Lymphocytes and Neutrophils-to-Lymphocytes Ratio variations after Selective Internal Radiation Treatment for HCC: a retrospective cohort study

Florian Estrade [1], Céline Lescure [1], Léa Muzellec [1], Maud Pedrono [1], Xavier Palard [2], Marc Pracht [1], Samuel Le Sourd [1], Yan Rolland [3], Thomas Uguen [4], Etienne Garin [2], Julien Edeline [5]

[1] Medical Oncology, Centre Eugène Marquis, Av bataille Flandres-dunkerque, 35042, Rennes, France.

[2] Nuclear Medicine, Centre Eugène Marquis, Rennes, France.

[3] Interventional Radiology, Centre Eugène Marquis, Rennes, France.

[4] Hepatology, CHU Pontchaillou, Rennes, France.

[5] Medical Oncology, Centre Eugène Marquis, Av bataille Flandres-dunkerque, 35042, Rennes, France. j.edeline@rennes.unicancer.fr.

Abstract:

Purpose: Selective internal radiation therapy (SIRT) has been proposed for combination with immunotherapy to treat hepatocellular carcinoma (HCC). However, the toxicity of radiation towards lymphocytes is understudied after SIRT. The aim of this study was to describe variations of lymphocytes following SIRT, and their potential prognostic impact.

Materials & Methods: This is a retrospective cohort study of 164 patients treated with SIRT for HCC Lymphocytes count and Neutrophils-to-lymphocytes (NLR) ratio were evaluated at baseline and at 3 months. Primary endpoint was Overall Survival (OS).

Results: Median baseline lymphocyte count was 1.32Giga/Liter (G/L) (Standard deviation (SD: 0.64) vs 0.68G/L (SD:0.41) at 3 months. The mean decrease of lymphocytes count was -44% (Standard deviation: 0.24). At 3 months, only 21% of patients had normal (1G/L or more) lymphocytes count, and 23% had lymphocytes count <0.5G/L. NLR at 3 months was

significantly and independently associated with OS in multivariate Cox model. Median OS was 9.9 months (95% Confidence Interval (CI): 6.2-13.5) for patients with NLR at 3 months higher than 7.2 compared to 19.9 months in patients with an NLR lower that the 7.2 threshold (95%CI: 16.3-23.3) (p=0.003).

Conclusions: The decrease of lymphocytes was frequent and deep after SIRT for HCC. NLR increase at 3 months was associated with poor survival.

Keywords: Radioembolization; Yttrium-90; immune checkpoint inhibitors; anti-PD-1; lymphopenia; liver malignancies

Introduction

Selective Internal Radiation Therapy (SIRT), also known as Yttrium-90 radioembolization, is an emerging treatment modality of hepatic malignancies, including Hepatocellular Carcinoma (HCC), with potential role in the intermediate and advanced stages (1,2). Another emerging treatment of HCC is immunotherapy. Phase 2 data of anti-PD-1 agent showed promising results (3,4). Recently, the IMBRAVE150 phase 3 study results were presented, showing significant benefit of the combination of atezolizumab-bevacizumab in comparison with sorafenib (5).

Baseline lymphopenia and high Neutrophils-to-Lymphocytes Ratio (NLR) have been showed in multiple cancers to have prognostic values, independently of treatment modality (6). Apart from this value at baseline, variations during treatment might also have an impact on survival. Radiation has a potential for direct toxicity toward blood white cells, especially lymphocytes (7). Moreover, variations of lymphocytes and Neutrophils-to-Lymphocytes Ratio (NLR) have been shown to be prognostic in many contexts after external beam radiotherapy, including HCC (8). Few data exist as regards to the toxicity of SIRT for lymphocytes, mostly from small series, with no sufficient power to allow for prognostic evaluation (9,10).

There is a growing interest for the combination of immunotherapy with locoregional approaches (11). SIRT has been described as a potentially interesting locoregional treatment to combine with immunotherapy, due to the theoretical immunosensitizing effect of radiation, albeit mostly studied with external beam radiotherapy (12). SIRT might induce local inflammation (10). However, this potential synergy might be mitigated if the direct toxicity toward lymphocytes reduces the availability of effectors of immunotherapy.

The main objective of the study was to study variations in blood cells counts after SIRT and to evaluate their prognostic values in terms of overall survival (OS).

