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Monofocal hepatocellular carcinoma: how much does size matter?

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Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; LR, liver resection; LT, liver transplantation; BSC, best supportive care; ITA.LI.CA, Italian Liver Cancer;

ECOG-PS, Eastern Cooperative Group performance status; SEM-HCC, small early monofocal hepatocellular carcinoma; LEM-HCC, large early monofocal hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; MELD, Model for End Stage Liver Disease; CRPH, clinically relevant portal hypertension; ABL, ablation; IAT, intra-arteria therapies; SOR, sorafenib; CI, confidence interval; OS, overall survival; HR, hazard ratio

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ABSTRACT

Background & Aims: According to the Barcelona Clinic Liver Cancer (BCLC) staging system, monofocal hepatocellular carcinoma (HCC) is classified as early (BCLC A) irrespective of its size, even though controversies still exist regarding staging and treatment of large tumors. We aimed at evaluating the appropriate staging and treatment for large (>5 cm) monofocal (HCC).

Methods: From the Italian Liver Cancer database, we selected 924 patients with small early monofocal HCC (2-5 cm; SEM-HCC), 163 patients with larger tumors (>5 cm; LEM-HCC) and 1,048 intermediate stage patients (BCLC B).

Results: LEM-HCC patients had a worse overall survival (OS) than SEM-HCC (31.0 vs. 49.0 months; p<0.0001), and this was confirmed at multivariate analysis (HR 1.63, 95% CI 1.29–2.05; p<0.0001). The small difference in OS between LEM-HCC and BCLC B patients (31.0 vs. 27.0 months; p=0.03) disappeared in the multivariate model (HR 0.98, 95% CI 0.77–1.25; p=0.89). In all monofocal tumors, treatment was the strongest independent predictor of survival, with a progressively decreasing survival benefit moving from “curative” to “palliative” therapies. The survival of resected patients with LEM-HCC was significantly shorter than that of SEM-HCC (44.0 vs. 78.0 months; p=0.002), but liver resection provided the highest survival benefit in both groups compared to other treatments.

Conclusions: Monofocal HCC larger than 5 cm should not be staged as BCLC A and either a different staging system or a different subgrouping of patients (e.g. BCLC AB) should be used. Liver resection, if feasible, remains the recommended treatment for all these patients.

Abstract word count: 248

Keywords: Monofocal hepatocellular carcinoma; BCLC staging system; Prognosis; Treatment; Liver resection

Lay summary

Staging and treatment of large monofocal hepatocellular carcinoma (HCC) are controversial. According to our results, the prognosis of large monofocal and intermediate stage HCC is similar and, therefore, large solitary tumors should not be classified in the early stage, but should be included in a separate subgroup (*i.e.* BCLC AB or B1 as in the ITALICA staging system). Liver resection offers the highest survival to these patients compared to other therapies, remaining the recommended treatment.

1. INTRODUCTION

Prognostic assessment in patients with hepatocellular carcinoma (HCC) is complex, being survival determined not only by tumor burden, but also by liver function and general health status.[1] Over the last 30 years, several prognostic systems have been proposed for HCC in the attempt to capture the complex interrelationship between the prognostic factors.[2–14] Among them, the Barcelona Clinic Liver Cancer (BCLC) system, endorsed by the European and American guidelines,[1,15] is the most widely used. In its original version,[7] the early stage (BCLC A) included solitary HCC <5 cm or up to 3 lesions each <3 cm; the classification of single large (>5 cm) tumors was ambiguous, as resectability, rather than tumor size, was considered to be the indicator for the allocation in the early or intermediate stage. In the 2011 updated[16] and in the last version of BCLC[1], all monofocal HCCs without macrovascular invasion and/or extrahepatic spread are classified in the early stage, irrespective of the tumor diameter. Despite some proposals to classify solitary HCC larger than 5 cm in the intermediate stage,[17–19] current Western guidelines recommend the allocation of these patients in the BCLC A stage[1,15], because of the higher survival when treated with liver resection (LR) compared to alternative treatments.[20,21] Nevertheless, the post-resection outcome worsens with increasing tumor size: the greater the diameter, the higher the risk of early tumor recurrence[22], vascular invasion, intra-/extra-hepatic spread[23] and mortality[17]. Liver transplantation (LT) is not indicated for patients with single HCC >5 cm according to Milan criteria.[24] In large HCC, thermal ablation with radiofrequency is unable to achieve response rates and outcomes comparable to those observed in smaller tumors,[1] and the efficacy of transarterial chemoembolization is debatable.[25,26] Recently, a therapeutic hierarchy (determined by the decreasing survival benefit starting from LT, through progressively less radical treatments, to best supportive care [BSC]) has been demonstrated, irrespective of stage.[27]

In this study, we performed a survival analysis aimed to evaluate the most appropriate stage allocation for large (>5 cm) monofocal HCC, the influence of tumor size on the therapeutic choices made in clinical practice and their outcomes. Considering that the 5 cm cut-off initially included in the BCLC staging system was based on Milan criteria,[24] and that nowadays the "up-to-

7"[28] criteria are widely used in the selection of patients for LT, we also conducted a sub-analysis taking into account the 7 cm threshold.

2. METHODS

2.1 Study groups

In this retrospective study, data were retrieved from the Italian Liver Cancer (ITA.LI.CA) database, a multicenter registry including 6,669 HCC patients consecutively managed at any of the 24 participating Institutions from January 1987 to March 2015. Among the patients diagnosed after January 2002 (n=4,867), we selected all the patients (n=1,087) with a monofocal HCC classifiable as early according to the latest version of the BCLC staging system (>2 cm in size, no macrovascular invasion or metastasis, preserved liver function and good general clinical conditions as assessed with Eastern Cooperative Oncology Group performance status [ECOG-PS]).[1] These patients were divided in two groups according to tumor size: the Small Early Monofocal (SEM)-HCC group (diameter ≤5 cm, n=924) and the Large Early Monofocal (LEM)-HCC group (>5 cm, n=163). For comparison, all the patients diagnosed with an intermediate stage tumor in the same time period (n=1,048) were also considered (BCLC B group). Moreover, in order to conduct the sub-analysis considering the 7 cm cut-off value, early monofocal HCC patients were subsequently regrouped as follows: HCC ≤7 cm (n=1,035; 95.2%) and tumors >7 cm (n=52; 4.8%).

The management of the ITA.LI.CA database conforms to the Italian legislation on privacy. According to Italian laws, no specific request and patient approval are needed for retrospective studies, but patients provided written informed consent for every diagnostic and therapeutic procedure, as well as for having their data recorded anonymously in the ITA.LI.CA database. This study was conducted in accordance to the ethical guidelines of the Declaration of Helsinki and it was approved by the Institutional Review Board of the participating Institutions.

