Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: A multicentre study

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List of abbreviaitons:

HCC- Hepatocellular Carcinoma

BCLB- Barcelona Clinic Liver Cancer

LRT- Loco-Regional Therapy

BCT- Best Supportive Care

MS- Median Survival

PST- Performance Status

ECOG- Easter Cooperative Oncology Group

CRPH- clinically relevant portal hypertension

IQR- interquartile range

HCV- hepatitis C virus

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Abstract

Background & Aims: Hepatic resection for hepatocellular carcinoma (HCC) in different Barcelona Clinic Liver Cancer (BCLC) stages is controversial. We aimed to measure the survival benefit of resection vs. non-surgical-therapies in each BCLC stage.

Methods: Using the ITA.LI.CA database we identified 2090 BCLC A, B, and C HCC patients observed between 2000 and 2012: 550 underwent resection, 1046 loco-regional therapy (LRT) and 494 best supportive care (BSC). A multivariate Log-logistic model was chosen to predict median survival (MS) after resection vs. MS after LRT or BSC. The results were expressed as net survival benefit of resection: (MS resection – MS LRT) / MS BSC.

Results: After stratifying for BCLC stage, the median net survival benefit of resection over LRT was: BCLC 0 = 62% (40%, 82%), A = 45% (13%, 65%), B = 46% (9%, 76%), C = -16% (-55%, 33%). Model for end stage liver disease (MELD) score > 9, Child B class, and performance status (PST) = 2 were the main risk factors for liver resection. 1181 Child A patients (57%) with MELD ≤ 9 and PST <2 had always a large positive net survival benefit of resection over LRT independently from BCLC stage: BCLC 0 = 64% (44%, 85%), A = 59% (45%, 74%), B = 71% (52%, 90%), C =56% (36%, 78%). Among the 909 (43%) patients with at least one risk factor (MELD>9 or PST=2 or Child B class), resection did not prove any survival benefit over LRT.

Conclusions: Resection could result in survival benefit over LRT for HCC patients regardless their BCLC stage, provided that liver dysfunction (Child B or MELD>9) and PST > 1 are absent.

Introduction

Prognostic assessment and treatment strategy for patients with hepatocellular carcinoma (HCC) and liver cirrhosis are extremely complex due to the simultaneous presence of two distinct diseases[1]. The Barcelona Clinic Liver Cancer (BCLC) classification is the only HCC staging system accounting for tumor burden, liver function, general conditions (as expression of symptomatic tumor), able to guide in the treatment decision[1]. The main limit of BCLC is the great prognostic heterogeneity within each stage[2]. In last years, some authors proposed a new model for prognostic prediction in HCC patients[3], the model to estimate survival in ambulatory HCC patients score (MESIAH). The MESIAH score showed a significantly higher predictive power than BCLC [3],but its main limit is that it doesn't help clinicians in treatment decision.

Although the BCLC classification is directly translated into a strict treatment algorithm, assigning different therapies to different subgroups of patients[1],there is a great overlap between treatments and prognostic stages in daily clinical practice. Recent studies demonstrated that radical therapies, such as hepatic resection and liver transplantation, are commonly preferred and have a great benefit even for intermediate and advanced HCC [4, 5], while locoregional therapies, such as radiofrequency (RF) percutaneous ablation and trans-arterial chemoembolization (TACE), are largely used as first line therapy even for early HCC [6].

With the exception of liver transplantation, which is greatly limited by scarce donor resources [5], liver resection is considered the best oncological treatment for HCC[4].

Only few randomized control trials comparing resection to percutaneous ablation in very selected subgroups of patients have been published until now [7]. These studies are often underpowered and propose percutaneous ablation as an alternative to resection in BCLC 0 HCC patients [1, 8].

There is a lack of well-designed large studies comparing resection versus the whole span of therapeutic alternatives for each BCLC stage. Moreover, while comparing resection and other therapies, the natural history of the disease should be taken into consideration, in order to determine the actual benefit/harm ratio of each therapy.

All this considered, we aimed to compare the net survival benefit of resection over non-surgical loco-regional-therapies (LRT) and best supportive care (BSC) in a large cohort of HCC patients with different BCLC stages.

Materials and Methods

Patient demographic and clinical data

A total of 2686 patients undergoing surgical or non-surgical treatment for HCC between 2000 and 2012 in the institutions partecipating in the Italian Liver Cancer (ITA.LI.CA.) database were identified. Patients with BCLC stage D (n=385), presence of extra-hepatic metastasis (n=114) and those treated with liver transplantation (n=77) were excluded from the study. Since only 40 patients received Sorafenib (< 2% of the entire cohort), these patients were also excluded from the analysis. The study group finally consisted of 2090 patients.

We considered three main therapeutic subgroups. Firstly we selected all patients undergoing liver resection (resection group, n=550) and we followed them from the time of resection onwards. These patients were considered in the resection group even if they underwent other HCC non-surgical therapies. Then, we selected patients undergoing at least one LRT such as RF or TACE (LRT group, n= 1046) and we followed them from the time of first LRT onwards, independently from other non-surgical treatment received during their follow-up. The remnant patients were considered in the BSC group (n=494).

Standard patient demographic and clinicopathological data were collected including age, sex, comorbidities, Easter Cooperative Oncology Group (ECOG) performance status (PST), general symptoms, modality of HCC and cirrhosis diagnosis (biopsy/surgical specimen or unequivocal clinical and radiological findings), serological parameters (sodium, bilirubin, albumin, INR, creatinine, platelet count, alfa-fetoprotein (AFP) levels), Child Pugh class, clinically relevant portal hypertension (CRPH) and BCLC stage. Tumor characteristics were also collected, including tumor location, size, number and vascular invasion.

CRPH diagnosis was based on unequivocal clinical signs (gastroesophageal varices, ascites, splenomegaly with a platelet count of less than 100,000/ml) since hepatic venous pressure gradients were not determined [1].

The BCLC classification was used to stratify the study population in different prognostic stages, after the adoption of the following changes: since recent evidences have re-assessed the role of PST in the BCLC classification [9], patients with PST=1 and without macroscopic vascular invasion were included in BCLC stage B; the definition of early HCC according to the BCLC classification is still debated (i.e. early HCC is single nodule of any size when the tumor is considered resectable, while it is a single nodule smaller than 5 cm when the tumor is considered unresectable), therefore we added a separate subgroup of patients (named stage AB) that included patients with a single nodule larger than 5 cm without vascular invasion, Child Pugh A-B cirrhosis, and PST 0 or 1 [1].

According to tumor characteristics, liver functional status, and patient will, several therapeutic strategies were used, such as resection, percutaneous tumor ablation, trans-arterial LRT, systemic therapy and BSC.

Statistical analysis

Qualitative data were described by frequency and percentage. Quantitative data were described by median (interquartile range (IQR)). In the comparison among different subgroups, quantitative variables were compared using Student's *t* or Wilcoxon Rank Sums tests, and categorical variables using χ^2 or Fisher's exact tests, as appropriate. Length of follow-up and survival are expressed as medians (IQR). Overall survival was calculated from the baseline visit until death from any cause or latest follow-up. Survival curves were estimated using the Kaplan-Meier method, whereas the statistical significance between survival curves was tested by the Log-Rank test.

We tested several multivariate survival models (the semi-parametric Cox model, and parametric exponential, log-normal, Weibull, and log-logistic models) including the following variables: patient-related covariates (age, and PST), liver function-related (MELD score, Child Pugh class,

CRPH); and tumor-related (diameter, number of nodules, AFP values, and macroscopic vascular invasion). The selection of these variables was based on recent literature reports [1, 2, 4, 5, 8]. Treatment (resection vs. LRT vs. BSC) was used as stratifying covariate.

The log-logistic model was finally chosen among semi-parametric and parametric ones since it the showed the lowest Akaike Information Criterion (AIC) and the highest Harrell C-index values.[10] This multivariate survival model was used to investigate the impact of patient-, liver-, and tumor-related variables on survival after each treatment. To overcome biases owing to the different distribution of covariates among patients undergoing resection and those undergoing LRT or BSC, we calculated three individual median survival predictions -after resection, after LRT therapies or after BSC- independently from therapy actually received. Subgroup analyses were then performed based on BCLC staging, Child Pugh class, MELD score, and presence of CRPH. Since MELD score in HCC patients undergoing loco-regional therapies is mainly used as dichotomous variable, MELD > 9 was used in the subgroup analysis [11]. In order to weight the benefit/harm ratio of therapy in each patient we calculated the net benefit of resection over LRT with the following formula: (median survival with resection – median survival with LRT) / median survival with BSC. The net benefit of resection over LRT represents a simple novel endpoint based on the commonly used concept of survival benefit (expressed as gain in survived months) adjusted for the median survival of patients not receiving any anti-cancer therapy (natural history of the disease). This measure gives an estimation of the net proportion (%) of survival in months gained or lost using resection instead of LRT in each patient. Net benefit results were presented as medians (interquartile range).

