment[4]

In the proposed treatment strategy for the BCLC group, hepatic resection is favorable for early stage HCC in patients with good liver function, whereas radiofrequency ablation (RFA) and liver transplantation are suitable for patients with the same tumor stage and poor liver function (portal hypertension/increased total bilirubin). For patients with BCLC stage B HCC (single nodule [5 cm or multinodular tumors; Okuda stage 1–2; Child-Pugh A–B; performance scale 0), transarterial chemoembolization (TACE) is clearly defined as the first-line therapy with improved 2-year survival compared with conservative treatment. Hepatic resection for BCLC stage B HCC has been considered a contraindication with unfavorable prognosis. However, some authors have demonstrated good results of hepatic resection for large (tumor [5 cm) or multinodular HCC. With these conflicting results and suggestions, surgical resection remains controversial.[4]

Based on this circumstances, we would like to assess the role of surgery therapy in the era of localized chemotherapy by comparing the efficacy of

hepatic resection with transcatheter arterial chemoembolization in improving the survival rates of early hepatocellular carcinoma patients using evidence based case report (EBCR).

CHAPTER 2
CASE RESUME

2.1 Case Resume

Male 62 years old came to the outpatient clinic with chief complain enlarged stomach since four months ago. The enlarged stomach was accompanied by pain on the right quadran of abdomen and nausea. There is no fever, hematemesis nor melena. His weight was loss up to five kilograms in four months. He has no history of hepatitis before. There is no history of hepatitis nor cancer in his family. He did not smoke, did not has any tattoo, did not use intravenous drug and did not has history of blood tranfusion.

His vital sign was stable and from the physical examination we found enlarged abdomen with hepatomegali two fingers below the costal arch, and pain with the slight pressure.

The laboratory result showed anemia with Hb 11.5 g/dL. Liver function test and bilirubin level was elevated (AST 90 U/L, ALT 49 U/L, total bilirubin 0.66 mg/dL with direct bilirubin 0.26 mg/dL). Albumin 3.53 g/dL, with PT 11.8 seconds (control 12.1 seconds) and APTT 32.9 seconds (control 33.8 seconds). HBsAg was non reactive and anti HCV total non reactive. AFP was elevated 4722 mg/dL.

USG abdomen showed hepatomegaly with lobulated tip, and poorly defined mass sized 3.0 x 4.0 cm in the left lobe of the liver.

CT scan abdomen with contrast showed hepatomegali with lobulated tip and poorly defined hipodensed mass with early arterial enhancement and early wash out with delayed enhancement on vein phase sized 3.1 x 4.1 x 4.2 cm in third segment and 3.4 x 3.7 x 3.5 cm in the fourth segment of the liver. There were no thrombus in the main, right and the left portal vein and there was not splenomegali and dilatation of the splenic vein.

He was diagnosed with early hepatocellular carcinoma Bacelona Clinic Liver Cancer classification stage B.

We planned to perform hepatic surgery to the patient. But there is another option of treatment for early or intermediate hepatocellular carcinoma by using

transcatheter chemoembolization, and it has been used for the option as less invasive therapy in several patients.

2.2 Clinical Question

“ Is transcatheter arterial chemotherapy effective in improving the survival rates of early to intermediate hepatocellular carcinoma patients compared to hepatic resection?”

CHAPTER 3
METHODS

3.1 Search The Evidence

P : adult, early to intermediate hepatocellular carcinoma patients

I : transcatheter arterial chemotherapy

C : hepatic resection

O : survival rate

We searched Pubmed and Cochrane library database on August 21st, 2015 using the terms : (survival rate OR prognosis) AND (hepatic resection OR hepatectomy) AND (hepatoma OR hepatocellular carcinoma) AND (transcatheter arterial chemoembolization). Our search produced 77 results from PubMed and 31 results from Cochrane library. We were looking for the full text on those articles and found 66 results from Pubmed and 31 from Cochrane. Then we searched only for trials with human subjects and found 133 results from Pubmed and 31 results from Cochrane. In order to attain the newest evidence, we limit our search to articles that was published within five years back from now (2010-2015), so we found 35 results from Pubmed and 29 results from Cochrane. Next, we screened the abstract for trials that only compare transcatheter arterial chemoembolization with hepatic surgery in the early stage of hepatocellular carcinoma and got 4 results from Pubmed and 0 results from Cochrane. We read the full text of these articles and decided all of them can be used in the next process.