HCC diagnosis was histological in 162 (14.9%) patients with monofocal HCC and in 169 (16.1%) patients in the BCLC B group, whereas in the remaining cases it was based on the typical features at imaging (dynamic computed tomography [CT] or magnetic resonance imaging [MRI]), according to guidelines.[1,15]

Standard demographic and clinicopathological data were recorded, such as age, sex, etiology of the underlying liver disease, main serological parameters (albumin, bilirubin, INR, creatinine, sodium, platelet count, alpha-fetoprotein [AFP]), Child-Pugh class, Model for End Stage Liver Disease (MELD) score, presence of ascites, clinically relevant portal hypertension (CRPH), ECOG-PS, tumor radiological characteristics (location and size, number of nodules, macrovascular invasion and extra-hepatic spread) and BCLC stage. Tumor burden was evaluated with dynamic CT or MRI. CRPH diagnosis was based on unequivocal signs (presence of splenomegaly, varices, ascites) and platelet count <100 x 10^9/L.[29]

In total, six therapeutic subgroups were considered: LT, LR, ablation (ABL: percutaneous ethanol injection, radiofrequency and microwave ablation), intra-arterial therapies (IAT: transarterial chemoembolization, simple embolization), sorafenib (SOR) and BSC. For patients managed along their clinical history with more than one treatment modality, only the main therapy was considered, defined as the more radical according to the following hierarchy: LT, LR, ABL, IAT, SOR and BSC.[27]

2.2 Statistical analysis

Categorical variables were reported as absolute and relative frequency, while quantitative data as median and interquartile range. Mann-Whitney test was used to compare quantitative data, meanwhile χ^2 test and Fischer's exact test were used for categorical variables, as appropriate.

Survivals were expressed as medians and 95% confidence interval (CI). Overall survival (OS) was calculated from the date of HCC diagnosis to the date of death from any cause, last follow-up evaluation or data censoring (December 31st, 2016). Survival curves were estimated using the Kaplan-Meier method and the difference between curves was assessed by the log-rank test.

Multivariate Cox proportional hazard models were used to identify the independent prognostic factors. Firstly, multivariate analyses were conducted in all patients with monofocal HCC, and separately in SEM-HCC and LEM-HCC, in order to identify independent predictors of survival in each group. Subsequently, another multivariate model was developed including all patients, aimed at estimating the survival differences between SEM-HCC, LEM-HCC and BCLC B groups adjusted for confoundings. In Cox regression models, continuous variables were categorized according to the following selected cut-offs: age 65 years, MELD score 9 (median value), platelet

count 100 x 10^9/L and AFP 200 ng/mL. Only variables significantly or borderline (p≤0.1) associated with survival at univariate analysis were included in multivariate models.

In all the analysis, a 2-tailed p-value <0.05 was considered statistically significant. IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism version 8.3.1 (GraphPad Software, La Jolla, California, USA) were used for all the calculations in this study.

3. RESULTS

3.1 Patient characteristics

The baseline characteristics of included patients with monofocal HCC are described in Table 1. Compared to LEM-HCC, female sex (29.5% vs. 19.0%, p=0.006), viral etiology (73.8% vs. 58.9%, p=0.0002) and CRPH (64.4% vs. 55.2%, p=0.03) were more frequent in SEM-HCC group. Moreover, SEM-HCC patients had lower platelet count (p<0.0001) and AFP levels (p<0.0001). Regarding the main treatment, LEM-HCC patients were more frequently treated with LR (41.7% vs. 25.8%) and IAT (27.0% vs. 18.7%), while ABL was less frequently adopted (14.1% vs. 44.9%).

There was a statistically significant difference among the causes of death between SEM-HCC and LEM-HCC groups (p=0.0004). At the end of the follow-up 474 SEM-HCC patients (51.8%) were dead, 212 (44.7%) from tumor progression, 106 (22.4%) from liver failure and 156 (32.9%) from sepsis, bleeding or other causes. During the follow-up, 95 LEM-HCC patients (58.3%) died, because of tumor progression (n=54, 56.8%), liver decompensation (n=29, 30.5%), and infections, bleeding or other causes (n=12, 12.7%).

3.2 Early monofocal HCC survival analysis

The median OS of all patients with solitary HCC was 47.0 months (95% CI 43.1–50.9), with a 5-year survival of 40.9%. The LEM-HCC group had a statistically significant shorter OS compared to the SEM-HCC group [31.0 months (95% CI 22.1–39.9) vs. 49.0 months (95% CI 45.2–52.8); hazard ratio (HR) 1.50 (95% CI 1.20–1.87); p<0.0001] (Figure 1). The 5-year survival rates were 33.3% and 42.2%, respectively.

The main treatment strategy had a strong impact on OS with a clear hierarchical order of survival benefit. As shown in Table 2, there was a progressive decrease in survival rates moving from "curative" to "not-curative" therapies (5-year survival rates of 63.6% in LT, 55.3% in LR, 39.8% in ABL, 28.7% in IAT, 10.2% in SOR and 9.5% in BSC). This declining benefit of different treatments modalities was maintained in both SEM-HCC and LEM-HCC groups (Table 2). When SEM-HCC and LEM-HCC patients were compared according to the treatment subgroups, SEM-HCC patients had better 5-years survival rates and longer median OS compared to LEM-HCC patients in every treatment subset.

In patients with solitary HCC, CRPH, platelet count, MELD score, Child-Pugh class and treatment, in addition to tumor diameter, were associated with survival at univariate analysis. AFP did not predict patients' survival, whatever the cut-off (20, 200 or 400 ng/mL) chosen. At the Cox multivariate analysis, platelet count ≤100 x 10^9/L [adjusted HR 1.41 (95% CI 1.17–1.70); p=0.0003], MELD >9 [adjusted HR 1.23 (95% CI 1.02–1.48); p=0.03], diameter >5 cm [adjusted HR 1.63 (95% CI 1.29–2.05); p<0.0001] and treatment, with a decreasing survival benefit following the sequence LT, LR, ABL and IAT (SOR was not statistically significant superior to BSC) were identified as independent prognostic factors for patients with monofocal HCC (Table 3). A multivariate Cox model was separately developed in SEM-HCC and LEM-HCC groups, including the variables significantly associated with survival at the univariate analysis in each group. In both, the main independent prognostic factor was the treatment, with a decreasing risk of mortality compared to BSC in a hierarchical sequence (Table 3).

3.3 Comparison with the intermediate stage (BCLC B)

In the unadjusted survival analysis, compared to BCLC B patients [median OS 27.0 months (95% CI 24.6–29.4); 5-year survival rate 20.6%], an advantage was found for the SEM-HCC group [median OS 49.0 months; HR 0.53 (95% CI 0.48–0.60); p<0.0001] and, although much smaller, for the LEM-HCC group [median OS 31.0 months; HR 0.79 (95% CI 0.64–0.98); p=0.03] (Figure 2A). However, when the comparison was adjusted for the variables affecting prognosis at the univariate analysis (platelet count, MELD, Child-Pugh class, AFP levels and treatment), the better prognosis of SEM-HCC patients compared to that of BCLC B stage patients was confirmed

[adjusted HR 0.63 (95% CI 0.53–0.74); p<0.0001], while the difference in survival between LEM-HCC and BCLC B disappeared [adjusted HR 0.98 (95% CI 0.77–1.25); p=0.89] (Table 4).