A boosting forest tree method (partition modelling) was finally used to measure the contribution of each covariate to resection net benefit over LRT [12]. Partition trees were constructed using a training set (corresponding to 70% of the entire cohort) and a validation set (corresponding to 30% of the entire cohort) and the final model was that with the highest R square in both training and

validation sets. Cox model results were reported as hazard ratios (95% confidence interval (95% CI)) estimates together with corresponding *p*-values.

A further log-logistic multivariate model was performed including the above mentioned covariates but splitting the LRT group in those undergoing RFA ± TACE and those undergoing TACE alone. In this way, we might calculate individual survival predictions for each of the 2090 enrolled after four treatment procedures (resection vs. RFA vs. TACE vs. BSC).

Finally, to validate and confirm our findings we performed a propensity score among patients undergoing resection and those undergoing LRT[13]. A one-to-one match was created and the survival curves of new matched cohorts were compared in different BCLC stages. Considering the matched nature of the analysis, differences in continuous baseline variables were assessed using the paired t test.

Statistical significance was set at $p < .05$. The calculations were done with the JMP package (1989–2003 SAS Institute Inc.) and R.app GUI 1.51 (S. Urbanek & H.-J. Bibiko, © R Foundation for Statistical Computing, 2012).

Results

Study groups characteristics

Among the 2090 patients treated for HCC between 2000 and 2012 in the institutions participating in the ITA.LI.CA database, 550 underwent liver resection, 1046 LRT and 494 BSC. As expected, there were differences in the baseline characteristics of the 3 groups. Patients undergoing resection were significantly younger, compared with patients in the LRT group and with patients in the BSC group. Among those who underwent resection, the majority of patients were male and the proportion of hepatitis C virus (HCV) positivity, Child Pugh B and CRPH were lower compared to the other 2 groups (Table 1). In addition, patients who underwent liver resection had larger tumors than the counterpart. All BCLC stages were well represented in the liver resection group and in the LRT groups.

As expected, patients who received BSC had a more impaired liver function and a higher rate of advanced tumors compared to the other two groups. (Table 1) The 20% of them were classified as BCLC stages 0 and A.

In supplementary table 1 we described patient-, liver function -, and tumor- characteristics in different BCLC stages. Interestingly, a considerable proportion of patients with MELD > 9 were identified in each BCLC stage. Among patients undergoing LRT, 617 (30%) underwent RF ± TACE as main therapy, while 429 (21%) had only trans-arterial therapies. These two subgroups among LRT patients were differently distributed in each BCLC stage (Supplementary table 1).

Survival analysis

An unmatched comparison of survival profile of patients in the three different treatment subgroups (Figure 1) and in different BCLC stages, showed that liver resection had higher long-term survival than LRT and BSC in early and intermediate stages. Differently, LRT had the highest long-term survival in advanced stages. All differences between resection, LRT, and BSC were statistically significant using Log Rank test.

Table 2 shows the prognostic impact of patient-, liver function-, and tumor-related variables on survival in the three different treatment groups based on a log-logistic parametric survival model. Interestingly, tumor variables, such as size, number of nodules and vascular invasion, had a higher discrimination power in non-surgical compared to surgical ones. Conversely, some patient- and liver function- variables, such as PST = 2, MELD score, and Child Pugh class B, were stronger survival predictors in patients who underwent liver resection. Conversely, MELD score and PST=2 had a low discrimination power in the LRT group.

The multivariate models obtained for each treatment subgroup showed a higher discrimination ability (lower AIC and higher C-index) than the same models calculated by semi-parametric Cox proportional hazard analysis, and than consolidated prognostic models for HCC patients such as the BCLC staging and the MESIAH score (Table 2).

Survival benefit of liver resection

Median net survival benefit of resection over LRT according to BCLC stage was: BCLC 0 = 62% (40%, 82%), A = 45% (13%, 65%), AB= 38% (3%, 60%), B = 49% (9%, 79%), C = -16% (-55%, 33%) (Figure 2A and 2B).

The different prognostic impact of patient-, liver function-, and tumor-related covariates in the three treatment groups (Table 2) corresponded to a different contribution of these variables on net survival benefit of resection. MELD score > 9, Child B class, and PST = 2 proved to be the strongest predictors of low net resection benefit (Figure 3). Conversely, tumor characteristics were negligible predictors of net resection benefit.

Based on these results, we inquired the impact of BCLC on net survival benefit of resection. We stratified the population in two subgroups, 1181 patients (57%) with a favorable profile for liver resection (MELD ≤ 9, Child A, and PST <2) and 909 (43%) with an unfavorable profile (MELD > 9, Child B, or PST = 2). Patients in the first subgroup always had a large positive net survival benefit of resection over LRT independently from BCLC stage. (Figure 4A and 4B). Among patients in the second group, liver resection did not prove any survival benefit over LRT. (Figure 4C and 4D).

A separate analysis comparing the outcome of patients undergoing resection, RFA ± TACE, TACE alone, or BSC was performed (Supplementary Table 2). Liver resection confirmed higher median survivals than both RFA and TACE in BCLC stages 0, A, AB, and B. Interestingly, RFA proved to be clearly superior to TACE in BCLC 0 and AB stages patients (Supplementary figure 1).

Propensity score analysis.

To validate and confirm our findings we performed a propensity score analysis among patients undergoing resection and those undergoing LRT. We selected 318 patients in the resection group and in the LRT group with similar patient -, liver function -, and tumor characteristics (Supplementary Table 3). We showed a relevant trend of better results in patients treated with

resection versus LRT both in early and advanced BCLC stages, when a positive resection profile was maintained (Supplementary figures 2A and C). Conversely, a negative resection profile contraindicated liver resection in these candidates (Supplementary figures 2B and D).

Discussion

Hepatocellular carcinoma has shown an extremely heterogeneous biological behavior [1], in fact, if in a relevant proportion of patients it has a relatively slow progression [14, 15], in other patients it presents an extremely aggressive behavior. In this setting, surgical and loco-regional therapies risk to not improve patient outcome and, more importantly, to negatively impact on overall survival and quality of life. Different staging systems have been proposed to predict survival of patients with HCC [16]. One of the most widely staging system used for its ability to account for tumor burden, liver function and general conditions, is the BCLC [1]. Nonetheless, in daily clinical practice, there is a great overlap between BCLC and the subsequent treatment. For this reason we aimed to compare the survival benefit of different therapeutic strategies in a large cohort of HCC patients assigned to different BCLC stages.

The availability of a large database of HCC patients allowed to calculate individual survival rates after resection, LRT, and BSC in each BCLC stage, and to introduce the concept of net survival benefit after liver resection. This novel measure takes into consideration: 1) the benefit/harm ratio of each patient after surgical and non-surgical therapies; 2) the survival gain based on the disease stage. This new net benefit formula could seem quite artificial. However, we think that this is a useful method to measure the benefit of liver resection over alternative therapies adjusted for the natural history of the disease (i.e. without anticancer therapy). Absolute differences in median survivals, in fact, don't consider the aggressiveness of the disease. For example, a gain in 3 months in BCLC stage 0 is quite irrelevant, while the same gain in advanced stages (BCLC C) may be more clinically relevant [17]. The concept of net benefit clearly captured these two different clinical situations: the net benefit would be 7% (3/46 months) for BCLC 0 patients and 20% (3/15 months)

for BCLC C patients.

A first perplexity may raise from our reference group (BSC) particularly in estimating the natural history of patients with early HCC. Our reference group included 20% of their patients in BCLC stages 0-A (Table 1). These are mainly patients who refused any kind of anti-cancer therapy. Recent evidences estimated the natural outcome of untreated HCC patients in BCLC 0-A stages to be about 36 months[1]. Our study confirmed this estimation showing a median survival for these patients between 30 and 40 months.