(survival rate OR prognosis) AND (hepatic resection OR hepatectomy) AND (hepatoma OR hepatocellular carcinoma) AND (transcatheter arterial chemoembolization)

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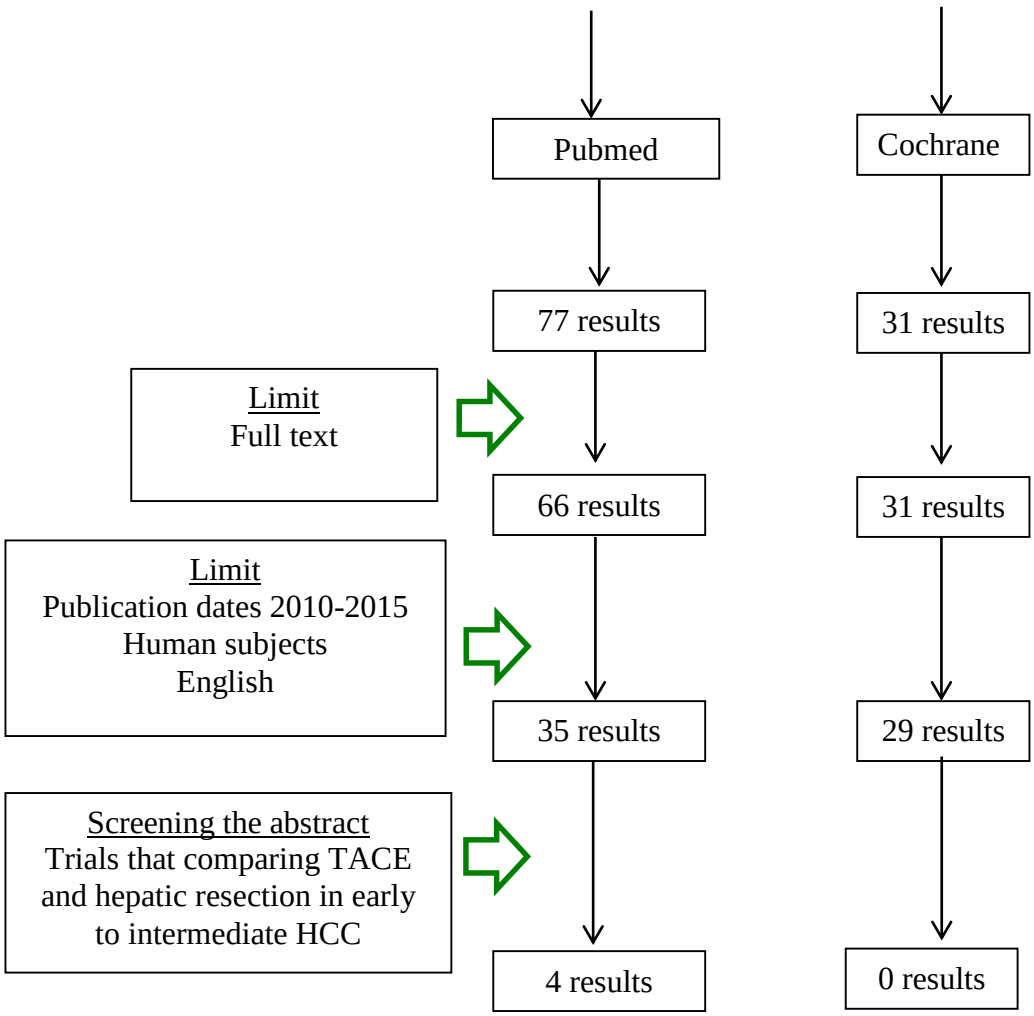