Excluding LT (the number of transplanted patients in LEM-HCC group was very small), LR was the treatment associated with the highest survival in both groups of monofocal tumors. Two hundred and thirty-eight SEM-HCC patients (25.8%), 68 LEM-HCC patients (41.7%) and 160 BCLC B patients (15.3%) were treated with LR. The median OS of resected patients was 78.0 months (95% CI 64.2-91.8) in the SEM-HCC group, 44.0 months (95% CI 27.1–60.9) in LEM-HCC group, and 44.0 months (95% CI 31.1–56.9) in BCLC B group. According to these figures, SEM-HCC patients had a significantly longer OS than LEM-HCC [HR 0.55 (95% CI 0.38–0.80); p=0.002] and BCLC B patients [HR 0.49 (95% CI 0.37–0.65); p<0.0001], while no difference was shown between these latter two [HR 0.89 (95% CI 0.62– 1.30); p=0.55] (Figure 2B). Compared to BCLC B patients undergoing IAT (median OS 25.0 months, 95% CI 22.4-27.6), LEM-HCC managed with the same treatment had a similar survival [28.0 months (95% CI 22.9-33.1); HR 1.39 (95% CI 0.92-2.11); p=0.12], while they achieved a significantly better prognosis when treated with LR [44.0 months (95% CI 27.1-60.9); HR 0.56 (95% CI 0.40-0.77); p=0.0005].

3.4 Sub-analysis according to the 7 cm cut-off

Patients with solitary HCC >7 cm had a significantly shorter median OS compared to patients with smaller tumors [30.0 months (95% CI 8.1-51.9) vs. 47.0 months (95% CI 43.1-50.9); HR 1.48 (95% CI 1.02-2.15); p=0.04]. The 5-years survival rates were 32.8% and 41.2%, respectively. Diameter at the cut-off of 7 cm confirmed to be an independent predictor at the Cox multivariate analysis with worse survival in patients with larger monofocal tumors [adjusted HR 1.55 (95% CI 1.06-2.28); p=0.03]. The survival of patients with monofocal HCC ≤7 cm was significantly longer compared to that of BCLC B patients [HR 0.56 (95% CI 0.50-0.62); p<0.0001], while no differences were detected between these latter patients and those with solitary tumors >7 cm [HR 0.82 (95% CI 0.56-1.18); p=0.28] (Figure 3A).

The above reported therapeutic hierarchy was confirmed in patients with a HCC ≤7 cm (5-year survival rates of 63.6% in LT, 56.3% in LR, 39.8% in ABL, 28.7% in IAT, 12.1% in SOR and 10% in BSC; p<0.0001). Excluding LT (due to the relatively small sample size), LR confirmed to be the treatment with the highest survival in patients with monofocal tumors ≤7 cm (median OS 73.0

months, 95% CI 61.3-84.7). Two hundred and seventy-nine patients (27.0%) in the ≤7 cm group and 27 patients (51.9%) in the >7 cm group were treated with LR. Despite the longer median OS of the former group, a statistically significant difference was not achieved [73.0 months (95% CI 61.3-84.7) vs. 44.0 months (95% CI 8.5-79.5); HR 0.59 (95% CI 0.34-1.01); p=0.055]. Probably the limited number of patients with HCC >7 cm undergoing surgery prevented to have enough statistical power to detect a difference in survival. Compared to BCLC B resected patients [median OS 44.0 months (95% CI 31.1–56.9)], those with a tumor ≤7 cm had a significantly longer survival [HR 0.54 (95% CI 0.41-0,70); p<0.0001], while patients with larger monofocal tumors had the same prognosis [HR 0.91 (95% CI 0.53-1.57); p=0.74] (Figure 3B).

4. DISCUSSION

In the BCLC staging system, monofocal tumors without macrovascular invasion and extra-hepatic metastasis, along with preserved liver function and good clinical conditions, are included in the early stage irrespective of their size.[1,15] Some authors, however, suggested that large (>5 cm) monofocal HCC should be staged as intermediate (BCLC B), because of the significantly worse survival with respect to smaller tumors.[17–19] Nevertheless, guidelines continue to support the classification of large tumors as BCLC A since these patients have the best survival benefit from LR, a treatment typically proposed for early tumors.[20,21] However, as resected large HCCs have a worse prognosis than tumors ≤5 cm, it was proposed to designate this subgroup as BCLC AB stage.[21] In line with this view, in the recently developed ITA.LI.CA tumor staging system, single tumors of 2-5 cm in size (SEM-HCC) are classified in stage A, while those >5 cm are classified as stage B1.[30]

In our study, patients with SEM-HCC had a statistically significant better prognosis than LEM-HCC patients, confirming previous results.[31] Moreover, the prognostic importance of tumor diameter was definitely established by the multivariate analysis, showing that exceeding the 5 cm threshold independently predicted an increased mortality risk.

Therefore, the pertinent unmet need is to know if, from a prognostic standpoint, LEM-HCC should be allocated to BCLC B stage or to a new stage in between BCLC A and B stages. In

previous papers,[17–19] authors came to the conclusion that these HCCs should be classified as intermediate stage. In particular, *Cho et al.*[17] revealed a superior prognostic ability of the classification system when single large tumors were allocated in the BCLC B stage. *Liu et al.*[18] and *Jung et al.*[19] also concluded that the prognosis of monofocal HCC >5 cm and multifocal intermediate patients were similar. In our study, patients with LEM-HCC had a statistically significant longer survival compared to BCLC B patients at the unadjusted univariate analysis, with a 4.0 months difference in terms of median OS, but the difference disappeared after adjusting for the other variables affecting prognosis. Also, focusing the attention to resected patients, LEM-HCC and BCLC B cases had similar median OS. Therefore, LEM-HCC patients should not be grouped in the same stage of smaller solitary tumors (BCLC A), given their significantly worse survival, that is instead similar to that of BCLC B patients.

