

Original Research Article

Survival Difference between Surgery Versus Non-Surgery for the Treatment of Hepatocellular Carcinoma Patients at Liver Centre, Malaysia

Azmawati MN¹(✉), Azmi MT¹, Krishnan R²

¹Department of Community Health, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, 56000 Cheras, Kuala Lumpur, Malaysia

²Department of Hepato-Pancreato-Biliary, Hospital Selayang, Lebu Raya Selayang-Kepong, Batu Caves, 68000 Selangor Darul Ehsan, Malaysia

Abstract

Hepatic resection, the only treatment that offers long term survival for patients with Hepatocellular carcinoma (HCC), have shown significant improvement in results over the past decades. The aim of the study was to compare the survival between patients receiving and not receiving surgery. A retrospective cohort study measured the survival of newly diagnosed cases of HCC patients who underwent treatment in Selayang Hospital from 1 January 2003 till 31 December 2006. Survival time was measured from the date of diagnosis until the subjects died or until the end of study period (31 December 2007). Overall survival was significantly longer in surgery group in comparison with non-surgery group with a median survival of 43 and 20 months, respectively ($p < 0.001$). The following factors were noted to have improved survival duration with surgical resection; Child Pugh Class B patients, tumor size less or more than 4cm and number of nodules less than 3. Subgroup analysis showed improved survival duration with surgical resection among patients with Child Pugh Class B with tumor size less than 4cm or with nodule less than 3 and patients who had less than 3 nodules, even with tumor size of less or more than 4cm. Multivariate Cox Regression showed surgical intervention significantly improved survival time for overall patients (Adjusted HR: 1.5) while non-surgery improved survival in patients with tumor size less than 4cm (Adjusted HR: 0.4). Surgical resection significantly improved the survival duration in overall patients while non-surgical procedure improved survival if the tumor size was less than 4cm.

Keywords: HCC, surgery, survival, Selayang Hospital, tumor size.

Correspondence:

Dr. Azmawati Mohammed Nawi, **Department** of Community Health, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaakob Latiff, 56000 Cheras, Kuala Lumpur, Malaysia. Tel: +603-91455901 Fax: +6 03-91737825 Email: atienawi@yahoo.com

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Introduction

Most researchers have found out that Hepatocellular Carcinoma (HCC) was increasing in trend as well as the mortality. HCC accounts for 6% of all cancers worldwide and the fifth commonest cancer in the world. The estimated number of people who develop HCC is 564,000 cases per year worldwide (1). In Malaysia, HCC is one of the commonest malignancies with an age-standardised annual incidence of 2.8 cases

per 100,000 populations (2). It accounts for 5.6% of all cancers and 8.1% of all cancer related death in this country. It is the twelfth commonest cancer in men and ranked eighteenth amongst women in Malaysia as reported by National Cancer Registries, 2002 (2).

Hepatic resection, the only treatment that offers long-term survival for patients with HCC, has shown significant improvement in results within past decade (3-6). Although few would contest this well-

established fact, the paradox is that no randomized study has clearly demonstrated the benefit of surgery especially in liver centre of Malaysia, Selayang Hospital. HCC is often associated with cirrhosis and the remnant hepatic functional reserve is not always preserved well and candidates for hepatic resection are limited (7-9). Recently, HCC have been often treated by nonsurgical therapeutic options such as transhepatic arterial chemoembolization (TACE), percutaneous ethanol injection treatment (PEI) (10), microwave coagulation therapy (MCT) (11) and percutaneous radiofrequency thermal ablation (RFA) (12).

The reported 5-year overall survival for surgery ranges from 35% to 60%, whereas the 3-year overall survival for non-surgery ranges from 13% to 26% (13-14). In view of that, we opine that surgery gives better survival for HCC patients compared to non-surgery. This study aims to give evidence based benefit of surgery in HCC patients at the liver centre of Malaysia with regard to survival. It is hypothesized that surgery gives a better survival compared to non-surgery procedures.

METHODS

Study Design

Selayang Hospital is known as liver centre of Malaysia in which start operated on 2000. Most of hepatobiliary disease was referred here for further management as well as HCC. This study was a retrospective cohort to all newly diagnosed HCC patients by CT Scan in liver centre, Malaysia (Selayang Hospital) from 1 January 2003 till 31 December 2006. All patients were followed up until achieving the primary endpoint (death) or until the end of the study as on 31 December 2007. It was universal sampling with inclusion and exclusion criteria being constructed. Inclusion criteria were based on all newly diagnosed HCC patients with CT Scan from 1 January 2003 till 31 December 2006 and exclusion criteria included multiple cancer.