Figure 2. Flowchart of Conducted Search

3.2 Appraise The Evidence

According to Oxford Centre for Evidence-based Medicine-Levels of Evidence, the best and highest level of evidence of therapeutic type clinical question is systematic review of randomized controlled trials (RCTs) [Level 1a]. The second best level of evidence is individual RCT with narrow confidence interval [Level 1b], followed by a systematic review of cohort studies [Level 2a], individual cohort study [Level 2b], systematic review of case-control studies [Level 3a], individual case-control study [Level 3b], case series [Level 4] and expert opninion [Level 5].[6] After searching PubMed and Cochrane to answer the clinical questions, we found only 4 articles with retrospective cohort studies.

We appraised the scientific evidence of these articles using guidance from Centre for Evidence-Based Medicine : Critical Appraisal for Therapy Articles and also Critical Appraisal Skills Programme (CASP).[7,8]. The result was shown below.

Table 1. Critical Appraisal of Cohort Studies

Appraisal Questions	Lin et al (2010)[4]	Hsu et al (2014)[5]	Guo et al (2014)[9]	Jianyong et al (2014)[10]
Validity				
1. Did the study address a clearly focussed issue?	Yes	Yes	Yes	Yes
2. Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes
3. Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes
4. Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes
5a. Have the authors identified all important confounding factors?	Yes	Yes	Yes	Yes
5b. Have they taken	Yes	Yes	Yes	Yes

account of the confounding factors in the design and/or analysis?				
6a. Was the follow up of subjects complete enough?	Yes	Yes	Yes	Yes
6b. Was the follow up of subjects long enough?	Yes	Yes	Yes	Yes
Importancy				
7. What are the results of this study?	TACE is inferior compared with hepatic resection	TACE is inferior compared with hepatic resection	TACE < hepatic resection in single tumor > 5cm or multinodular ≤ 3cm; TACE = hepatic resection in single tumor ≤ 5cm	TACE < hepatic resection in 1-3 nodules; TACE = hepatic resection in > 3 nodules
8. How precise are the results?	95% CI 3.71-8.71 P < 0.0001	95% CI 1.65-3.59 P < 0.001	P < 0.001	P < 0.01
9. Do you believe the results?	Can't tell	Yes	Yes	Can't tell
Applicability				
10. Can the results be applied to the local population?	Yes	Yes	Yes	Yes
11. Do the result of this study fit with other available evidence?	Yes	Yes	Yes	Yes
12. What are the implications of this study for practice?	Consider performing hepatic resection	Consider performing hepatic resection	Consider performing hepatic resection	Consider performing hepatic resection

Level of evidence*	2a	2a	2a	2a

*Level of Evidence obtained from Centre for Evidence Based Medicine, University of Oxford (available at : http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/)

After apprasing those articles, we found that the fourth of retrospective cohort studies were valid, important, and applicable in our local population.

CHAPTER 4

RESULTS

In this evidence based case report, we try to answer if transcatheter arterial chemoembolization is effective in improving the survival rates of early hepatocellular carcinoma patients compared to hepatic resection. We found four retrospective cohort studies that were focused on answering this question. Results of these studies have been summarized in table shown below.