The BCLC system links stage with therapy and proposes only one treatment option for each stage or, for BCLC A, for each sub-stage.[1,32] In the last version of European guidelines, the "treatment stage migration" strategy has been introduced in an attempt to attenuate the rigidity of the stage-dictated approach of this system which greatly limits the adherence to BCLC recommendations in clinical practice.[1,33] Recently, it has been proposed the alternative concept of "therapeutic hierarchy", which postulates that, in each stage, the therapy with the highest survival benefit should be proposed and, when it is not feasible due to specific contraindications, alternative options should be considered in an order dictated by the declining survival benefit.[27] For early stage tumors, outside the LT setting, LR is identified as the therapy with the highest survival benefit, followed by ABL, IAT and systemic therapies.[27] Accordingly, in our population of early stage monofocal tumors we confirmed the highest survival rates with LT (that was however rarely adopted), followed by LR, ABL, IAT, SOR and BSC. Furthermore, treatment was the most important independent predictor of survival, with a confirmed decreasing benefit following the above reported hierarchy in the whole population and in both SEM-HCC and LEM-HCC. Excluding LT (in the LEM-HCC group only 5 patients were treated with LT, making impossible every comparison), LR was the best treatment option regardless of HCC size, although the median OS of the resected patients was remarkably influenced by this parameter. Indeed, in patients bearing small cancer, it exceeded by 34 months that of cases with large lesions. This is an expected result, as the post-surgical risk of early tumor recurrence[22], vascular invasion and intra-

/extra-hepatic spread[23] is higher in large tumors. As a matter of fact, after resection, patients with large HCCs had an outcome similar to that found in those with surgically treated intermediate stage tumors, but this result does not stand against the preferential use of LR in large solitary tumors, considering its survival benefit over the other therapeutic options. Moreover, the survival of LEM-HCC compared to that of BCLC B patients undergoing IAT was significantly longer if they were treated with LR, while no differences existed if they were managed with transarterial palliative treatments. Our data lend support to the belief that, in well selected candidates, LR is superior to non-surgical treatments, irrespective of the BCLC stage.[21,27]

The sub-analysis adopting the 7 cm cut-off, despite being limited by the number of patients in the large volume group, confirmed the results obtained whit the 5 cm threshold. The prognosis of patients with large monofocal tumor (>7 cm) was significantly worse compared to patients with smaller lesions and similar to that of BCLC B. The same was true in patients treated with LR (despite a statistically significant difference in survival was not demonstrated between small and large HCC). In monofocal tumors up to 7 cm in size, we confirmed that curative therapies offer a survival advantage compared to palliative approaches, according to the established therapeutic hierarchy, and surgery remains the therapy of choice even when this threshold is considered. A direct comparison is not possible in this study, because of the overlap between the two subgroups, but in patients with tumors ≤7 cm we found an outcome after LR similar to that obtained in SEM-HCC group (median OS of 73.0 and 78.0 months, respectively). Due to the very limited number of patients in each therapy subgroup, it was not possible to compare LR with other treatment options in patients with HCC >7 cm. However, when resected these patients achieved the same median OS obtained in the LEM-HCC group (44.0 months in both cases).

The main limitation of our study is its retrospective design that makes selection and confounding biases unavoidable. Moreover, the number of patients with LEM-HCC was relatively small, probably affecting the results of sub-analyses on survival by treatment. A further limitation relies on the fact that, in patients managed with different therapies, we considered only one treatment strategy for each patient, whereas the survival is a function of all the treatments received. However, we think that these biases may have been mitigated by the fact that we considered not the first line therapy, but the main hierarchical therapy (according to the above reported

hierarchy) that the patients had received in his/her history. Moreover, our results support the concept that the main treatment, as indicated by the suggested therapeutic hierarchy, represents a prognostic corner stone for HCC patients, regardless of the therapeutic sequence adopted.

In conclusion, the prognosis of patients with monofocal HCC >5 cm is significantly worse than that of those with smaller tumors and it is similar to that of BCLC B patients. Hence, from the prognostic point of view, BCLC A should not be the designation stage for these patients. Nevertheless, as far as therapeutic allocation is concerned, LR is the recommended therapy for these tumors, considering its higher survival benefit in comparison to alternative treatments. The same is true if a higher cut-off (7 cm) is adopted. The approach proposed by the ITA.LI.CA study group, that classify this tumors as B1, could be useful in solving the dimensional issue regarding monofocal HCC, since it differentiates in the prognostic evaluation small tumors from larger lesions, thus capturing their diverse outcomes[30]. Alternatively, the inclusion in the BCLC system of an additional stage, i.e. BCLC AB stage, could be considered.[21]

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TABLES

Table 1. Baseline demographic and clinical characteristics of Early Monofocal HCC patients, with the comparison between SEM-HCC and LEM-HCC groups.

Variable		Early monofocal HCC (n = 1087, 100%)	SEM-HCC (n = 924, 85%)	LEM-HCC (n = 163, 15%)	p†
Males		783 (72.0%)	651 (70.5%)	132 (81.0%)	0.006
Age (years)		70 (63-75)	70 (63-75)	71 (63-77)	0.22
Viral etiology		778 (71.6%)	682 (73.8%)	96 (58.9%)	0.0002
CRPH		685 (63.0%)	595 (64.4%)	90 (55.2%)	0.03
Ascites		254 (23.4%)	211 (22.8%)	43 (26.4%)	0.32
Platelets (x 10^9/L)		126 (93-157)	126 (91-152)	130 (107-187)	<0.0001
MELD score		9 (7-11)	9 (7-11)	9 (7-11)	0.66
Child-Pugh class A		869 (79.9%)	743 (80.4%)	126 (77.3%)	0.39
AFP (ng/mL)		24.0 (6.0-315.0)	21.0 (6.0-315.0)	68.0 (7.0-1810.0)	<0.0001
Main treatment	LT	33 (3.0%)	28 (3.0%)	5 (3.1%)	<0.0001
	LR	306 (28.1%)	238 (25.8%)	68 (41.7%)	
	ABL	438 (40.3%)	415 (44.9%)	23 (14.1%)	
	IAT	217 (20.0%)	173 (18.7%)	44 (27.0%)	
	SOR	27 (2.5%)	18 (2.0%)	9 (5.5%)	
	BSC	66 (6.1%)	52 (5.6%)	14 (8.6%)	

† Mann-Whitney test, χ^2 test and Fischer's exact test, as appropriate

Categorical variables are shown as absolute frequency and percentage, while continuous data are shown as median and range.

There were no statistically significant differences between SEM-HCC and LEM-HCC group in the following serological parameters: albumin, bilirubin, INR, creatinine and sodium levels (Data not shown).

Abbreviations: HCC, hepatocellular carcinoma; SEM-HCC, small early monofocal hepatocellular carcinoma; LEM-HCC, large early monofocal hepatocellular carcinoma; CRPH, clinically relevant portal hypertension; MELD, Model for End-Stage Liver Disease; AFP, alpha-fetoprotein; INR, international normalized ratio; LT, liver transplantation; LR, liver resection; ABL, ablation; IAT, intra-arterial therapies; SOR, sorafenib; BSC, best supportive care.

Table 2. Five-year survival rates (%) and median overall survival of the whole population of early monofocal HCC, SEM-HCC group and LEM-HCC group according to the main treatment.