Sample size of 210 was based on study by Verhoef et al (15) with power of 90%. Demographic information (age, gender, ethnic, alcohol intake, hepatitis status) and clinical variables (tumor size, number of nodules, Child Pugh Class, types of treatment) were obtained from medical records. The surgeon decided on the type of treatment that depended on findings of CT Scan in which this study only focussed on tumor size, number of nodules and Child Pugh Class. Small tumor, less nodules involved with Child Pugh class A or early B were considered as candidate for surgical resection.

Data was collected between February to April 2009 by review all the variables in medical record. The CT

Scan finding was noted in view of tumor size and number of nodules involved. All the patients were followed up for their survival status by registering death and via telephone.

Statistical Analysis

All data were collected and analyzed with statistical computer software (SPSS 13.0). Categorical variables were compared using the chi-square test and overall survival analyses were carried out using the Kaplan-Meier methods. Comparisons between different groups were carried out using log rank test. Multivariate analyses for survival were carried out using Cox's Regression model. Tests were deemed to be significant at the 0.05 levels. The survival status coded as death (1) and censored (0).

RESULTS

Demographic

A total of 210 HCC patients were evaluated from 1 January 2003 till 31 December 2006 with 123 patients dead and 87 being censored case. Most of HCC patients were aged between 40-60 years, males, Chinese ethnic, with no alcohol intake and positive hepatitis status as shown in Table 1. Out of 210 HCC patients, 114 patients underwent surgical resection and 96 patients received non-surgical procedure. The choice of surgery significantly depended on age group and alcohol status.

Majority of HCC patients were Child Pugh Class A in which 65.6% underwent surgical resection while Child Pugh Class B and Child Pugh Class C were mostly received non-surgery procedures. The difference was significant as well as in number of nodules involved. As shown in Table 2, most of HCC patients who underwent surgical resection involved nodules less than 3(59%) compared to only 36.4% patients with nodules more than 3. Out of 210 patients, 128 patients presented with tumor size more than 4cm with 59.4% were having surgical resection. However, only 46.3% of tumor size less than 3cm underwent surgical resection.

Survival

Overall median survival time for patients having surgical resection was 43 months (95%CI: 31.7-54.3) with a 3-year and 5-year survival rate of 55% and 26%, respectively. It showed that surgery had a better survival compared to non-surgical procedures in which overall median survival time was only 20 months (95%CI: 15.5-24.4) with a 3-year and 5-year survival rate of only 23% and 13%, respectively (Table 3, Figure 1).

Table 1: Demographic of HCC patients

Variables	Total (n=210)	Had Surgery		p value
		Yes (n=114)	No (n=96)	
Age				
<40 years old	14(6.7%)	12(85.7%)	2(14.3)	0.02
40-60 years old	112(53.3%)	54(48.2%)	58(51.8%)	
>60 years old	84(40.0%)	48(57.1%)	36(42.9%)	
Gender				
Male	166(79%)	86(51.8%)	80(48.2%)	0.16
Female	44(21%)	28(63.6%)	16(36.4%)	
Ethnic				
Chinese	159(75.7%)	87(54.7%)	72(45.3%)	0.83
Malay	42(20%)	23(54.8%)	19(45.2%)	
Indian	9(4.3%)	4(44.4%)	5(55.6%)	
Alcohol				
No	124(59%)	75(60.5)	49(39.5)	0.03
Yes	86(41%)	39(45.3)	47(54.7)	
Hepatitis Status				
No	49(19%)	25(62.5)	15(37.5)	0.25
Yes	170(81%)	89(52.4)	81(47.6)	