Table 2. Summary of The Studies

Variables	Lin et al (2010)[4]	Hsu et al (2014)[5]	Guo et al (2014)[9]	Jianyong et al (2014)[10]
Total patients	171 patients	723 patients	581 patients	923 patients
TACE	73 patients	146 patients	152 patients	490 patients
Hepatic resection	98 patients	146 patients	152 patients	433 patients
Study population	HCC patients BCLC B Child-Pugh A	HCC patients beyond Milan criteria	HCC patients BCLC A	HCC patients BCLC B Child-Pugh A or B
Randomization	No	No	No	No
Propensity model	No	Yes	Yes	No
Primary outcome	Survival rates	Survival rates	Survival rates	Survival rates
Survival TACE vs HR	**1 year:** 39% vs 83%	**1 year:** 65% vs 82%	**1 year:** 64.5% vs 75.5%	**1 year:** 84.1% vs 85.2%
	2 years: 5% vs 62%	**3 years:** 29% vs 68%	**3 years:** 24.1% vs 44.8%	**3 years:** 62.2% vs 71.1%
	3 years: 2% vs 49%	**5 years:** 22% vs 46%	**5 years:** 13.7% vs 30.2%	**5 years:** 45.1% vs 61.2%

From those result, we can see that overall survival rates was significantly higher in the hepatic resection group than in transcatheter arterial chemoembolization group.

In Lin et al study at 2010, the retrospective cohort study was done between February 2001 and December 2007 by HCC patients BCLC B Child-Pugh A in Tri-Service General Hospital, Taiwan. The demographic data of the 171 patients who underwent hepatic resection (group I; n = 93) and TACE (group II; n = 78). The 1-, 2-, and 3-year overall survival rates in group I and group II were 83%, 62%, 49%, and 39%, 5%, 2%, respectively (P < 0.0001). Patients in group I had a median overall survival time of 27.6 months, whereas those in group II had a median overall survival time of 15.8 months.[4]

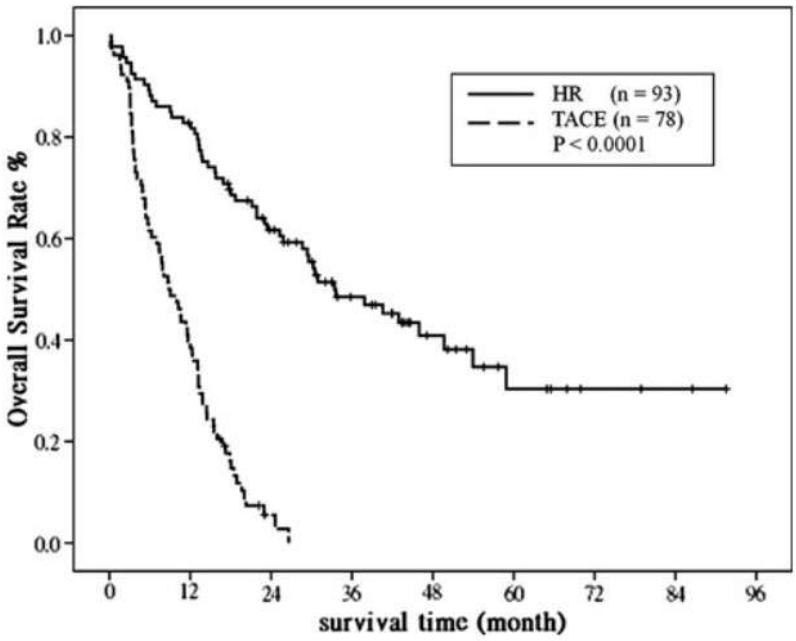

Figure 2. Overall Survival Curves for HR vs TACE group[4]

In Hsu et al study at 2011, the retrospective cohort study was done between January 2002 and October 2010 by HCC patients beyond Milan criteria in a single hospital at Taiwan. A total of 268 and 455 HCC patients who were beyond the Milan criteria and received HR and TACE, respectively, as the primary anti-HCC treatment were identified. To investigate the association between treatment and outcome in an observational database rather than a randomized controlled trial, a propensity score study was developed to reduce any bias in patient selection. During a mean follow-up period of 18 ± 16 months, 77 (29%) and 240 (53%) of patients who underwent SR and TACE, respectively,

died. The 1-, 3-, and 5-year survival rates of patients receiving SR and TACE were 81% vs 68%, 63% vs 30%, and 43% vs 15%, respectively (P < 0.001).