	Early monofocal HCC			SEM-HCC group			LEM-HCC group		
	5-year survival rate (%)	Median OS (months)	p	5-year survival rate (%)	Median OS (months)	p	5-year survival rate (%)	Median OS (months)	p
LT	63.6	87.0 (NE – NE)	<0.0001	67.6	87.0 (NE – NE)	<0.0001	45.2	66.0 (16.6 – 115.4)	<0.0001
LR	55.3	72.0 (60.5 – 83.5)		59.5	78.0 (64.2 – 91.8)		37.7	44.0 (27.1 – 60.9)	
ABL	39.8	48.0 (43.6 – 52.4)		40.0	49.0 (44.3 – 53.7)		31.1	37.0 (15.0 – 59.0)	
IAT	28.7	37.0 (31.5 – 42.5)		28.1	38.0 (33.5 – 42.5)		22.6	28.0 (22.9 – 33.1)	
SOR	10.2	25.0 (12.0 – 38.0)		14.1	31.0 (21.3 – 40.7)		0.0	8.0 (5.2 – 10.8)	
BSC	9.5	13.0 (7.5 – 18.5)		8.9	15.0 (6.4 – 23.6)		0.0	8.0 (0.7 – 15.3)	

OS is presented as median and 95% confidence interval.

Abbreviations: HCC, hepatocellular carcinoma; SEM-HCC, small early monofocal hepatocellular carcinoma; LEM-HCC, large early monofocal hepatocellular carcinoma; OS, overall survival; NE, not estimable; LT, liver transplantation; LR, liver resection; ABL, ablation; IAT, intra-arterial therapies; SOR, Sorafenib; BSC, best supportive care; NE, not estimable.

Table 3. Multivariate analysis for factors independently associated with survival in the whole Early Stage Monofocal HCC population, SEM-HCC group and LEM-HCC group.

		Early Monofocal HCC		SEM-HCC		LEM-HCC	
Variable		*Adjusted* HR (95% CI)	p	*Adjusted* HR (95% CI)	p	*Adjusted* HR (95% CI)	p
Gender	Female	-	-	Ref	-	-	-
	Male			0.88 (0.72 – 1.08)	0.22		
Ascites	No	-	-	Ref	-	Ref	-
	Yes			0.98 (0.76 – 1.26)	0.88	2.26 (1.32 – 3.88)	0.003
Platelets	> 100	Ref	-	Ref	-	-	-
($x10^9$/L) †	≤ 100	1.41 (1.17 – 1.70)	0.0003	1.36 (1.11– 1.67)	0.003		
MELD score	≤ 9	Ref	-	Ref	-	-	-
	> 9	1.23 (1.02 – 1.48)	0.03	1.31 (1.06 – 1.62)	0.01		
Child-Pugh	A	Ref	-	Ref	-	-	-
class	B	1.16 (0.93 – 1.45)	0.19	1.15 (0.89 – 1.50)	0.29		
Diameter	≤ 5	Ref	-	-	-	-	-
(cm)	> 5	1.63 (1.29 – 2.05)	<0.0001				
Treatment	BSC	Ref	-	Ref	-	Ref	-
	LT	0.11 (0.06 – 0.22)	< 0.0001	0.12 (0.05 – 0.25)	< 0.0001	0.12 (0.03 – 0.39)	0.001
	LR	0.20 (0.14 – 0.28)	< 0.0001	0.20 (0.14 – 0.29)	< 0.0001	0.15 (0.07 – 0.32)	< 0.0001

	ABL	0.26 (0.19 – 0.36)	< 0.0001	0.27 (0.19 – 0.39)	< 0.0001	0.18 (0.07 – 0.32)	< 0.0001
	IAT	0.33 (0.23 – 0.46)	< 0.0001	0.36 (0.24 – 0.52)	< 0.0001	0.18 (0.08 – 0.39)	< 0.0001
	SOR	0.74 (0.45 – 1.20)	0.22	0.64 (0.36 – 1.15)	0.14	0.82 (0.32 – 2.07)	0.82

† Both platelet count and CRPH were associated with survival at univariate analysis [HR 1.56 (95% CI 1.31-1.85) and HR 1.47 (95% CI 1.21-1.78), respectively], but in multivariate models only platelets were included to avoid collinearity between these two co-variates.

Abbreviations: HCC, hepatocellular carcinoma; SEM-HCC, small early monofocal hepatocellular carcinoma; LEM-HCC, large early monofocal hepatocellular carcinoma; CRPH, clinically relevant portal hypertension; MELD, Model for End-Stage Liver Disease; BSC, best supportive care; LT, liver transplantation; LR, liver resection; ABL, ablation; IAT, intra-arterial therapies; SOR, sorafenib.

Table 4. Multivariate Cox regression model for survival in the whole population of patients enrolled in the study.

Variable		Multivariate model		
		Adjusted HR	95% CI	p
Group	BCLC B	Ref	Ref	-
	SEM-HCC	0.63	0.53 – 0.74	< 0.0001
	LEM-HCC	0.98	0.77 – 1.25	0.89
Platelets (x 10^9/L) †	> 100	Ref	Ref	-
	≤ 100	1.26	1.08 – 1.46	0.003
MELD score	≤ 9	Ref	Ref	-
	> 9	1.25	1.07 – 1.45	0.004
Child-Pugh class	A	Ref	Ref	-
	B	1.13	0.95 – 1.35	0.18
AFP (ng/mL)	≤ 200	Ref	Ref	-
	> 200	1.20	1.03 – 1.39	0.02
Main treatment	BSC	Ref	Ref	-
	LT	0.08	0.04 – 0.14	< 0.0001
	LR	0.18	0.14 – 0.24	< 0.0001
	ABL	0.25	0.19 – 0.33	< 0.0001
	IAT	0.32	0.24 – 0.42	<0.0001
	SOR	0.56	0.38 – 0.83	0.004

† Both platelet count and CRPH were associated with survival at univariate analysis [HR 1.39 (95% CI 1.21-1.60) and HR 1.27 (95% CI 1.16-1.64), respectively], but in multivariate models only platelets were included to avoid collinearity between these two co-variates.