Methods:

Study design

This retrospective and non-interventional cohort study enrolled HCC patients undergoing SIRT at the Centre Eugene Marquis in Rennes (Brittany, France) from January 2008 to January 2017. They could have been previously treated or not. They all met the following inclusion criteria: age ≥ 18 years old, PS ≤ 2, SIRT therapy recommended by specialized multidisciplinary team. This study was approved by the Ethic Committee of the CHU of Rennes. This report complies with the STROBE guidelines on cohort studies.

Treatment procedure

The SIRT procedure was performed as previously described (13). The aim of the diagnostic angiography was to define the best catheter position for right, left, or segmental treatment in order to target the lesion. Percentage of pulmonary shunting and absence of digestive uptake were assessed after ^{99m}Tc macroaggregated albumin was injected selectively in the hepatic artery (185MBq). Planar and SPECT/CT acquisitions were performed. SPECT/CT acquisitions were conducted using the following parameters: window 140 ± 7.5KeV; 32 projections; 180°; 128 * 128; 30s/projection (Symbia T2 gantry, Siemens). The data was reconstructed using an iterative method (OSEM, 5 iterations, 8 subsets) with CT based attenuation correction and scatter corrections.

SIRT was performed 8 to 15 days later at a second angiography. SIRT was performed either with glass-microspheres (TheraSphere®, BTG, London, UK) or resin-microspheres (SIR-Spheres®, Sirtex Medical, Sydney, Australia). For patients treated with glass-microspheres, activity administrated was calculated with the aim of administering a dose between 80 and 150 Gy to the targeted liver volume without exceeding a cumulative dose of 30 Gy to the lungs; however, in case of segmental or bisegmental injection, dose to the segment could be

higher than 150 Gy as previously described (14). Segmentation (targeted liver and tumor) was performed on SPECT/CT data and not on the angiographic and CT data usually used, as previously described (15).

Follow-up

The patients had blood test performed during the two weeks before SIRT treatment, then at 3 months, at the same time as radiological evaluation. Primary objective was OS. OS was defined as the time between first SIRT treatment and death or last follow-up visit. Response was studied according to mRECIST. Toxicity was graded according to NCI-CTCAE v4.03.

Statistical analysis

Correlation between values and dose delivered to the whole liver, the tumor and the non-tumoral liver were assessed with a Spearman's Rho test. To determine the most discriminating thresholds for continuous variables, a Receiver over Curve (ROC) analysis was performed, to select for the availability to predict a survival lower than the median (patients alive with shorter follow-up were censored). Survival was analyzed by the Kaplan-Meier method and by a univariate and multivariate Cox model. The multivariate model included variables associated with OS ($p<0.05$) in univariate analysis. Statistical analyses were done using SPSS software v18.0.

Results:

Between January 2008 and January 2017, 232 patients were treated with SIRT for HCC, and 164 patients had blood test values available at both baseline and 3 months. Baseline characteristics are reported on Table 1. Median activity injected was 2.5Gbq (range: 0.23-350), median dose delivered to the treated liver was 120Gy (range: 26-248), median dose delivered to the tumor was 277Gy (range: 96-880), median dose delivered to the non-tumoral liver was 85Gy (range: 0-194). Median OS of the cohort was 17.7 months (95% Confidence Interval (CI): 14,2-21,1). Response rate by mRECIST was 71% with 58% partial response and 13% complete response. 53 patients (23%) experienced grade 3 or more toxicities, the most frequent being development of ascites in 25 (10.8%).

There was frequent decrease of lymphocytes count following SIRT. Median lymphocyte count was 1.32Giga/Liter (G/L) (Standard deviation (SD: 0.64) at baseline vs 0.68G/L (SD:0.41) at 3 months. The mean variation of lymphocytes count between baseline and 3-months was -44% (SD: 0.24), and 45% of patients had decrease higher than -50%. At baseline, 49 of the 164 patients (29.9%) had lymphocytes count <1G/L, while at 3 months, 132 of the 164 patients (80.5%) had lymphocytes count <1G/L. At 3 months, 52 (31.7%) patients had lymphocytes count between 0.5G/L and 0.75G/L, and 38 (23.2%) had lymphocytes counts lower than 0.5G/L, while corresponding figures at baseline were only 13 (7.9%) and 6 (3.7%) (Figure 1). There was a weak negative correlation between lymphocyte count at 3 months and dose delivered to the non-tumoral liver (spearman's rho =-0.29, p=0.001). There was no correlation between lymphocyte count at 3 months and dose delivered to the tumor or dose delivered to the injected liver.