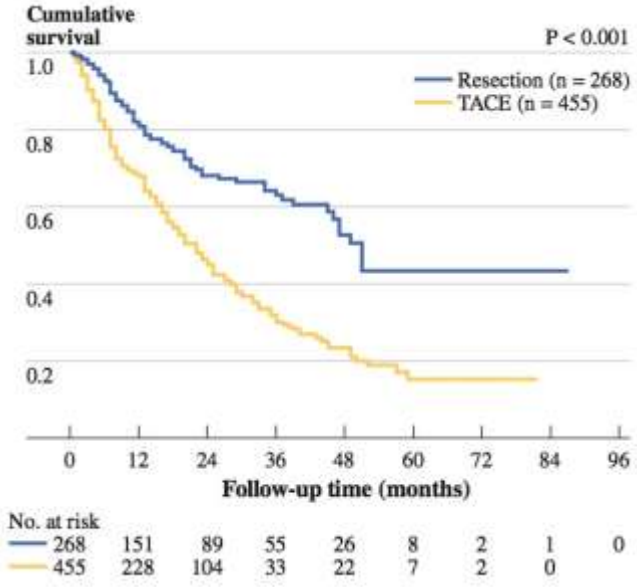

Figure 3. Overall Survival Curves for HR vs TACE group[5]

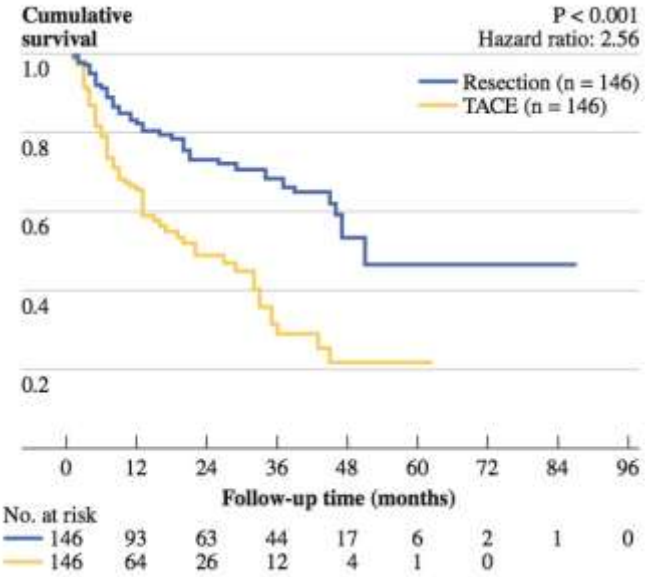

Figure 4. Overall Survival Curves for HR vs TACE Group in Propensity Score Model[5]

In Guo et al study at 2014, the retrospective cohort study was done between March 2003 and March 2008 by HCC patients BCLC A in Tumor Hospital of Guangxi Medical University, China. The 581 patients with Child-

Pugh A liver function were included analysis in this retrospective study. Of these patients, 360 (62 %) received HR and 221 (38 %) received TACE. n order to reduce the risk of such selection bias and simulate the effects of randomization, propensity score matching was used to balance treatment choice-related characteristics. Median follow-up was 35.0 months in the HR group and 20.8 months in the TACE group. During follow-up, 209 (58.1 %) patients in the HR group and 184 (83.3 %) in the TACE group died. The 1-, 3-, and 5-year overall survival were 80.6, 53.1, and 38 % in the HR group and 57, 22.5, and 14.4 % in the TACE group ($P < 0.001$).[9]