Table 2: Clinical variables of HCC patients

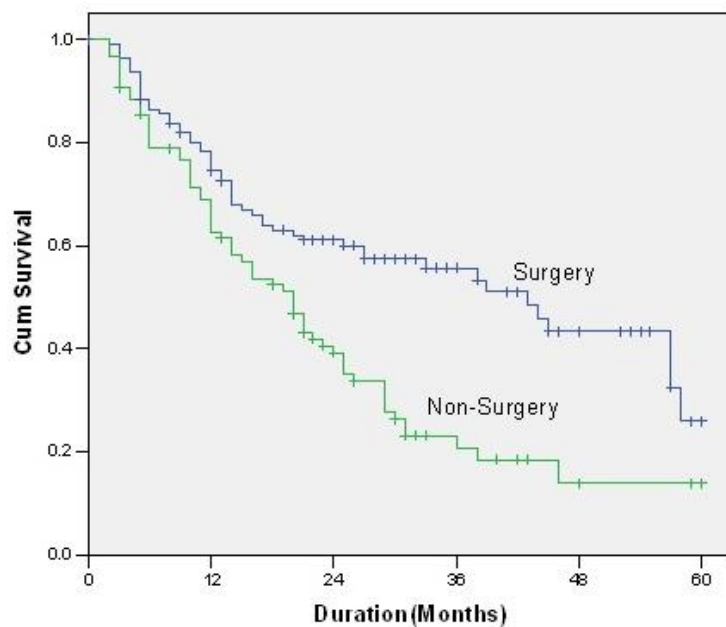
Variables	Total (n=210)	Had Surgery		p value
		Yes (n=114)	No(n=96)	
Child Pugh Class				
A	125(59.5%)	82(65.6%)	43(34.4%)	<0.001
B	80(38.1%)	32(40%)	48(60%)	
C	5(2.4%)	0	5(100%)	
Tumor Size				
<4cm	82(39%)	38(46.3%)	44(53.7%)	0.064
>4cm	128(61%)	76(59.4%)	52(40.6%)	
Number of nodules				
<3	166(79%)	98(59%)	68(41%)	0.007
>3	44(21%)	16(36.4%)	28(63.6%)	

Table 3 summarized the differences between HCC patients who underwent surgical resection or not with clinical variables which played an important factor especially before deciding the types of treatment. For

the surgery group, the median survival time was better with Child Pugh Class B (25 months, 95% CI: 5.8-44.2), tumor size less than 4cm (57 months, 95% CI: 44.4-69.6), tumor size more than 4cm (21 months,

Table 3: Univariate Analysis of Survival

Variables	n	Died	Median(months)	95%CI	1 year	3 year	5 year	p value
Overall								
Surgery	114	54	43	31.7-54.3	74	55	26	<0.0001
No Surgery	96	69	20	15.5-24.4	61	23	13	
Child Pugh Class A								
Surgery	82	34	57	39.2-74.7	75	61	35	0.22
No Surgery	43	22	26	19.9-32.0	86	37	37	
Child Pugh Class B								
Surgery	32	20	25	5.8-44.2	65	47	23	0.04
No Surgery	48	42	13	10.1-15.9	76	14	0.4	
HCC <4cm								
Surgery	37	11	57	44.4-69.6	88	84	30	0.003
No Surgery	41	24	25	17.7-32.3	73	38	25	
HCC >4cm								
Surgery	77	43	21	11.4-30.6	66	39	24	0.005
No Surgery	55	45	15	9.6-18.3	48	0.7	0.7	
Nodule <3								
Surgery	98	40	57	38.9-75.1	76	62	34	<0.005
No Surgery	68	46	21	15.1-26.8	69	27	13	
Nodule >3								
Surgery	16	14	12	2.5-21.5	56	19		0.632
No Surgery	28	23	12	9.5-14.5	60	15	13	

**Figure 1:** Kaplan-Meier survival estimates by treatment

95% CI: 11.4-30.6) and number of nodules involved less than 3 (57 months, 95% CI: 38.9-75.1)

Subgroup analysis of survival showed that HCC patients of Child Pugh Class B with tumor size less than 4cm or nodule less than 3, the surgical approach gave benefit of survival as well as in group of nodule less than 3 with tumor size less or more than 4cm (Table 4).

Table 4 summarized the prediction model in survival of HCC patients according to overall patients and tumor size. Negative prognostic factors for overall HCC patients were non surgery (aHR: 1.5), Child Pugh Class B (aHR:2.0), Child Pugh Class C (aHR: 3.0) and tumor size more or same than 4cm (aHR:2.3). In view of HCC patients with tumor size less than 4cm, the non surgery procedure gave benefit of HCC patients survival (aHR: 0.4) while for tumor size more or same with 4cm, both of procedure did not benefit off HCC patients survival.

Discussion

Nowadays, the management of HCC offers many treatment options in relation to the tumor stage (16). Among these, liver transplantation has the best results in terms of overall survival (17). However, this procedure was not performed in Malaysia because of organ shortage. Liver surgery for HCC has improved its results in patients during the last decades with mortality lower than 5% in most series (18). The availability of non-surgery approach makes treatment options wider and some will benefit on survival of HCC patients.