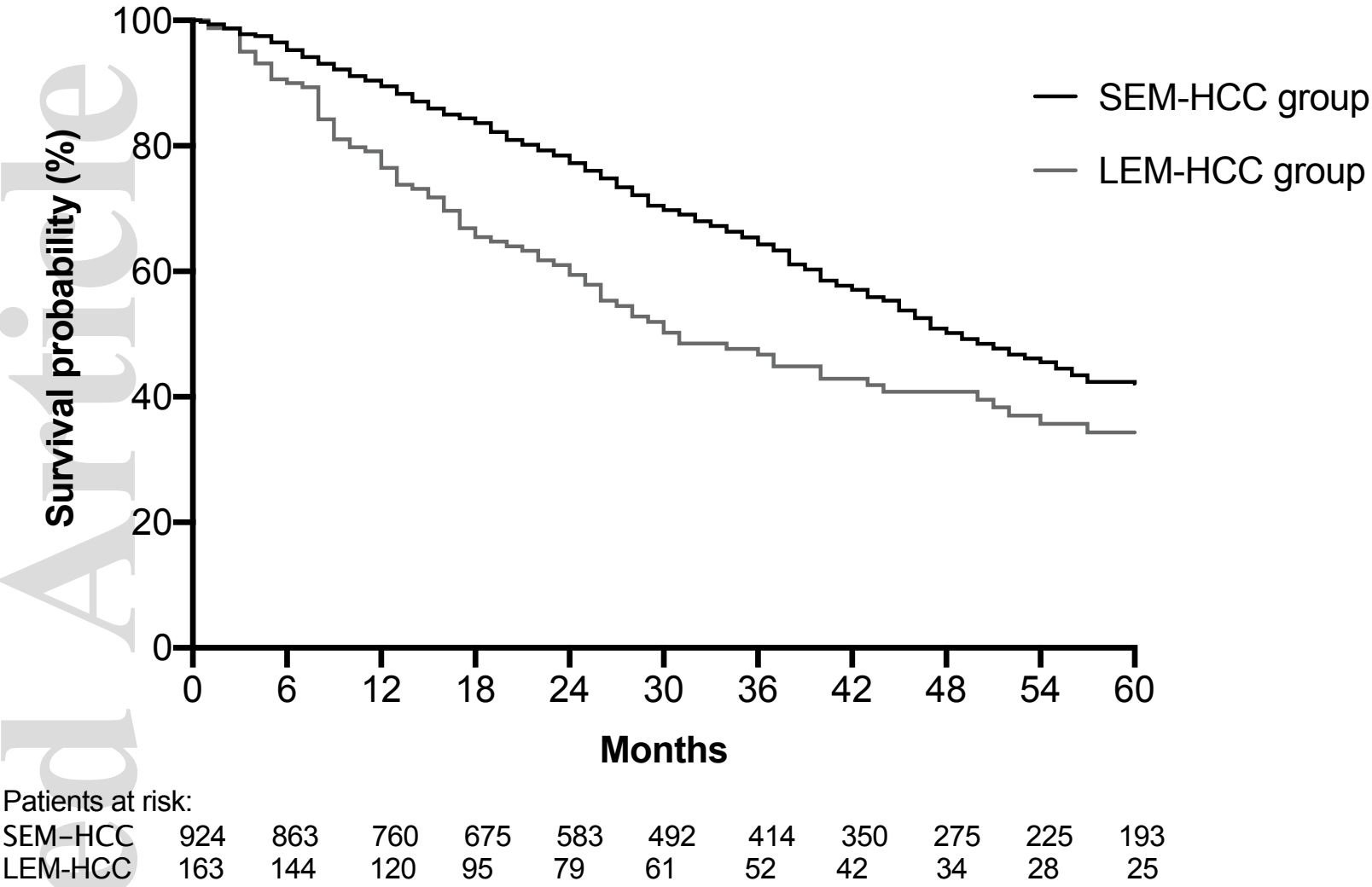
Abbreviations: SEM-HCC, small early monofocal hepatocellular carcinoma; LEM-HCC, large early monofocal hepatocellular carcinoma; BCLC-B, Barcelona Clinic Liver Cancer stage B; CRPH, Clinically Relevant Portal Hypertension; MELD, Model for End stage Liver Disease; AFP, alpha-fetoprotein; BSC, best supportive care; LT, liver transplant; LR, liver resection; ABL, ablation; IAT, intra-arterial therapies; SOR, sorafenib.

FIGURE LEGENDS

Figure 1. Kaplan-Meier survival curves of patients with a monofocal HCC subdivided according to the 5 cm diameter cut-off. Small Early Monofocal (SEM)-HCC patients had a statistically significant longer survival compared to Large Early Monofocal (LEM)-HCC patients ($p<0.0001$).

Figure 2. Kaplan-Meier survival curves for Small Early Monofocal (SEM)-HCC, Large Early Monofocal (LEM)-HCC and BCLC B patients. **(A)** SEM-HCC patients had a statistically significant longer survival compared to both LEM-HCC ($p<0.0001$) and BCLC B patients ($p<0.0001$), with a relatively small difference between the latter two ($p=0.03$). **(B)** Considering only the subgroups of patients treated with liver resection, SEM-HCC patients had a statistically significant longer survival compared to both LEM-HCC ($p<0.0001$) and BCLC B patients ($p<0.0001$), with no differences between the latter two ($p=0.55$).

Figure 3. Kaplan-Meier survival curves for monofocal HCC ≤7 cm, monofocal HCC >7 cm and BCLC B patients. **(A)** Patients with monofocal HCC ≤7 cm had a statistically significant longer survival compared to patients with larger monofocal tumors ($p=0.04$) and BCLC B patients ($p<0.0001$); there was no difference in survival between patients with monofocal tumors >7 cm and BCLC B patients ($p=0.28$). **(B)** In patients treated with liver resection, the median survival of patients with a monofocal HCC ≤7 cm was longer compared to BCLC B patients ($p<0.0001$) and almost statistically significant longer compared to monofocal tumors >7 cm ($p=0.055$); no differences in prognosis were found between the latter two groups ($p=0.74$).



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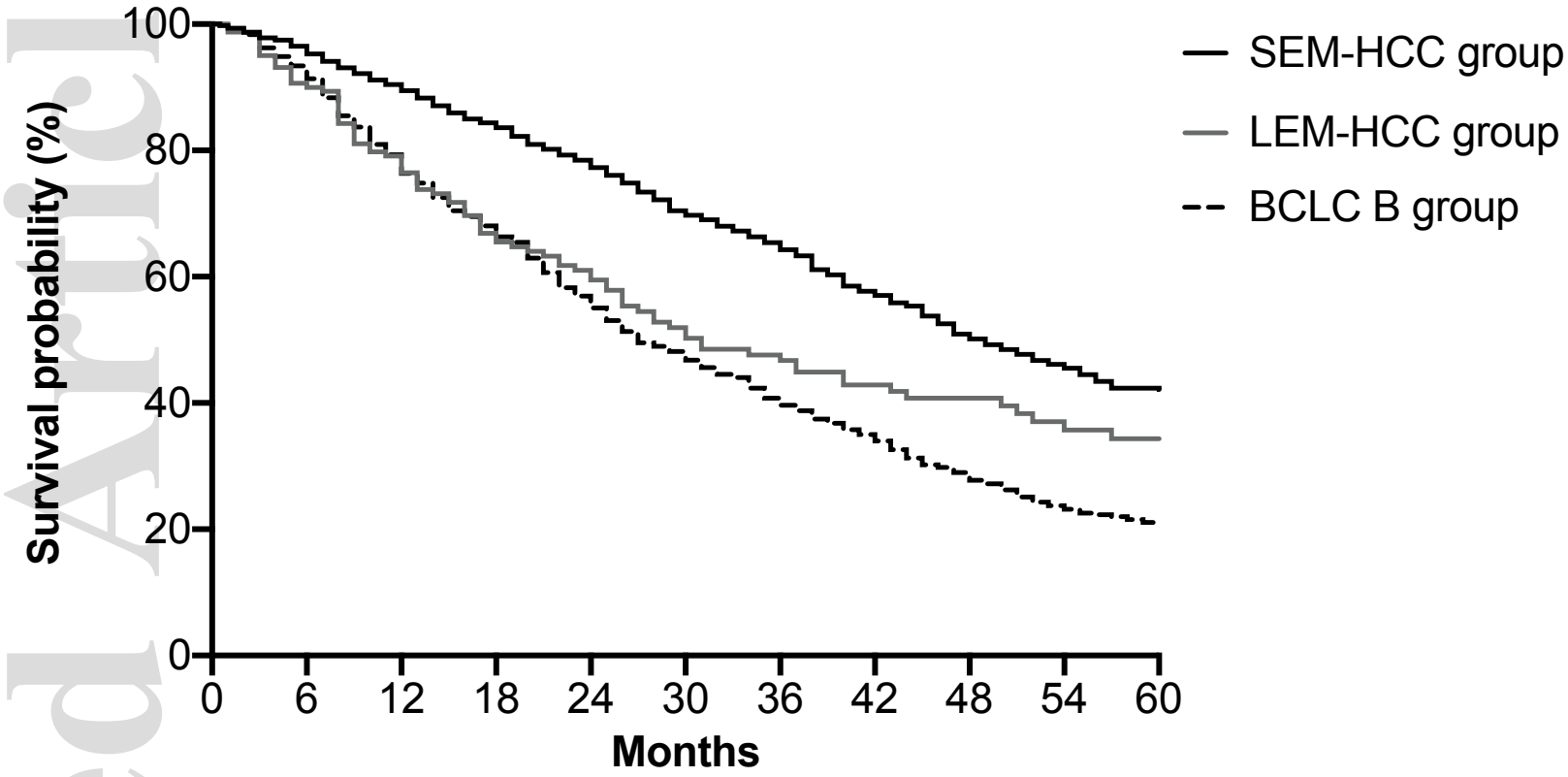