A second perplexity may be related to our statistical methodology. Our analysis is not based on "observed" outcomes but on "predicted outcomes". We searched the best possible prediction models (Table 2) for each treatment group in order to simulate the outcome that each patient should have undergoing four possible therapeutic strategies (resection, RFA, TACE or BSC). In the simulation we obtained four populations, including a total of 2090 patients and undergoing four different therapeutic procedures.

In this way we might study in detail each BCLC stage finding the main predictors of liver resection failure or success over alternative therapies. Unadjusted Kaplan Meier survival curves (Figure 1) are not able to give this piece of information.

Differently than previously reported, patients with single tumor >5 cm without macroscopic vascular invasion, with Child A-B cirrhosis and PST were considered as stage BCLC AB patients, in order to better stratify for patient characteristics the survival benefit of different treatment approaches [4].

In a cohort of 2090 HCC patients with cirrhosis, liver resection was associated with a significant net benefit over LRT. Surprisingly, the benefit was noted not only in early stage (BCLC A) but also in intermediate stages (B/C). Importantly, this benefit persisted after a robust adjustment for adverse factors including clinically significant portal hypertension. As expected, tumor size does not negatively impact on net benefit of resection (Figure 4). Indeed, the oncological radicality of ablative procedures dramatically decreases for tumor >2-3 cm, possibly due to an incomplete

necrosis of its peripheral and satellite lesions. Conversely, anatomic resections proved to guarantee a high efficiency in large lesions [15]. Interestingly enough, the number of nodules also did not decrease the net benefit of resection over LRT, indicating a survival gain after liver resection even in case of multi-nodular HCC.

These findings may radically change the prognostic evaluation and management of HCC patients, suggesting that BCLC stage does not influence the prognostic impact of different therapeutical approach [18], and that liver resection should be preferred when technically feasible and clinically appropriate [11]. As a consequence, aggressive treatments beyond the current guidelines, should be considered when clinically applicable, in order to achieve the maximum survival benefit. This consideration is particularly important for intermediate and locally advanced HCC patients, whose comparative study groups more strictly reflected standard of care therapies [1].The only exception to this statement is represented by BCLC 0 HCC patients, who are also amenable for LRT, such as radiofrequency ablation.

Furthermore, after stratifying for MELD score, Child class and PST, in patients with MELD ≤ 9, Child A and PST<2 the net survival benefit of liver resection over other therapies increased and was independent from the BCLC stage. Differently, in patients with MELD > 9 or Child B class or PST=2 the net survival benefit of liver resection was negligible or negative, indicating the superiority of LRT.

Liver function and general conditions are well known prognostic factors in HCC patients undergoing liver resection. However, these are significant survival predictors also in patients undergoing LRTs [19]. To the best of our knowledge, this is the first direct comparison between resection and LRT not only in a positive prognostic scenario (well compensated cirrhosis and PST <2) but also in a negative prognostic scenario. Recent evidences are trying to extent the indications for liver resection to patients in BCLC stages B and C [4, 20]. Our results showed that this extension is possible only in a well-controlled scenario (MELD ≤ 9, Child A and PST <2), where the risk of post-operative liver failure is very low. These results reinforce the impact of cirrhosis

stage and clinical conditions on the therapeutic management of HCC patients. In case of advanced cirrhosis and high PST a non-surgical approach should be preferred.

In the supplementary figure 1 and supplementary Table 2 we performed a separate analysis to compare the outcome after RFA ± TACE and TACE alone. In this context, our study supports current guidelines indicating RFA as the best alternative to resection in BCLC 0 patients.

The current study has several limitations. As with all retrospective studies, there were undoubtedly some selection and confounding biases. In addition, the intrinsic limitation of BCLC classification in delineating advanced HCC stages should be taken into account. This definition does not discriminate the extent of portal vein thrombosis, even if its prognostic role after resection is well known [21]. Recent studies, in fact, suggested a prognostic distinction between patients with peripheral portal thrombosis and those with thrombosis of the portal trunk [2, 21, 22]. Unfortunately, in the present study we were not able to discriminate the net survival benefit of resection according to type of portal thrombosis, because of the lack of information in the dataset. Another limitation of this study can be represented by the need to exclude patients treated with Sorafenib, due to the recent introduction of this drug in clinical practice and therefore having a small cohort of patients under this treatment in the dataset [17]. Nevertheless, a consistent body of evidence [23, 24] and the results of the present study suggest that resection should not be denied in well-selected BCLC C patients with preserved liver function (Child Pugh class A). The median survival of BCLC C patients treated with Sorafenib is about 10 months in Western countries and even lower in eastern countries [17, 25]. Future randomized trials or well-designed cohort studies are needed to compare net survival benefit of resection over Sorafenib in BCLC C patients.

In the absence of adequately powered randomized clinical trials (RCT), we think that the statistical methodology used in this study has the highest potential to simulate a RCT. The availability of three independent prognostic models (Table 2), one for resection, one for LRT, and one for BSC, allows individual predictions for three possible therapeutic scenarios in each enrolled patient simulating a three-arms RCT. The prognostic performance of our models was significantly

better than the one of the conventional BCLC system and that of the MESIAH score (Table 2), which was recently introduced as the best prognostic score in HCC patients[3].

To validate and confirm our findings we performed a propensity score analysis (Supplementary table 3 and Supplementary figure 2). Although propensity score intrinsically decreased sample size and thus the possibility to find significant differences, we proved a relevant trend of better results with resection versus LRT both in early and advanced BCLC stages, when a positive resection profile was maintained. Conversely, a negative resection profile contraindicated liver resection in these candidates.

In conclusion, we are proposing a novel measure to weight the liver resection over the natural history of the disease for any HCC BCLC stage, and we showed that this therapeutic approach has a higher net survival benefit compared with non-surgical treatments, regardless of the BCLC stage in well selected HCC patients (MELD ≤ 9, Child A, and PST 0-1). These findings suggest that an interdisciplinary approach to patients with HCC is critical in managing this complex entity. Independently form the BCLC stage, different treatment options should be investigated for their feasibility and potential oncological radicality.

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References

1. European Association For The Study Of The, L., R. European Organisation For, and C. Treatment Of, *EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma.* J Hepatol, 2012. **56**(4): p. 908-43.
2. Bolondi, L., et al., *Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions.* Semin Liver Dis, 2012. **32**(4): p. 348-59.
3. Yang, J.D., et al., *Model to estimate survival in ambulatory patients with hepatocellular carcinoma.* Hepatology, 2012. **56**(2): p. 614-21.
4. Torzilli, G., et al., *A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group.* Ann Surg, 2013. **257**(5): p. 929-37.
5. Vitale, A., et al., *Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study.* Lancet Oncol, 2011. **12**(7): p. 654-62.
6. Nathan, H., et al., *Surgical Therapy for Early Hepatocellular Carcinoma in the Modern Era: A 10-Year SEER-Medicare Analysis.* Ann Surg, 2013.
7. Qi, X., et al., *Radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma: a meta-analysis of randomized controlled trials.* J Clin Gastroenterol, 2014. **48**(5): p. 450-7.
8. Italian Association for the Study of the, L., et al., *Position paper of the Italian Association for the Study of the Liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma.* Dig Liver Dis, 2013. **45**(9): p. 712-23.

9. Hsu, C.Y., et al., *Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system.* Hepatology, 2013. **57**(1): p. 112-9.

10. Zare, A., et al., *Comparison between parametric and semi-parametric cox models in modeling transition rates of a multi-state model: application in patients with gastric cancer undergoing surgery at the Iran cancer institute.* Asian Pac J Cancer Prev, 2013. **14**(11): p. 6751-5.

11. Cescon, M., et al., *Indication of the extent of hepatectomy for hepatocellular carcinoma on cirrhosis by a simple algorithm based on preoperative variables.* Arch Surg, 2009. **144**(1): p. 57-63; discussion 63.

12. Sexton, J. and P. Laake, *Boosted regression trees with errors in variables.* Biometrics, 2007. **63**(2): p. 586-92.

13. Cucchetti, A., et al., *Is portal hypertension a contraindication to hepatic resection?* Ann Surg, 2009. **250**(6): p. 922-8.

14. Midorikawa, Y., et al., *Marginal survival benefit in the treatment of early hepatocellular carcinoma.* J Hepatol, 2013. **58**(2): p. 306-11.

15. Cucchetti, A., et al., *Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma.* J Hepatol, 2013. **59**(2): p. 300-7.

16. Marrero, J.A., et al., *Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort.* Hepatology, 2005. **41**(4): p. 707-16.