At baseline, a lymphopenia <1G/L was not associated with worse OS (p=0.28), but at 3-months, there was a trend towards lower OS (median OS 17.3 months vs 19.9 months,

p=0.058). However, lower lymphocytes count at 3 months as a continuous variable was not significantly associated with worse OS (Cox univariate model, Hazard Ratio (HR) of 0.89 (95%CI: 0.61-1.32, p=0.58).

As the NLR was shown in different contexts to have better prognostic abilities than lymphocytes or neutrophils counts, NLR variations were then studied. Median NLR was 3.47 (SD:1.86) at baseline vs 5.74 (SD:6.12) at 3 months. Mean NLR variation at 3 months was +82% (standard deviation: 1.94). Higher NLR at 3 months as a continuous variable was associated with worse OS, with a HR=1.06 (95%CI: 1.03-1.09) p<0.001. The best thresholds were defined by ROC analysis associated with the prediction of OS, which were 7.2 for NLR and 0.67G/L for lymphocytes, both at 3 months. AUC of ROC curves were 0.64 (95%CI: 0.55-0.73, p=0.003) for NLR and 0.58 (95%CI: 0.49-0.67, p=0.10) for lymphocytes, showing better prognostic abilities for NLR than for lymphocytes. Using these thresholds, OS was significantly worse in patients with NLR at 3 months higher than 7.2, with median OS of 9.9 (95%CI: 6.2-13.5) vs 19.9 months (95%CI: 16.3-23.3) (p=0.003) (Figure 2A). It was also significantly worse in patients with lymphocytes at 3 months lower than 0.67G/L, with median OS of 14.3 (95%CI: 16.6-30.1) vs 23.4 months (95%CI: 10.0-18.7) (p=0.004) (Figure 2B).

Results were then studied in a multivariate Cox model (Table 2). In univariate analysis, baseline parameters associated with OS were HCV infection, PVT, albumin (as continuous variable), alpha-feto protein (as continuous variable). When NLR and lymphocytes count at 3 months were studied in a multivariate model in conjunction with baseline parameters, only PVT and NLR at 3 months were independently with OS. Respective Hazard Ratio for PVT and NLR at 3 months were HR=1.69, 95%CI: 1.18-2.43, p=0.005 and HR=1.07, 95%CI: 1.04-1.10, p<0.001 when NLR was studied as continuous variable and HR=1.56, 95%CI: 1.09-2.23,

p=0.016 HR=1.67, 95%CI: 1.19-2.34, p=0.003 when studied with the 7.2 threshold. Results were identical when mRECIST response and grade ≥3 toxicities were also entered into the model.

Discussion

The main results of this study are the following: (1) lymphocytes frequently decrease following SIRT, and lymphocytes counts are frequently very low (about a quarter of patients with lymphocytes <0.5G/L at 3 months); (2) the decrease of lymphocytes were correlated to the dose delivered to the non-tumoral liver; (3) a NLR at 3 months higher than 7.2, or a lymphocytes count lower than 0.67G/L are associated with statistically and clinically significant worse OS (about 2-fold decrease of the median); and (4) NLR at 3 months is an independent prognostic factors when studied concomitantly with baseline characteristics and response evaluation. Taken together, these results suggest that SIRT, as other radiation modalities, has a significant toxicity towards lymphocytes, and that the decrease of lymphocytes, as well as increase of NLR, after SIRT, have important consequences in terms of survival for the patients.