Surgical resection was considered the treatment of choice for patients with absent of alcohol intake, Child Pugh Class A and number of nodules less than 3. The surgeon may have their own reason before deciding the types of treatment in which majority study agreed that Child Pugh Class A and less nodules involved should be offered for surgical resection. The absence of alcohol intake in HCC patients will clarifies the liver status, should it be good with no cirrhosis. Therefore surgical may not be offer to this patients and non-surgery treatment will be the choice.

As agreed upon by many researchers (19, 20), surgery gives a better survival compared to non-surgery procedure with median 43 months and 20 months, respectively. Few studies did not opine (21, 22) in which the sample size was too small, compared to this study which agreed with surgery give a better survival. Surgical resection will remove the entire cancer cell while non-surgery procedure needs a repetition of

procedure. The time taken longer in non-surgery procedure explained the survival duration become shorter besides of other factors such as cirrhosis or late stage of cancer.

There was no difference of survival in Child Pugh Class A in view of treatment. However, for Child Pugh Class B, surgery gave a prolonged survival with median 20 months. Tumor size and number of nodules involved, plays an important deciding factor of types of treatment. As we observed in this study, it was shown that patients who had tumor size of less or more than 4cm and nodules involved less than 3, had a good survival with surgery procedure (23). It explained that multiple nodules involved will make surgery difficult and non-surgery approach will benefit the survival. However, the difference was not significant.

Subgroup analysis showed that HCC patients of Child Pugh Class B with tumor size less than 4cm or nodules less than 3 gave a better survival with surgical resection. Good clinical stage contributed to a better survival with surgery as shown by Ari et al (2000) (13). The size does not matter in survival of HCC patients but with fewer nodules involvement, there was a longer duration of survival (24).

The prediction model after controlling other factors proved that for overall HCC patients, surgery gave longer duration of survival by 1.5 times compared to non-surgery procedure (25). If patients had tumor size less than 4cm, non-surgery procedure produced benefit of survival by 0.4 times compared to surgery in univariate and multivariate analysis. However, for patients who had tumor size more or same than 4cm, the comparison of treatment did not reach statistical significance in multivariate analysis.

Besides surgery, the prediction model for overall patients also showed that good clinical stage of HCC (Child Pugh Class A, small tumor, less nodules involved) gives a better prognostic factor as majority of studies reported the same findings. There is no argument about this prediction model as most studies in the past decades and current study agreed on this aspect (20, 21, 25). Therefore, in Malaysian people with HCC, we also may apply this prediction towards a better survival. If the patients comes with tumor size less than 4cm, the non-surgery procedure and Child Pugh Class A will give improvement in duration of survival as we observe in Table 5. However, if tumor size is more or equal to 4cm, the choice of surgery or non-surgery will not make difference in survival outcome but Child Pugh Class A and involvement of less nodules will give a better survival.

Table 4: Subgroup analysis of HCC patient's survival

Variables	n	Median(months)	95%CI	p value
Child Pugh Class A & HCC <4cm				
Surgery	26	57	35.16-78.84	0.506
No Surgery	21	44*means	34.80-53.95	
Child Pugh Class A & HCC ≥4cm				
Surgery	56	27	0.09-53.90	0.074
No Surgery	22	20	13.52-26.48	
Child Pugh Class B & HCC <4cm				
Surgery	11	57		0.005
No Surgery	18	14	10.16-17.83	
Child Pugh Class B & HCC ≥4cm				
Surgery	21	14	4.27-23.73	0.703
No Surgery	30	12	7.71-16.30	
Child Pugh Class A & Nodule <3				
Surgery	72	58	31.08-84.91	0.261
No Surgery	33	29	24.98-33.02	
Child Pugh Class A & Nodule ≥3				
Surgery	10	5	3.54-6.46	0.452
No Surgery	10	6	0.0-29.24	
Child Pugh Class B & Nodule <3				
Surgery	26	25	3.40-46.60	0.035
No Surgery	31	14	8.67-19.33	
Child Pugh Class B & Nodule ≥3				
Surgery	6	12	0.0-39.85	0.509
No Surgery	17	12	10.11-13.89	
HCC <4cm & Nodule <3				
Surgery	34	57	35.31-78.70	0.014
No Surgery	32	29	22.08-35.91	
HCC <4cm & Nodule ≥3				
Surgery	3	57		0.298
No Surgery	9	12	6.76-17.24	
HCC ≥4cm & Nodule <3				
Surgery	64	27	0.0-55.72	0.002
No Surgery	36	16	8.36-23.64	
HCC ≥4cm & Nodule ≥3				
Surgery	13	5	3.33-6.67	0.369
No Surgery	19	12	7.7-16.27	