17. Llovet, J.M., et al., *Sorafenib in advanced hepatocellular carcinoma.* N Engl J Med, 2008. **359**(4): p. 378-90.

18. Bruix, J., et al., *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): p. 421-30.

19. Livraghi, T., et al., *Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice?* Hepatology, 2008. **47**(1): p. 82-9.

20. Zhong, J.H., et al., *Hepatic Resection Associated With Good Survival for Selected Patients With Intermediate and Advanced-Stage Hepatocellular Carcinoma.* Ann Surg, 2013.

21. Shi, J., et al., *Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus.* Ann Surg Oncol, 2010. **17**(8): p. 2073-80.

22. Minagawa, M., et al., *Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan.* Ann Surg, 2007. **245**(6): p. 909-22.

23. Roayaie, S., et al., *Resection of hepatocellular carcinoma with macroscopic vascular invasion.* Ann Surg Oncol, 2013. **20**(12): p. 3754-60.

24. Hasegawa, K., et al., *Impact of histologically confirmed lymph node metastases on patient survival after surgical resection for hepatocellular carcinoma: report of a Japanese nationwide survey.* Ann Surg, 2014. **259**(1): p. 166-70.

25. Cheng, A.L., et al., *Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial.* Lancet Oncol, 2009. **10**(1): p. 25-34.

Figures

Figure 1. **Unadjusted prognostic impact of treatment within each BCLC stage**

Kaplan Meier survival curves showing the unadjusted prognostic impact of treatment within each BCLC stage: 0-A (A), B (B), C (C). HR, hepatic resection; LRT, non surgical loco regional therapy; BSC, best supportive care.

Figure 2. **Adjusted comparison between hepatic resection and non surgical loco regional therapy.**

The net benefit of hepatic resection over non surgical loco regional therapy in the entire population (A). Median survival predictions (based on the Log-logistic model in Table 2) for HCC patients undergoing liver resection, loco regional therapy, or best supportive care in the entire population (B). Dashed lines represented interquartile range.

Figure 3. **Multivariate analysis to identify main predictors of net resection benefit.**

Contribution of each covariate to net survival benefit of liver resection over LRT.

Figure 4. **Impact of main prognostic factors on the net resection benefit over non surgical loco regional therapy.**

The net benefit of hepatic resection over non surgical loco regional therapy in subgroups with a positive (A) and a negative profile (B) for resection. Median survival predictions (based on the Log-logistic model in Table 2) for HCC patients undergoing liver resection, loco regional therapy, or best supportive care in subgroups with a positive (C) and a negative profile (D) for resection. Dashed lines represented interquartile range.

Tables

Table 1. Characteristics of the enrolled HCC patients

Variables	*Resection group (n = 550)*	*LRT group (n=1046)*	*BSC group (n=494)*
Female sex*§	93 (17%)	273 (26%)	104 (21%)
Age*	66 (59-71)	70 (63-75)	70 (61-75)
History of alcohol abuse*§	226 (41%)	492 (47%)	262 (53%)
HBV positivity*	110 (20%)	146 (14%)	74 (15%)
HCV positivity*§	264 (48%)	659 (63%)	247 (50%)
Performance Status§			
0	411 (75%)	833 (80%)	313 (63%)
1	125 (23%)	152 (15%)	99 (20%)
≥ 2	14 (2%)	61 (5%)	82 (17%)
Child Pugh class B*§	72 (13%)	340 (33%)	227 (46%)
CRPH*§	161 (29%)	537 (51%)	282 (57%)
MELD	8 (6-9)	6 (6-6)	6 (6-7)
AFP (ng/mL)§	15 (5-80)	13 (6-54)	32 (7-523)
Diameter of the largest nodule (mm)*§	40 (25-60)	29 (20-40)	32 (20-70)
Number of nodules§			
1			
2 or 3	366 (67%)	625 (60%)	156 (32%)
> 3	127 (23%)	306 (29%)	120 (24%)
	57 (10%)	115 (11%)	218 (44%)
Macrovascular invasion§			
	43 (8%)	62 (6%)	174 (35%)
BCLC stage*§			
0	30 (5%)	73 (7%)	13 (3%)
A	214 (39%)	499 (48%)	84 (17%)
AB	93 (17%)	39 (4%)	15 (3%)
B	171 (31%)	327 (31%)	198 (40%)
C	42 (8%)	108 (10%)	184 (37%)

LRT, non-surgical loco regional therapy; BSC, systemic therapy or best supportive care; HCV, hepatitis C virus; HBV, hepatitis B virus; CRPH, clinically relevant portal hypertension; MELD, model for end stage liver disease; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.
* $p<0.05$ in the comparison Resection vs. LRT; § $p<0.05$ in the comparison LRT vs BSC

Table 2. Multivariate Log-logistic parametric survival analysis including patient, liver function and tumor-related variables and using treatment as stratifying covariate

Variables	*Resection group coefficient± SE, p value*	*LRT group coefficient± SE, p value*	*BSC group coefficient± SE, p value*
Age/10 per unit	-0.16±0.07, 0.0168	-0.09 ± 0.0323, 0.0043	-0.06 ± 0.04, 0.2115
Child Pugh class B vs. A	-0.46±0.18, 0.0118	-0.14 ± 0.06, 0.0244	-0.39 ± 0.12, 0.0007
CRPH yes vs. no	-0.07±0.14, 0.5979	-0.19 ± 0.06, 0.0017	-0.10 ± 0.11, 0.3754
MELD score	-0.11±0.02, <0.0001	-0.02 ±0.02, 0.2944	-0.07 ± 0.02, 0.0008
ECOG performance status			
0 (reference)	-	-	-
1	0.06±0.15, 0.7687	-0.04 ± 0.08, 0.6306	-0.12 ± 0.12, 0.3154
≥2	-0.82±0.33, 0.0144	-0.27 ± 0.12, 0.0276	-0.40 ± 0.12, 0.0012
lnAFP (per unit)	-0.12±0.03, <0.0001	-0.07 ± 0.02, <0.0001	-0.09 ± 0.02, <0.0001
Number of nodules			
1 (reference)	-	-	-
2 or 3	-0.24±0.14, 0.1090	-0.18 ±0.06, 0.0044	-0.47 ± 0.13, 0.0003
> 3	-0.43±0.20, 0.0328	-0.48 ±0.09, <0.0001	-0.61 ± 0.12, <0.0001
Diameter of the largest nodule			
< 2 cm (reference)	-	-	-
2-5 cm	-0.21±0.22, 0.3479	-0.29 ± 0.09, 0.0008	0.01 ± 0.13, 0.9156
> 5 cm	-0.43±0.24, 0.0675	-0.58 ± 0.12, <0.0001	-0.18 ± 0.13, 0.1453
Macrovascular invasion	-0.50±0.24, 0.0387	-0.52 ± 0.12, <0.0001	-0.45 ± 0.10, <0.0001
AIC and C-index of the whole Log-logistic parametric model ± standard error	2904 0.670 ± 0.019	6378 0.660 ± 0.013	2772 0.723 ± 0.018
AIC and C-index of the whole Cox model ± standard error	3056 0.652 ± 0.019	7968 0.649 ± 0.013	3742 0.716 ± 0.018
AIC and C-index of the MESIAH score ± standard error	3010 0.653 ± 0.020	7568 0.651 ± 0.013	3598 0.664 ± 0.019
AIC and C-index of the BCLC staging ± standard error	3110 0.596 ± 0.018	8044 0.583 ± 0.012	3830 0.620 ± 0.017

SE, standard error; LRT, loco regional therapy; BSC, systemic therapy or best supportive care; CRPH, clinically relevant portal hypertension; MELD, model for end stage liver disease; ECOG, Eastern Oncology Cooperative Group; AFP, alpha-fetoprotein; AIC, Akaike Information Criterion; C-index, concordance index; MESIAH; Model to Estimate Survival in Ambulatory HCC patients score; BCLC, Barcelona Clinic Liver Cancer classification