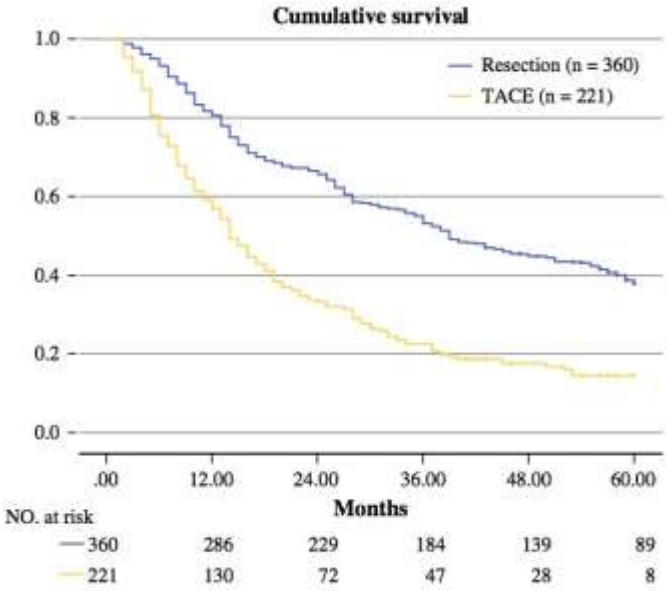

Figure 5. Overall Survival Curves for HR vs TACE Group[9]

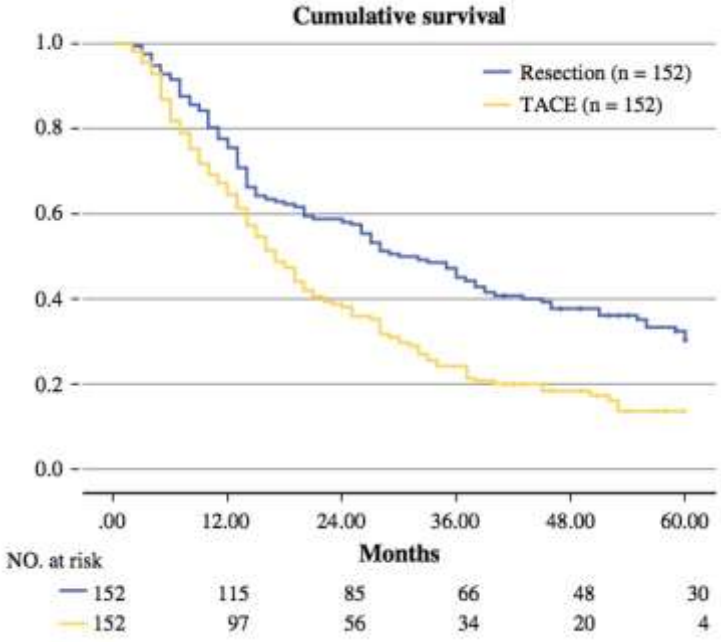

Figure 6. Overall Survival Curves for HR vs TACE Group Propensity Score Model[9]

In Jianyong et al study at 2014, the retrospective cohort study was done between July 2002 and November 2008 by HCC BCLC B patients with Child-Pugh A or B in West China Hospital of Sichuan University. Among the 923 patients with BCLC stage B HCC enrolled in this study, 433 received liver resection and 490 received TACE. The TACE and resection groups showed similar survival rates at 1 year posttreatment (84.1% vs 85.2%), whereas the benefit of resection on overall survival was more obvious at 3 years (71.1% vs 62.2%, respectively) and even more so after 5 years (61.2% vs 45.1%, respectively).[10]

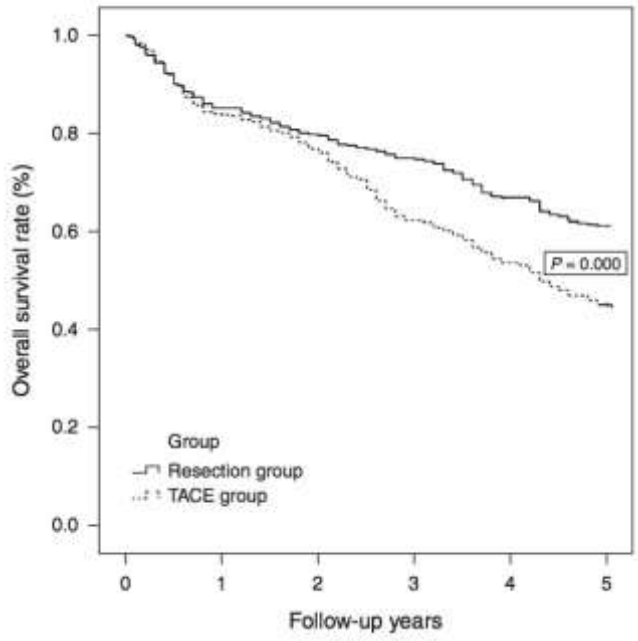

Figure 7. Overall Survival Curves for HR vs TACE Group[10]