Table 5: Predictor model for HCC patient's survival

Variables	Simple Cox Regression			Multiple Cox Regression*		
	β	95%CI	Crude HR	β	95%CI	Adjusted HR
Overall						
Non-Surgery vs Surgery(96 vs 114)	-0.65	0.36-0.75	0.52	0.4	1.03-2.25	1.52
Child B vs A(80 vs 125)	0.84	1.61-3.33	2.31	0.7	1.30-2.82	1.91
Child C vs A(5 vs 125)	1.46	1.73-10.85	4.33	1.1	1.19-7.94	3.08
HCC <4cm vs HCC \geq 4cm(128 vs 82)	0.81	1.52-3.33	2.25	0.8	1.52-3.36	2.26
Nodule < 3 vs Nodule \geq 3(44 vs 166)	0.84	1.57-3.40	2.31	0.4	0.97-2.27	1.49
HCC < 4cm(n=78)						
Non-Surgery vs Surgery(37 vs 41)	-1.06	0.16-0.73	0.35	-0.9	0.18-0.83	0.39
Child B vs A(29 vs 47)	-2.19	0.02-0.51	0.11	1.1	1.48-6.33	3.06
Child C vs A(2 vs 47)	-0.02	0.08-1.57	0.36	1.8	1.27-27.79	5.96
Nodule < 3 vs Nodule \geq 3(66 vs 16)	-0.92	0.18-0.89	0.4	0.6	0.75-4.64	1.87
HCC \geq 4cm(n=132)						
Non-Surgery vs Surgery(77 vs 55)	0.57	1.17-2.69	1.78	0.3	0.81-2.07	1.3
Child B vs A(51 vs 78)	0.68	1.29-3.02	1.97	0.5	1.09-2.68	1.71
Child C vs A(3 vs 78)	1.12	0.94-9.95	3.06	1.2	1.01-10.74	3.3
Nodule < 3 vs Nodule \geq 3(100 vs 32)	-0.65	1.23-2.97	1.92	0.5	1.02-2.63	1.64

*Backward stepwise Cox proportional hazards regression applied. Log-minus-log plot and hazard function plot were applied to check the model assumption.

The choice of treatment depends on the surgeon expectation of the variety. Therefore, it is our limitation in looking into the different type of treatment and the survival of HCC patients. The choice of treatment sometimes not only depends on the tumor size, nodules involved or Child Pugh Class only but other factors such as co-morbidity, cirrhosis, fibrosis, vascular invasion which contributes to poor survival or when the surgical procedure cannot be performed. However, this study findings will give a view of Malaysian prognostic factor of HCC patients and as a pilot study for future research in survival of HCC patients as not much study done on survival.

As in conclusion, surgery will remain a best option in HCC patients for a better survival but for small HCC, non-surgery approach also will benefit on the survival. Therefore, an expert opinion from the Surgeon whether to perform surgery or not, should consider the prediction model for a longer survival in HCC patients. Keeping in mind, the public health view, the 3-step prevention should be more emphasized in view of education, promotion, early diagnosis, early

treatment as early stage of HCC will improve the survival. These findings will help the Surgeon to choose the type of treatment depending on Child Pugh Class, tumor size and number of nodules involved. The effort should be made to ensure that every patient receives an appropriate treatment.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden. *Inter J Cancer* 2001; 94(2): 153– 156.
2. National Cancer Registry. The first report of the National Cancer registry cancer incidence in Malaysia. Kuala Lumpur: Ministry of Health 2002. http://www.radiologymalaysia.org/index/Directories_index.html. Last accessed on 24.05.2011
3. The Liver Cancer Study Group of Japan. Predictive factors for long term prognosis after partial hepatectomy for patients with