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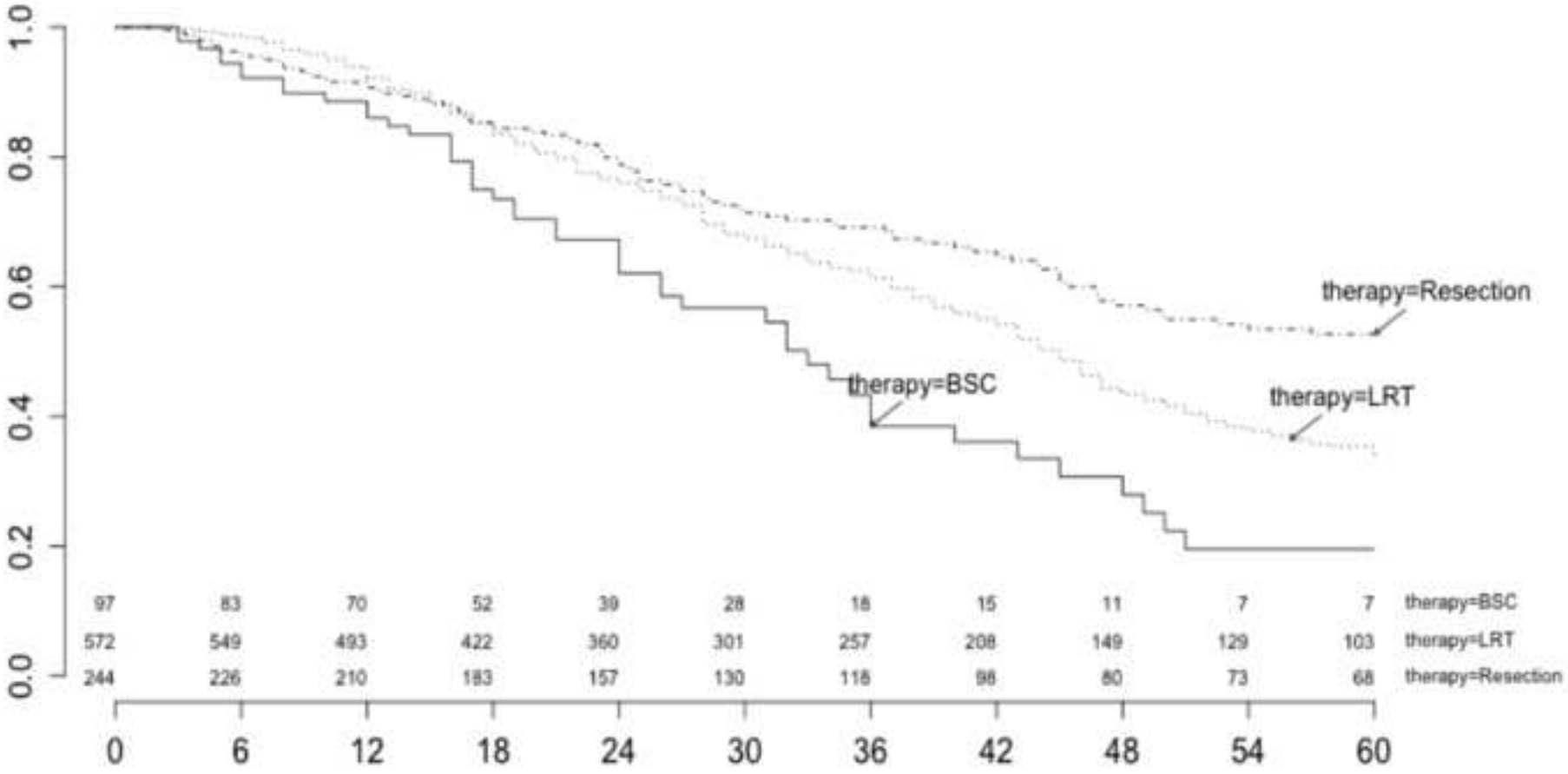

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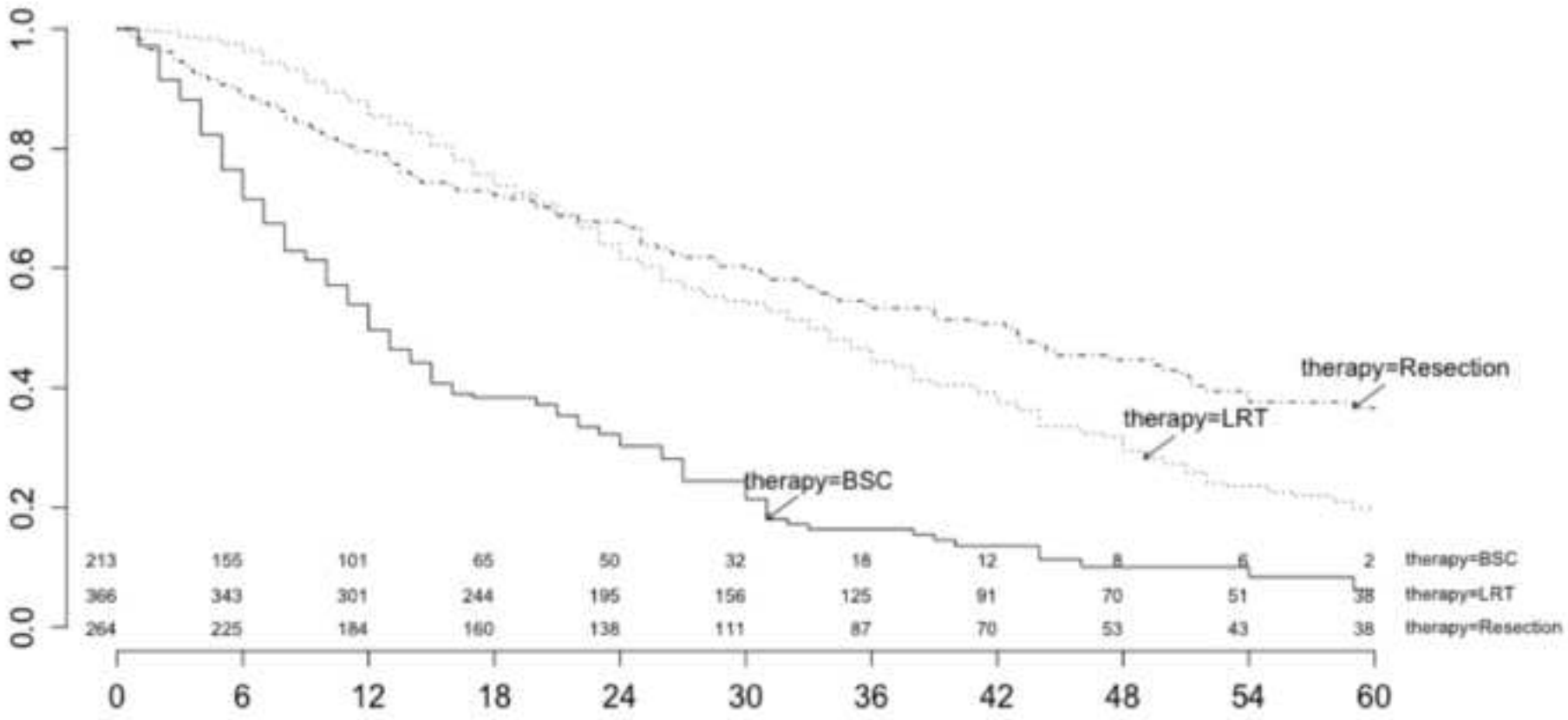