CHAPTER 5
DISCUSSION

Based by Asian Pacific Association for the Study of the Liver (APASL) consensus recommendations on hepatocellular carcinoma, early stage hepatocellular carcinoma was treated by liver resection, or liver transplantation.[2] This recommendation was consistent with American Association for the Study of Liver Diseases (AASLD) and The Barcelona Approach for treatment of hepatocellular carcinoma.[11] Meanwhile transcatheter arterial chemoembolization is recommended as a first-line treatment for patients with unresectable, large/multifocal HCCs who do not have vascular invasion or extrahepatic spread.[2]

However, liver transplantation has not been supported by national health insurance in some Asian countries, including Indonesia and it is quite costly. Sometimes the liver donor is not available. Liver resection also came with long waiting list procedure. Based on that issue, according to Asian Pasific Association for the Study of the Liver (APASL), bridge treatments, including TACE are commonly adopted while patients are on the waiting list to prevent tumor progression.[2]

TACE is the current standard of care for patients presenting with multinodular HCC and relatively preserved liver function, with no cancer related symptoms, and with no evidence of vascular invasion or extrahepatic spread, i.e., those classified as intermediate stage according to the Barcelona Clinic Liver Cancer (BCLC) staging system. While conventional TACE comprising administration of an anticancer-in-oil emulsion followed by embolic agents is the most popular technique, the introduction of embolic, drug-eluting beads (DEB) has provided an attractive alternative to lipiodol-based regimens. Experimental and clinical studies have shown that the use of DEB loaded with doxorubicin has a safe pharmacokinetic profile with lower systemic drug exposure and significantly reduced liver toxicity compared with conventional TACE.[12]

In a multicenter phase 2 RCT including 201 European patients (PRECISION V), use of doxorubicin-eluting beads resulted in a marked reduction in liver toxicity and drug-related adverse events compared with conventional

TACE with doxorubicin. The mean maximum aspartate aminotransferase increase and alanine aminotransferase increase in the DEB bead group were 50% and 41% lower than those in the conventional TACE group ($p < 0.001$). Because of the improved safety and tolerability profile, high-dose doxorubicin treatment could be applied according to the planned schedule in all members of the DEB group, resulting in consistently high rates of objective response and disease control in all subgroup analyses. In contrast to the results for the DEB arm, the objective response rate (ORR) and the disease control rate (DCR) for conventional TACE in the subgroups of patients with more advanced disease were significantly reduced ($p = 0.038$ for ORR; $p = 0.026$ for DCR), although the differences were not statistically significant in the overall patient population (ORR, 52% vs 44%; DCR, 63% vs 52%). A recent case–control study conducted in Asian patients with HCC confirmed higher ORR for DEB-TACE compared with conventional TACE.[12]

Table 3. Conventional TACE vs DEB-TACE for HCC Treatment[12]

Study/Subgroup	Design	Treatment group	No. of patients	ORR	p value
Lammer et al. [12]	RCT*				NS
		cTACE	108	44	
		DEB-TACE	93	52	
					0.038
Child-Pugh B		cTACE	19	21	
		DEB-TACE	16	44	
ECOG 1		cTACE	28	29	
		DEB-TACE	19	63	
Bilobar disease		cTACE	45	40	
		DEB-TACE	41	49	
Recurrent disease		cTACE	13	31	
		DEB-TACE	11	55	
Song et al. [29]	Case–control study **				0.001
		cTACE	20	30	
		DEB-TACE	20	85	

cTACE = conventional transarterial chemoembolization; DEB-TACE = drug-eluting bead transcatheter arterial chemoembolization. * Primary endpoint: 6-month ORR; ** Primary endpoint: 1-month ORR.