Patients at risk:

SEM−HCC	924	863	760	675	583	492	414	350	275	225	193
LEM-HCC	163	144	120	95	79	61	52	42	34	28	25
BCLC-B	1048	952	775	640	513	417	331	274	212	167	137

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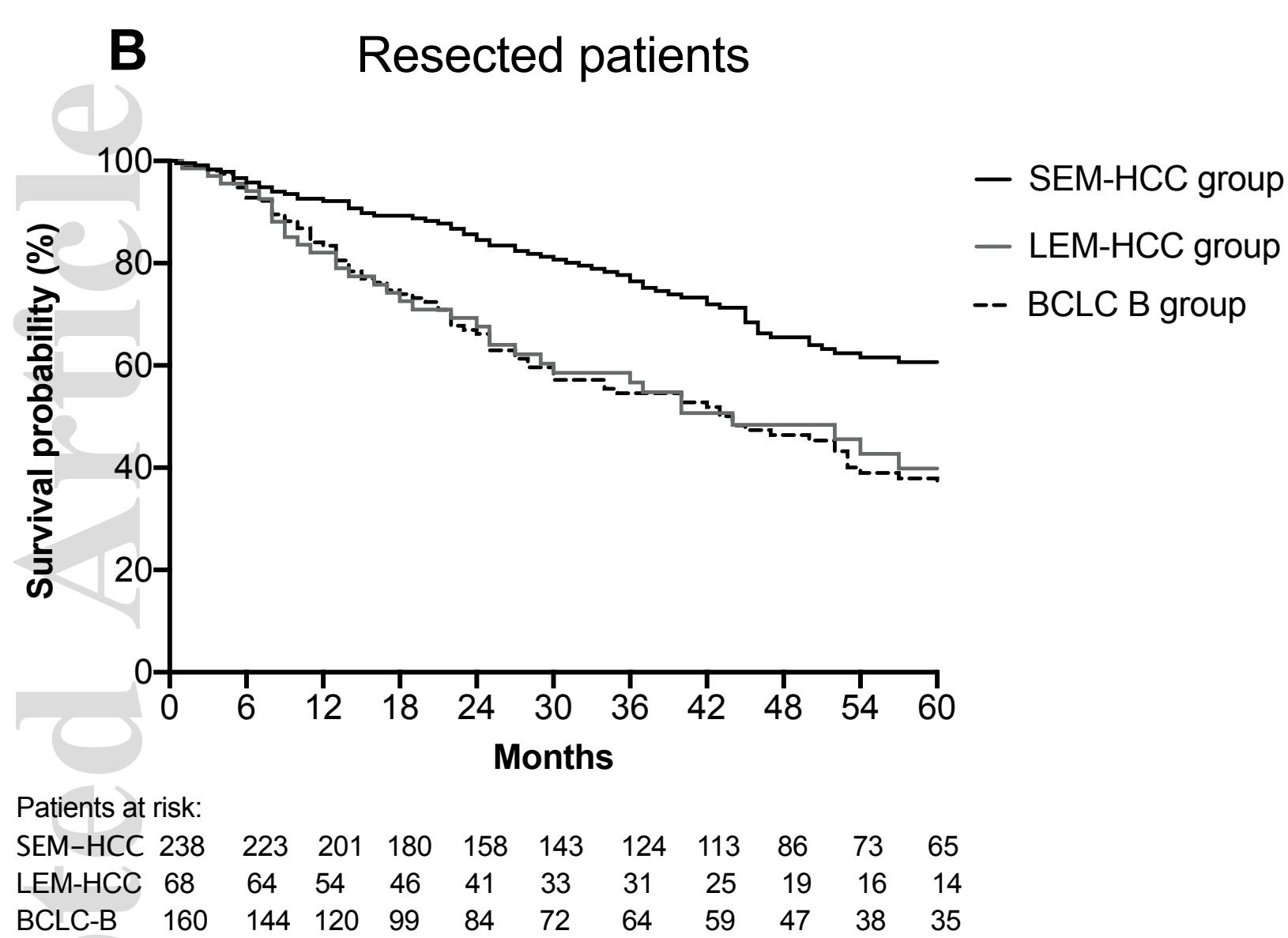