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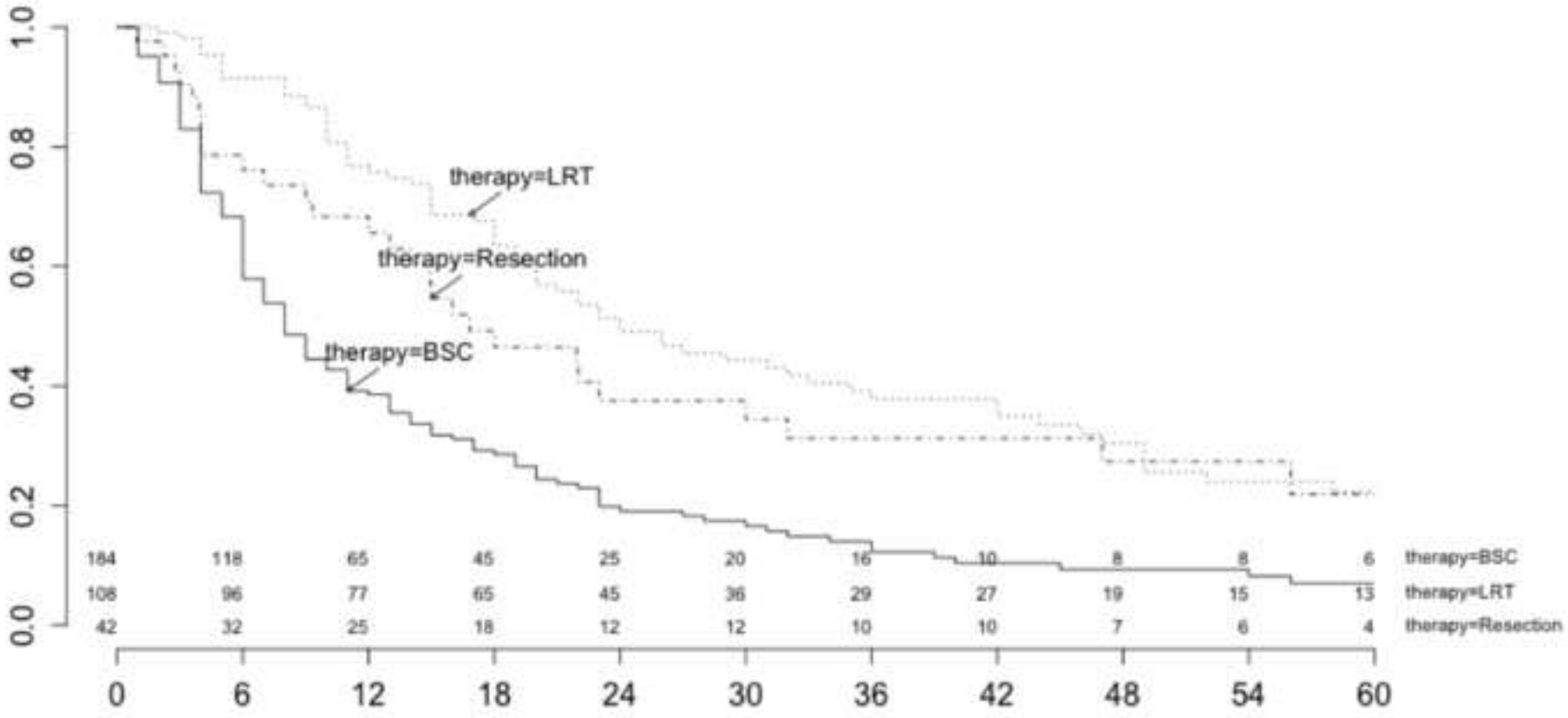

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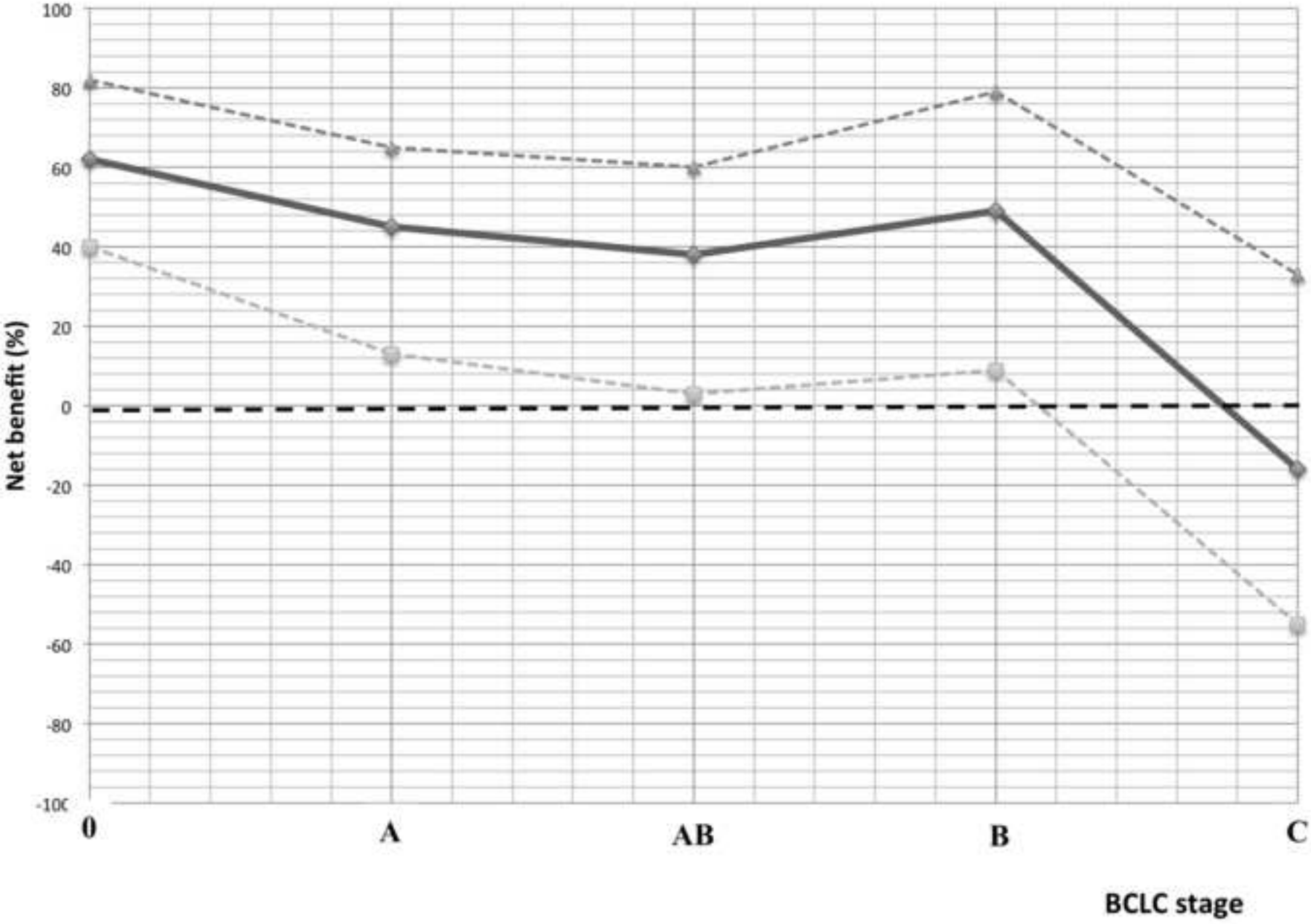

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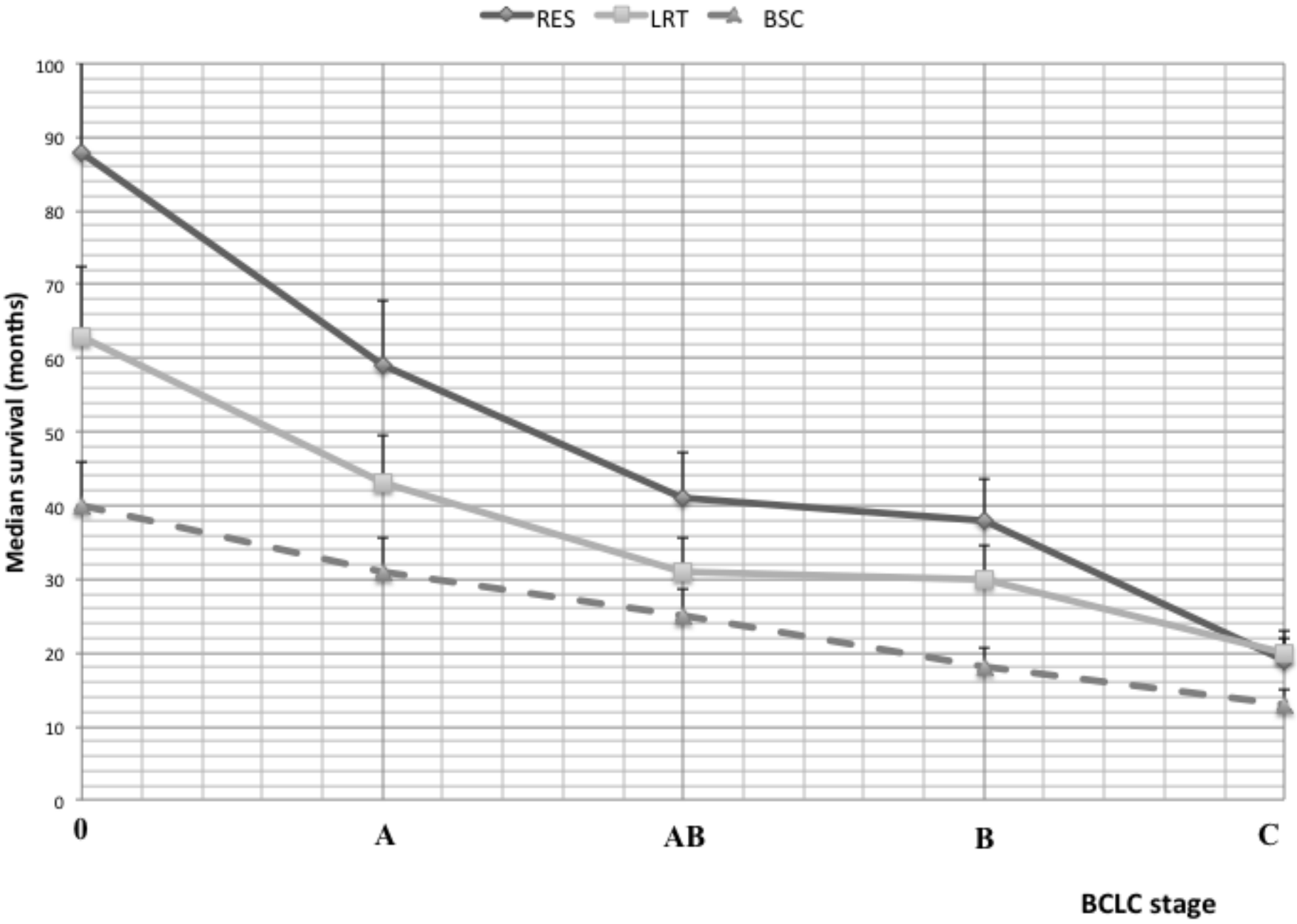