This work was the first to evaluate lymphocytes and NLR variations in a large series of HCC treated with SIRT. Previous studies focused on other aspects of lymphocytes activity after SIRT. Domouchtsidou et al studied 25 patients and analyzed lymphocytes functions following SIRT (11). They showed immediate decrease of lymphocyte proliferation as well as impairment of immune response. These results might suggest that lymphocytes might be less effective against HCC following SIRT. Combined with our results of decrease lymphocytes counts, this could suggest that SIRT might negatively impact the anti-tumoral immune response. This could also explain why the increase of NLR strongly and independently correlated with worse survival. In contrast, Chew et al evaluated 31 patients with in-depths characterization of circulating immune cells (12). They showed that resected tumors following SIRT were more inflamed than tumors resected without neoadjuvant treatment. They also showed that the types of circulating lymphocytes were different

between responding and non-responding tumors following SIRT. While important as they gave insight in functional parameters, Domouchtsidou's and Chew's studies were limited in numbers and could not demonstrate prognostic value of the variations of lymphocytes in terms of OS. The present study used easily available parameters that could be directly used clinically to offer prognostication.

In this context of frequent decrease of lymphocytes, the correlation of this decrease with the dose delivered to the non-tumoral liver emphasizes the need for appropriate dosimetry studying separately tumoral dose (to improve efficacy), but also non-tumoral liver doses (to ensure safety), not only to avoid liver deterioration but also to avoid lymphotoxicity (15,18). Importantly, many previous works in different contexts have suggested that baseline higher NLR was an important negative prognostic factor in patients treated with immune checkpoint inhibitors (19,20). However, it is not clear whether this could be considered only a prognostic factor, or also a predictive factor of response. The present study raises questions about the frequent decrease of lymphocytes and increase of NLR following SIRT, that has the potential to negatively affect the outcomes for patients subsequently treated with immune checkpoint inhibitors. While this could be only a working hypothesis, one might still question the rationale to study the combination of SIRT with immune checkpoint inhibitors, while this appears to have mainly suggested with hypo-fractionated regimen of radiation (21). One suggestion might be that studies combining SIRT with immunotherapy should better start the immunotherapy before administrating SIRT, to ensure that a sufficient number of active lymphocytes are still present.

This study has limitations. The retrospective nature of the work was associated with a significant number of missing data at 3 months (164 patients available from a cohort of 232 patients). Moreover, we were able to study only one time-point. The study of multiple time-

points would have allowed to more precisely describe the course of lymphotoxicity of SIRT, as well as to better understand how long this toxicity might persist. However, as Yttrium-90 half-life is about 64 hours, the decrease described in this work at 3 months could represent long-term toxicity of the treatment. There was no validation cohort. However, this is the larger study focusing on variations of lymphocytes following SIRT. Finally, the possible consequences of these variations of lymphocytes as regards to immune checkpoint inhibitors efficacy are speculative and should be studied separately in cohorts of patients treated with these agents.

In conclusion, lymphopenia is a frequent toxicity of SIRT in HCC, and increase NLR at 3 months is independently associated with worse OS. These results should be taken into account when designing potential clinical trials of combination of immune checkpoint inhibitors with SIRT in HCC.

References:

1. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. déc 2016;151(6):1155-1163.e2.

2. Edeline J, Crouzet L, Campillo-Gimenez B, Rolland Y, Pracht M, Guillygomarc'h A, et al. Selective internal radiation therapy compared with sorafenib for hepatocellular carcinoma with portal vein thrombosis. Eur J Nucl Med Mol Imaging. avr 2016;43(4):635-43.

3. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. The Lancet. juin 2017;389(10088):2492-502.

4. Zhu AX, Finn RS, Edeline J, Cattan S, Ogasawara S, Palmer D, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. juill 2018;19(7):940-52.

5. Cheng A-L, Qin S, Ikeda M, Galle P, Ducreux M, Zhu A, et al. LBA3 - IMbrave150: Efficacy and safety results from a ph III study evaluating atezolizumab (atezo) + bevacizumab (bev) vs sorafenib (Sor) as first treatment (tx) for patients (pts) with unresectable hepatocellular carcinoma (HCC). Annals of Oncology. 1 nov 2019;30:ix186-7.

6. Templeton AJ, McNamara MG, eruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. JNCI Journal of the National Cancer Institute. 29 mai 2014;106(6):dju124-dju124.

7. Nakamura N, Kusunoki Y, Akiyama M. Radiosensitivity of CD4 or CD8 positive human T-lymphocytes by an in vitro colony formation assay. Radiat Res. août 1990;123(2):224-7.