- hepatocellular carcinoma Japan. *Cancer* 1994; 74(10):2272–80.
4. Fan ST, Lo CM, Liu CL, et al. Hepatectomy for hepatocellular carcinoma toward zero hospital deaths. *Ann Surg* 1999; 229(3):322–30.
 5. Torzilli G, Makuuchi M, Inoue K, et al. No mortality liver resection for hepatocellular carcinoma in cirrhotic and non cirrhotic patients: Is there a way? A prospective analysis of our approach. *Arch Surg* 1999; 134(9):984–92.
 6. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a western center. *Ann Surg* 1999; 229(6):790–800.
 7. Hanazaki K, Kajikawa S, Shimozawa N, et al. Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. *J Am Coll Surg* 2000; 191(4):381–8.
 8. Fuster J, Garcia-Valdecasas JC, Grande L, et al. Hepatocellular carcinoma and cirrhosis: results of surgical treatment in a European series. *Ann Surg* 1996; 223(3):297–302.
 9. Lau H, Fan ST, Ng IOL, Wong J. Long term prognosis after hepatectomy for hepatocellular carcinoma: a survival analysis of 204 consecutive patients. *Cancer* 1998; 83(11):2302.
 10. Farmer DG, Rosove MH, Shaked A, Busuttill RW. Current treatment modalities for hepatocellular carcinoma. *Ann Surg* 1994; 219(3):236–47.
 11. Seki T, Wakabayashi M, Nakagawa T, et al. Ultrasonically guided percutaneous microwave coagulation therapy for small hepatocellular carcinoma. *Cancer* 1994; 74(3):817–25.
 12. Allgaier HP, Deibert P, Zuber I, et al. Percutaneous radiofrequency interstitial thermal ablation of small hepatocellular carcinoma. *Lancet* 1999; 353(9165):1676–7.
 13. Arii S, Yamaoka Y, Futagawa S. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000; 32(6):1224–9.
 14. Poon RT, Fan ST, Lo CM. Improving survival results after resection of hepatocellular carcinoma: a prospective study of 377 patients over 10 years. *Ann Surg* 2001; 234(1):63–70.
 15. Verhoef C, Visser O, de Man RA, Wilt J, Ijzermans JNM & Janssen-Heijnen MNG. Hepatocellular Cancer in the Netherlands incidence, treatment and survival patterns. *European journal of cancer* 2004; 40(10): 1530-1538.
 16. Bruix J, Sherman M, Llovet JM. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; 35(3):421–430.
 17. Hashikura Y, Kawasaki S, Terada M. Long-term results of living-related donor liver graft transplantation: a single center analysis of 110 patients. *Transplantation* 2001; 72(1):9599.
 18. Hong SN, Lee SY, Choi MS et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg* 2001; 234(1):71–78.
 19. Farinati F, Gianni S, Marin, Fagioli S, Rinaldi M, Naccarato R. Does the choice of treatment influence survival of patients with small Hepatocellular Cancer in compensated cirrhosis? Lippincott Williams & Wilkins 2001; 13(10): 1217-1224.
 20. Livraghi T, Bolondi L, Buscarini L et al. No treatment, resection and ethanol injection in Hepatocellular Cancer: A retrospective analysis of survival in 391 patients with cirrhosis. Italian Cooperative HCC Study Group. *Journal of Hepatology* 1995; 22(5):522-6.
 21. Maluccio M., Covey AM, Gandhi R, Gonen, Mithat, Getrajdman GI et al. Comparison of Survival Rates after TransArterial Embolization and Ablation Versus Surgical Resection for Treating Solitary Hepatocellular Carcinoma up to 7cm. *Journal Of vascular and interventional radiology* 2005; 16(7): 955-961.
 22. Atsushi N, Junichi M, Satoshi M et al. Selection of treatment modality for hepatocellular carcinoma according to the modified Japan Integrated score. *World Journal Gastroenterology* 2008; 14(1): 58-63.
 23. Jerome HL, Pauline WC, Steven MA, Ronald WB, & Clifford YK Surgery for Hepatocellular

- Carcinoma: Does It Improve Survival? *Annals of Surgical Oncology* 2004;11(3):298–303.
24. Tito L, Luigi B, Luigi B, Mario C et al. No treatment, resection and ethanol injection in hepatocellular carcinoma: A retrospective analysis of survival in 391 patients with cirrhosis. *J Hepatol* 1995; 22(5):522-526.
 25. Alfredo G, Andrea R, Alessandro V et al. Radiofrequency Ablation Versus Surgical Resection for the Treatment of Hepatocellular Carcinoma in Cirrhosis. *J Gastrointest Surg* 2008; 12(1):192–198.