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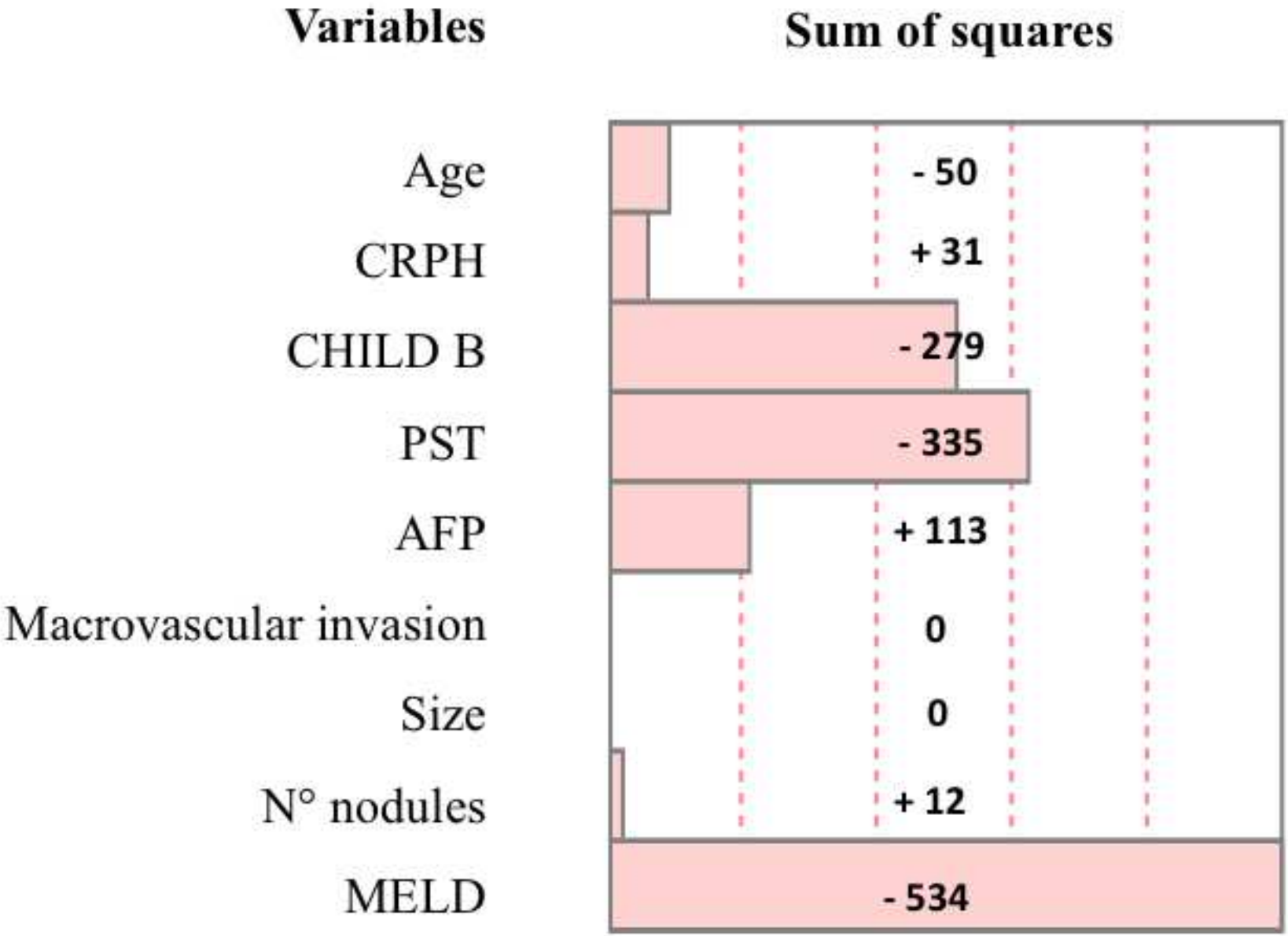

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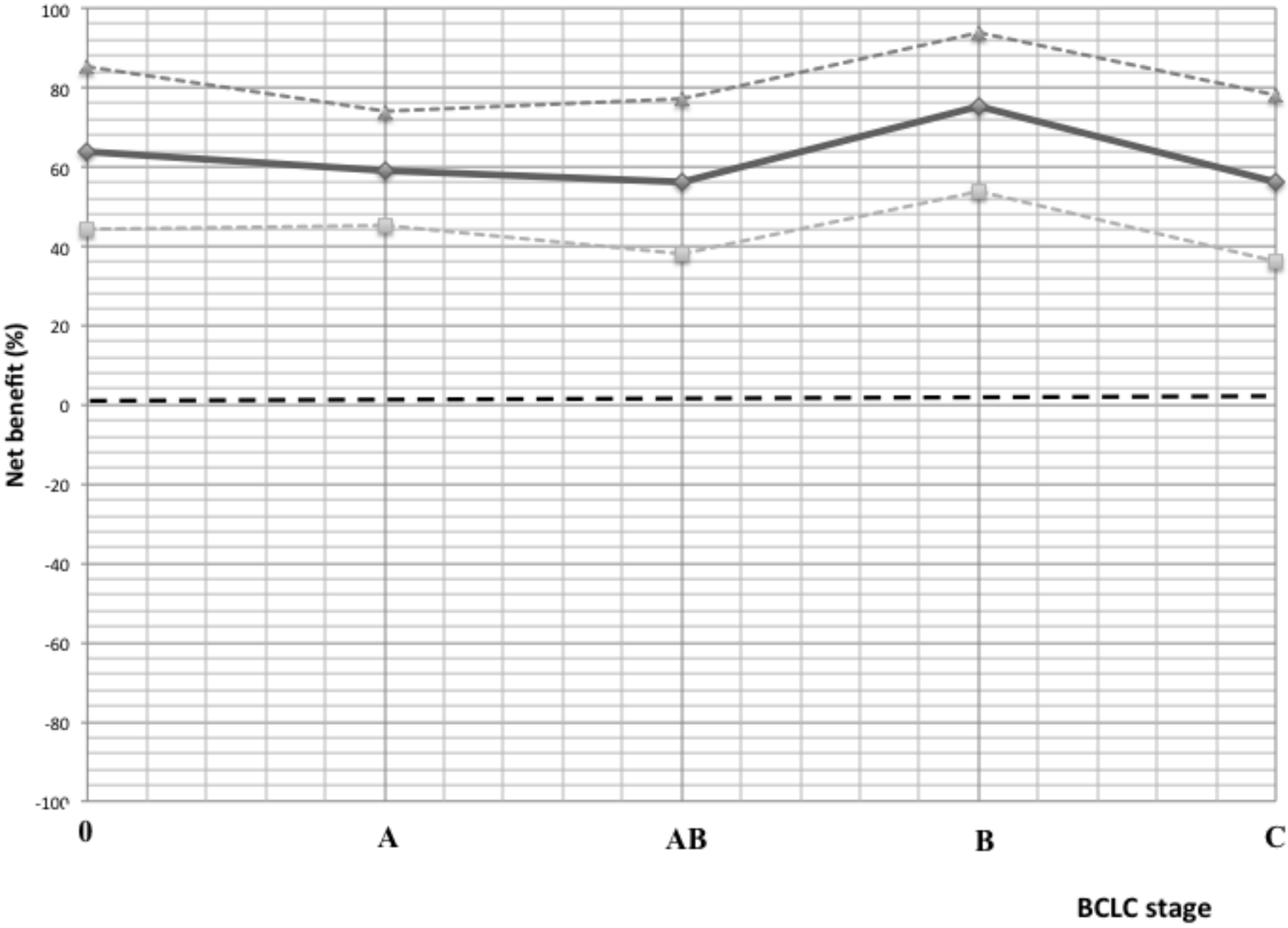