In Lin et al study and Jianyong study, the result showed that in HCC BCLC B patients for previous years has been done hepatic resection and TACE. Both study included the HCC patients with Child-Pugh A or B, meanwhile the Child-Pugh C patients were excluded. Both study showed that overall survival rates for TACE is inferior than hepatic surgery. Lin et al study suggests that hepatic resection for BCLC B with significant differences in two groups. Janyong et al study suggests that patients with HCC BCLC B should be recommended for resection when 1 to 3 targets are presents, whereas TACE should be recommended when > 3 targets are present.[4,10]

Guo et al study showed that TACE also had been done to HCC BCLC A since January 2002. The result was one, three, and five-year overall survival rates for hepatic surgery is better than TACE, with serum AST level, serum AFP level, tumor size are also independently predicted survival in Cox regresion analysis.[9]

Hsu et al included HCC beyond Milan criteria. According to the guidelines of HCC management published by the American Association for the Study of Liver Diseases (AASLD), curative treatments are suggested for patients with single HCC tumor less than 5 cm in diameter or 3 or fewer tumors less than 3 cm in diameter (the Milan criteria).[11] For HCC patients beyond the Milan criteria, SR is considered equally safe as TACE and provides better long-term survival. SR may be regarded as the priority treatment for these patients.[5]

CHAPTER 6
CONCLUSION

Transchateter arterial chemoembolization is inferior to hepatic resection in improving the survival rates of early to intermediate hepatocellular carcinoma patients.

REFERENCES

1. Yaacob et al. Consensus on hepatobilary imaging practice guideline. College of Radiology Academy of Medicine of Malaysia. 2014;1:1-8.
2. Omata M, Lesmana L a, Tateishi R, Chen P-J, Lin S-M, Yoshida H, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int. 2010;4(2):439–74.
3. Al-Mahtab M, Uddin H, Akbar SM. Epidemiology and risk factors of hepatocellular carcinoma in asia. Journal of Gastroenterology and Hepatology Research. Bangladesh. 2014; 3(4): 1019-23.
4. Lin et al. Comparing hepatic resection and transarterial chemoembolization for barcelona clinic liver cancer (BCLC) stage B hepatocellular carcinoma: change for treatment of choice? World Journal of Surgery. 2010;34:2155-61.
5. Hsu et al. Comparison of surgical resection and transarterial chemoembolization for hepatocellular carcinoma beyond the milan criteria: a propensity score analysis. Annals of Surgical Oncology. 2012;19:842-49.
6. Howick J. Oxford Centre for Evidence-based Medicine – Levels of Evidence [Internet] Oxford : University of Oxford; 1998 [updated March 2009; cited 2015, August 21]. Available from : http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
7. Centre For Evidence-Based Medicine [Internet] Oxford : University of Oxford; 2005 [cited 2015 August 21]. Available from : http://cebm/net
8. Critical Appraisal Skills Programme [Internet] Oxford : Critical Appraisal Skills Programme Team; 2013 [cited 2015, August 21]. Available from : http://www.casp-uk.net
9. Guo et al. Comparison of survival of patients with BCLC stage A hepatocellular carcinoma after hepatic resection or transarterial

chemoembolization: a propensity score-based analysis. Annals of Surgical Oncology. 2014;21:3069-76.

10. Jianyong et al. Barcelona clinic liver cancer stage B hepatocellular carcinoma: transarterial chemoembolization or hepatic resection? Medicine. 2014;93(26):1-9.
11. Bruix J, Sherman M. Management of hepatocellular carcinoma: An update. Hepatology. 2011;53(3):1020–2.
12. Lencioni R. Chemoembolization in patients with hepatocellular carcinoma. Liver Cancer. 2012;1:41-50.