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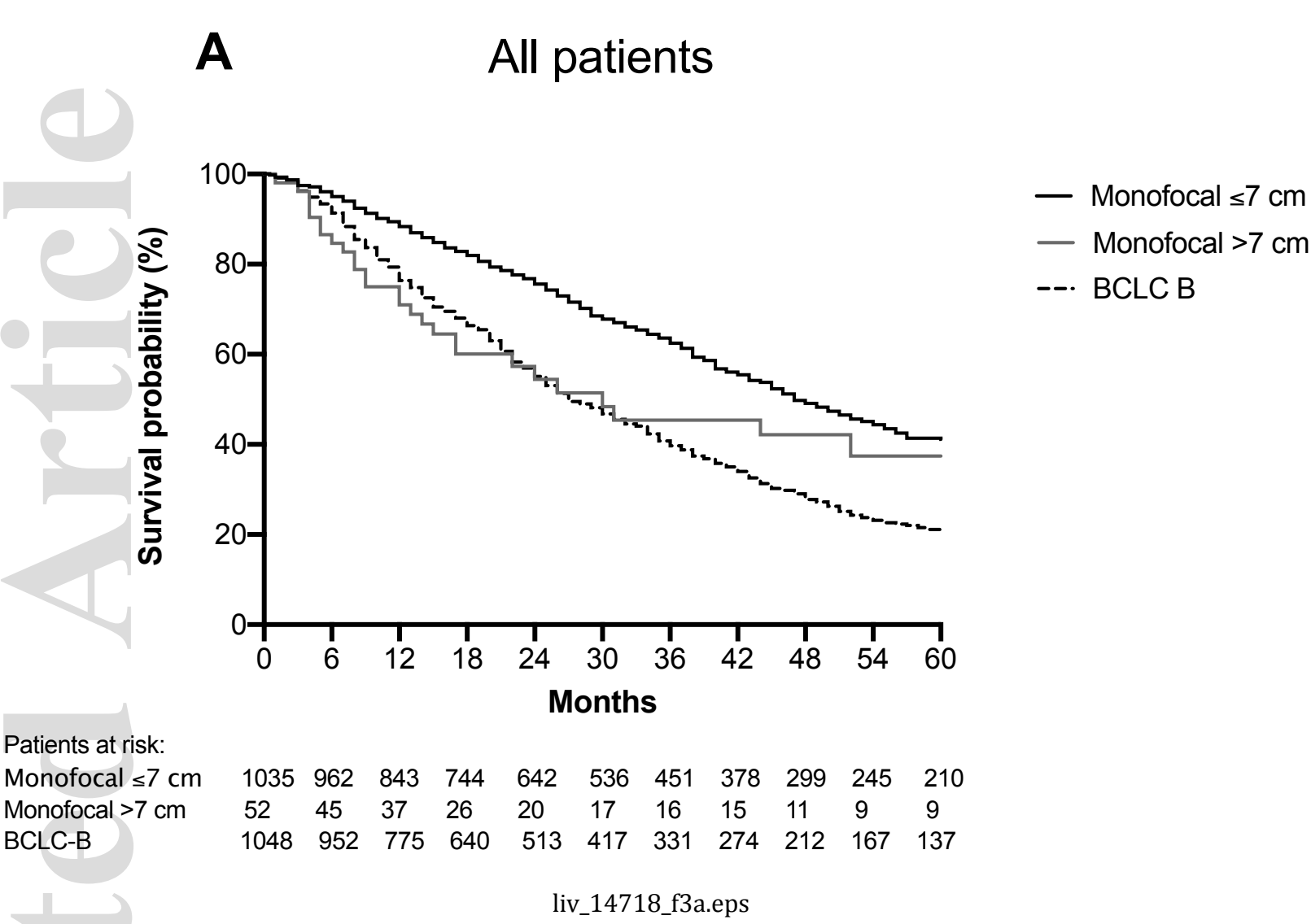

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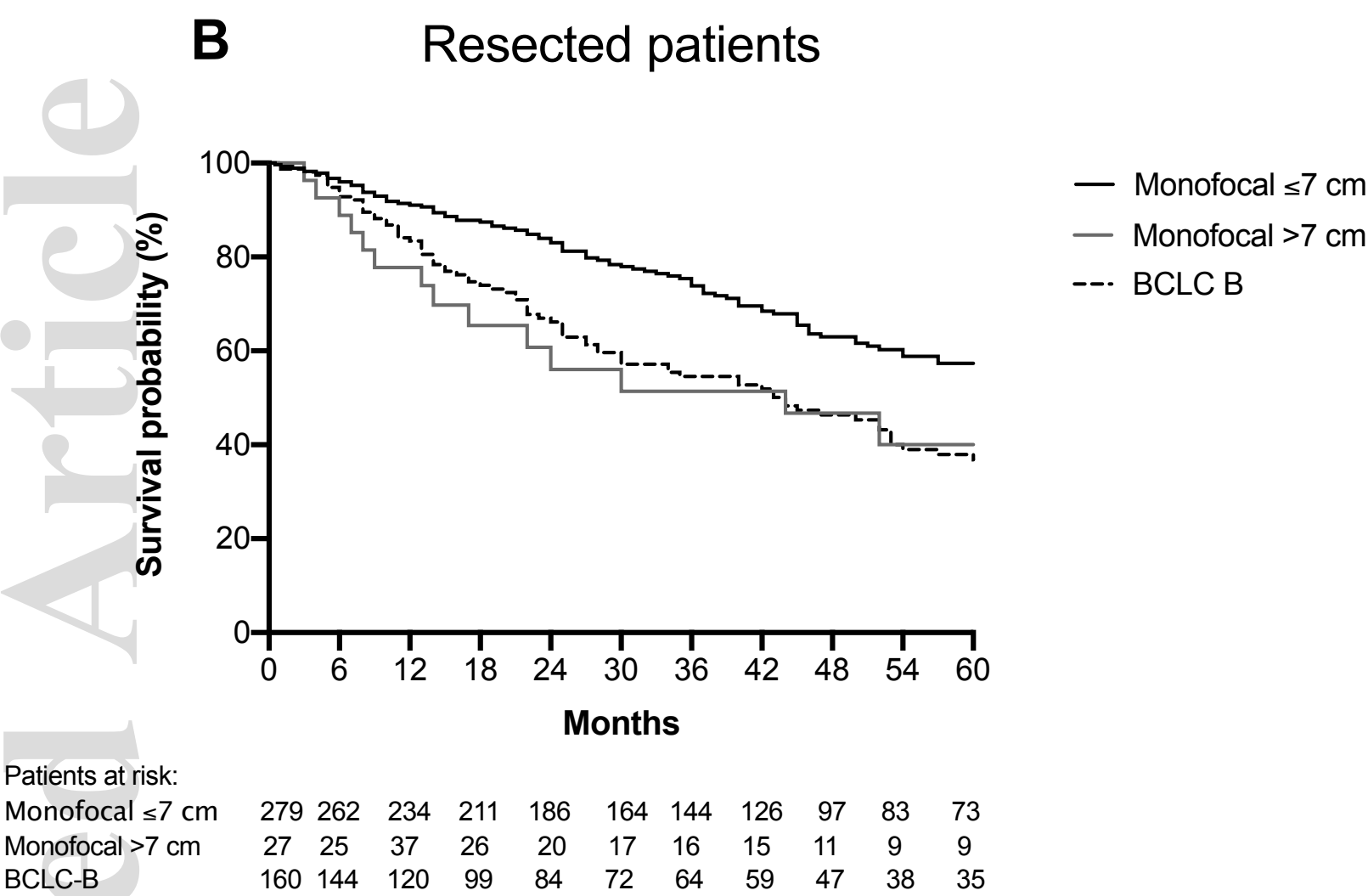

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