8. Zhao Q, Xu X, Yue J, Zhu K, Feng R, Jiang S, et al. Minimum absolute lymphocyte counts during radiation are associated with a worse prognosis in patients with unresectable hepatocellular carcinoma. Therap Adv Gastroenterol. févr 2017;10(2):231-41.

9. Domouchtsidou A, Barsegian V, Mueller SP, Best J, Ertle J, Bedreli S, et al. Impaired lymphocyte function in patients with hepatic malignancies after selective internal radiotherapy. Cancer Immunol Immunother. mai 2018;67(5):843-53.

10. Chew V, Lee YH, Pan L, Nasir NJM, Lim CJ, Chua C, et al. Immune activation underlies a sustained clinical response to Yttrium-90 radioembolisation in hepatocellular carcinoma. Gut. févr 2019;68(2):335-46.

11. Greten TF, Mauda-Havakuk M, Heinrich B, Korangy F, Wood BJ. Combined locoregional-immunotherapy for liver cancer. J Hepatol. mai 2019;70(5):999-1007.

12. Formenti SC, Demaria S. Combining Radiotherapy and Cancer Immunotherapy: A Paradigm Shift. JNCI Journal of the National Cancer Institute. 20 févr 2013;105(4):256-65.

13. Salem R, Lewandowski RJ, Gates VL, Nutting CW, Murthy R, Rose SC, et al. Research reporting standards for radioembolization of hepatic malignancies. J Vasc Interv Radiol. mars 2011;22(3):265-78.

14. Garin E, Lenoir L, Edeline J, Laffont S, Mesbah H, Porée P, et al. Boosted selective internal radiation therapy with 90Y-loaded glass microspheres (B-SIRT) for hepatocellular carcinoma patients: a new personalized promising concept. Eur J Nucl Med Mol Imaging. juill 2013;40(7):1057-68.

15. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med. mars 2015;56(3):339-46.

16. Avritscher R, Jo N, Polak U, Cortes AC, Nishiofuku H, Odisio BC, et al. Hepatic Arterial Bland Embolization Increases Th17 Cell Infiltration in a Syngeneic Rat Model of Hepatocellular Carcinoma. Cardiovasc Intervent Radiol. 7 oct 2019;

17. Seidensticker M, Powerski M, Seidensticker R, Damm R, Mohnike K, Garlipp B, et al. Cytokines and (90)Y-Radioembolization: Relation to Liver Function and Overall Survival. Cardiovasc Intervent Radiol. août 2017;40(8):1185-95.

18. Chiesa C, Mira M, Maccauro M, Romito R, Spreafico C, Sposito C, et al. A dosimetric treatment planning strategy in radioembolization of hepatocarcinoma with 90Y glass microspheres. Q J Nucl Med Mol Imaging. déc 2012;56(6):503-8.

19. Bigot F, Castanon E, Baldini C, Hollebecque A, Carmona A, Postel-Vinay S, et al. Prospective validation of a prognostic score for patients in immunotherapy phase I trials: The Gustave Roussy Immune Score (GRIm-Score). Eur J Cancer. oct 2017;84:212-8.

20. Capone M, Giannarelli D, Mallardo D, Madonna G, Festino L, Grimaldi AM, et al. Baseline neutrophil-to-lymphocyte ratio (NLR) and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab. J Immunother Cancer. 16 juill 2018;6(1):74.

21. Duffy AG, Ulahannan SV, Makorova-Rusher O, Rahma O, Wedemeyer H, Pratt D, et al. Tremelimumab in combination with ablation in patients with advanced hepatocellular carcinoma. J Hepatol. mars 2017;66(3):545-51.

Table 1: Baseline characteristics of the 164 patients

Median age	Median	68 (range: 37-83)
Sex	Male	146 (89.0%)
Performance Status	0	110 (67.1%)
Cirrhosis		141 (86.0%)
Alcohol consumption		112 (68.3%)
Dysmetabolic syndrom		71 (43.3%)
HBV infection		4 (2.4%)
HCV infection		19 (11.6%)
Previous treatment for HCC before SIRT	Any	87 (53.0%)
	Surgery	26 (15.9%)
	Radiofrequency ablation	16 (9.8%)
	Sorafenib	32 (19.5%)
	Transarterial Chemoembolisation	45 (27.4%)
Extent of the disease	Left liver	49 (29.9%)
	Right liver	108 (65.9%)
	Bilateral	7 (4.3%)
Maximal size of the lesion	Median	6.7cm (range: 1.2-17.0)

AFP	Median	17 (range: 1-188,300)
Portal Vein Thrombosis		65 (39.6%)
	Trunk	27 (16.5%)
	Branch	38 (23.2%)
Child-Pugh score	A5	95 (57.9%)
	A6	47 (28.7%)
	B7	21 (12.8%)
	B8	1 (0.6%)
Number of tumors	One	72 (43.9%)
	Two	30 (18.3%)
	> 2	62 (37.8%)
BCLC stage	A	2 (1.2%)
	B	60 (36.6%)
	C	102 (62.2%)
Glass-microspheres		155 (94.5%)
Resin-microspheres		9 (5.5%)

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; SIRT: Selective Internal Radiation Therapy; BCLC: Barcelona Clinic of Liver Cancer

Table 2: Univariate and multivariate Cox model for Overall Survival

Variable	Univariate analysis		Multivariate analysis	
	HR (IC 95%)	p	HR (IC 95%)	p
Age (continous variable)	0.99 (0.98-1.01)	p = 0.6		
Sex (male)	1.14 (0.75-1.72)	p = 0.54		
Cirrhosis (present)	1.2 (0.80-1.8)	p = 0.37		
Underlying liver disease :				
- Alcohol	1.01 (0.75-1.36)	p = 0.93		
- HBV	1.03 (0.52-2.01)	p = 0.94		
- HCV	1.57 (1.04-2.37)	p = 0.03	1.04 (0.59-1.81)	p = 0.9
- Dysmetabolic	1.01 (0.77-1.35)	p = 0.92		
Previous treatment	0.92 (0.6-1.23)	p = 0.58		
- Chemoembolization	1.19 (0.97-1.45)	p = 0.09		
- Sorafenib	0.99 (0.67-1.47)	p = 0.96		
Portal Vein Thrombosis	**1.41 (1.06-1.88)**	**p = 0.02**	**1.53 (1.07-2.19)**	**p = 0.02**
Size (continuous)	1 (0.99-1.01)	p = 0.19		
Performance status (>0)	1.26 (0.91-1.76)	p = 0.16		
Child score (A)	0.59 (0.40-0.87)	p = 0.08	0.82 (0.45-1.50)	p = 0.52
Number of lesions	1 (0.86-1.17)	p = 0.98		
AFP (continuous)	1 (1-1)	p = 0.01	1 (1-1)	p = 0.79
BCLC (C)	1.40 (1.07-1.84)	p = 0.02	1.09 (0.73-1.63)	p = 0.67
Albumin (continuous)	0.95 (0.92-0.97)	p < 0.01	0.98 (0.94-1.03)	p = 0.41
Bilirubin (continuous)	1.01 (1-1.02)	p = 0.19		

NLR 2 (continuous)	**1.06 (1.03-1.09)**	**p < 0.01**	**1.07 (1.04-1.1)**	**p < 0.01**
NLR 2 ≥ 7,2			**1.66 (1.16-2.37)**	**p < 0.01**
mRECIST response			1.19 (0.93-1.52)	p = 0.16

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; AFP: Alpha-feto-protein; BCLC: Barcelona Clinic of Liver Cancer classification; NLR: Neutrophil to Lymphocyte ratio; mRECIST: modified Response Criteria for Solid Tumors

Figure 1: Percentage of patients with different levels of lymphocytes counts, at baseline and at 3 months following SIRT

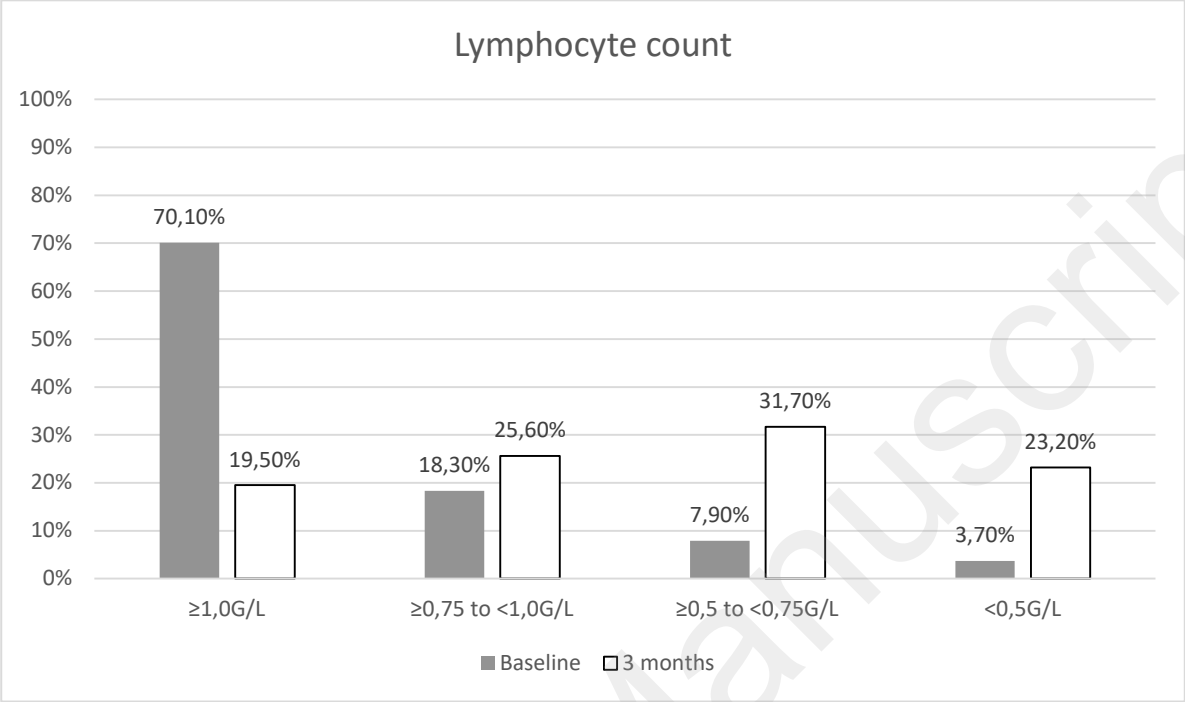
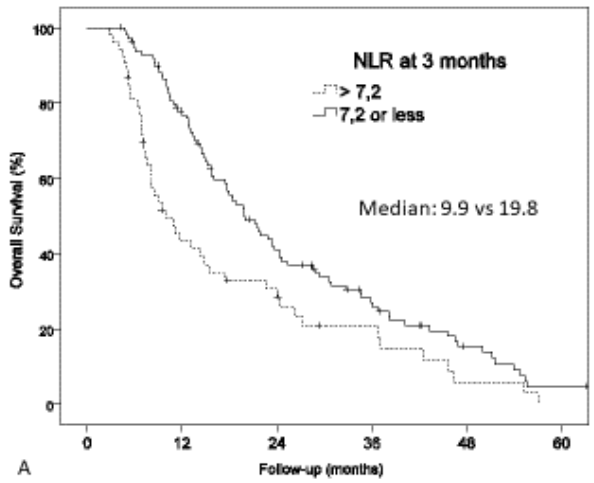
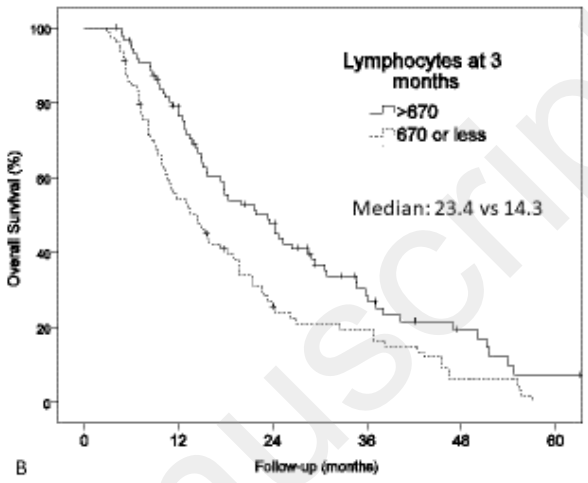


Figure 2: Overall survival according to (A) NLR at 3 months; (B) lymphocytes count at 3 months.



Numbers at risk

111	81	30	20	9	2
53	21	14	7	2	0



Numbers at risk

88	62	37	17	8	3
78	71	19	13	4	0