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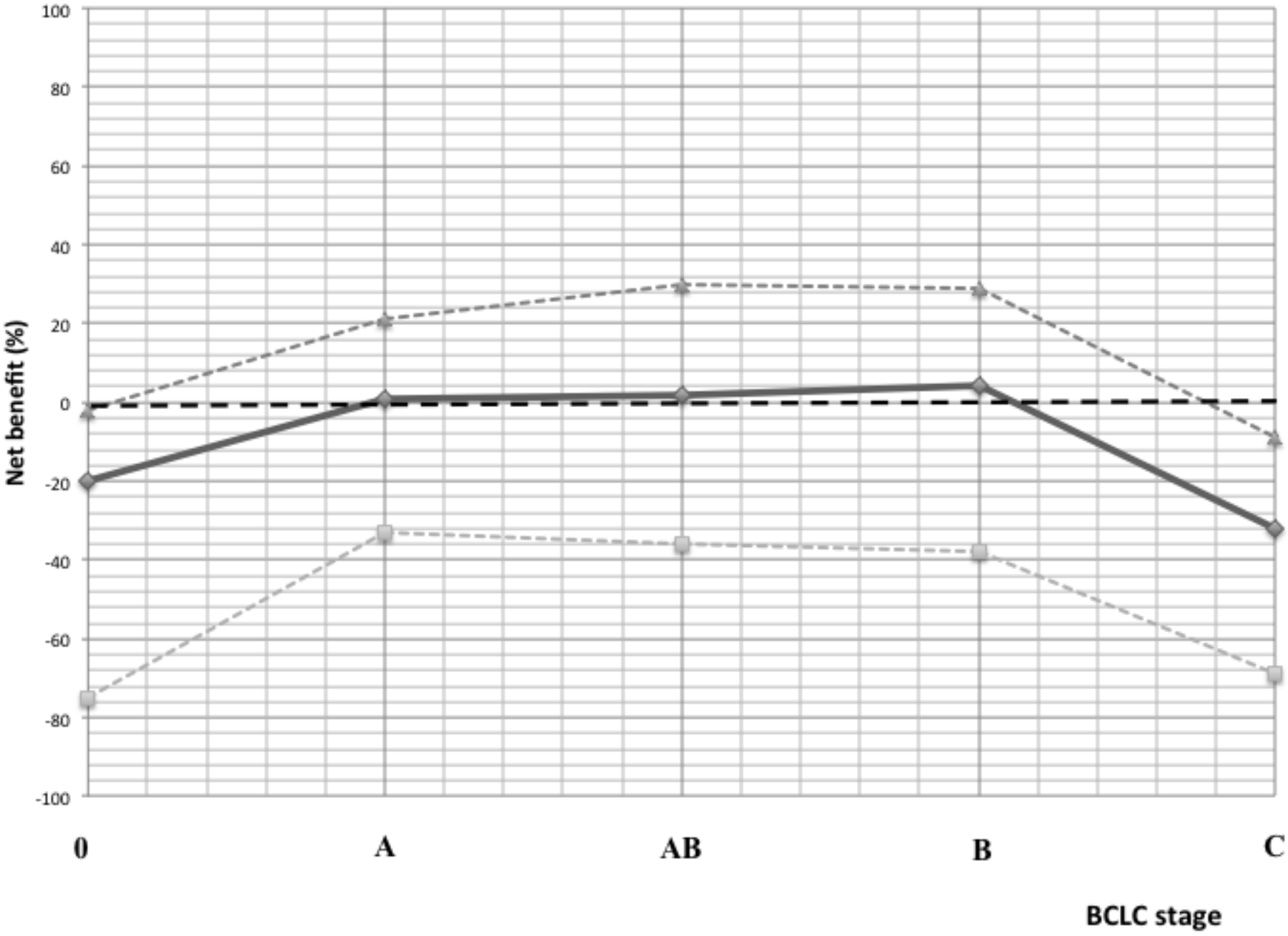

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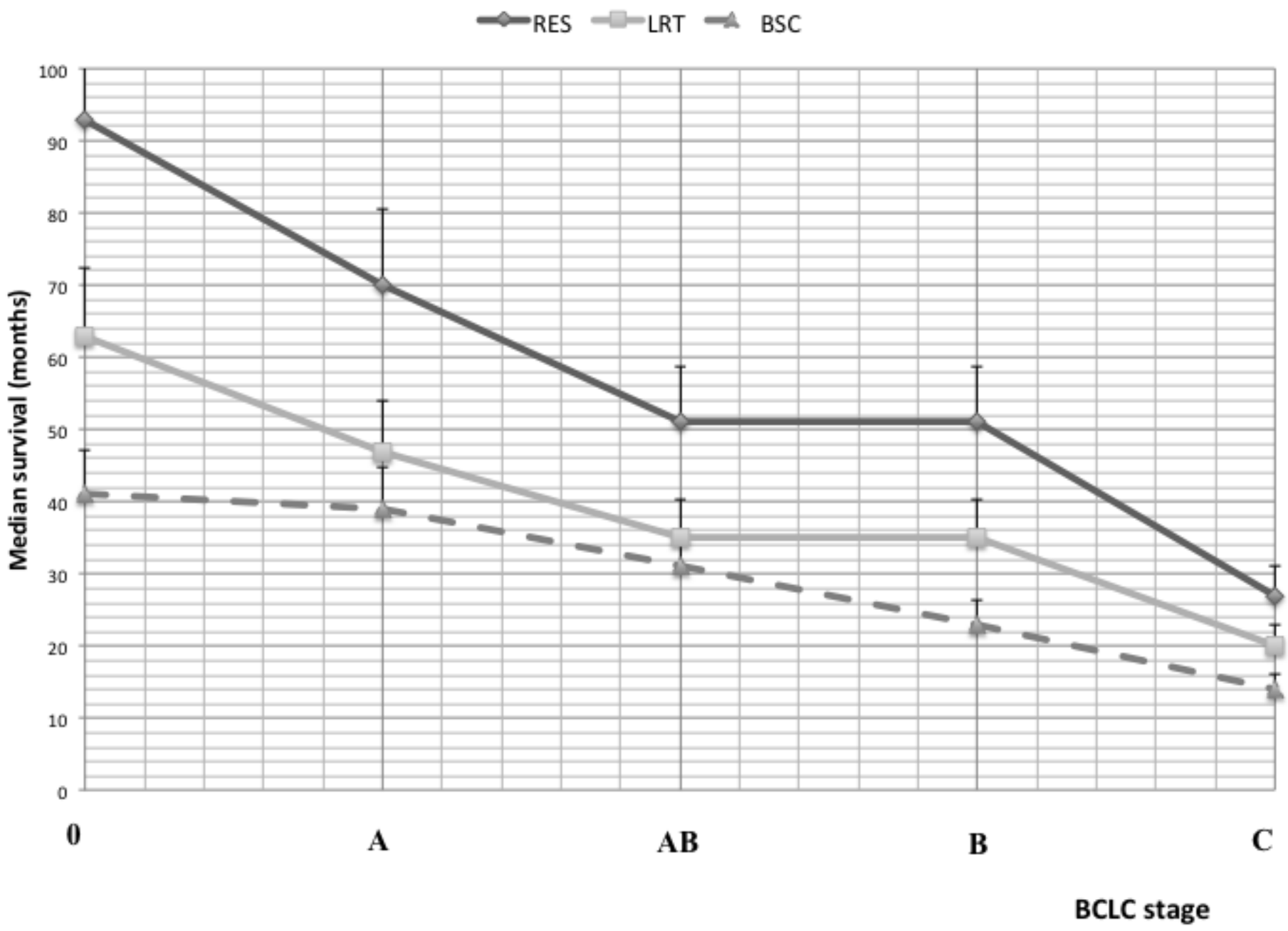

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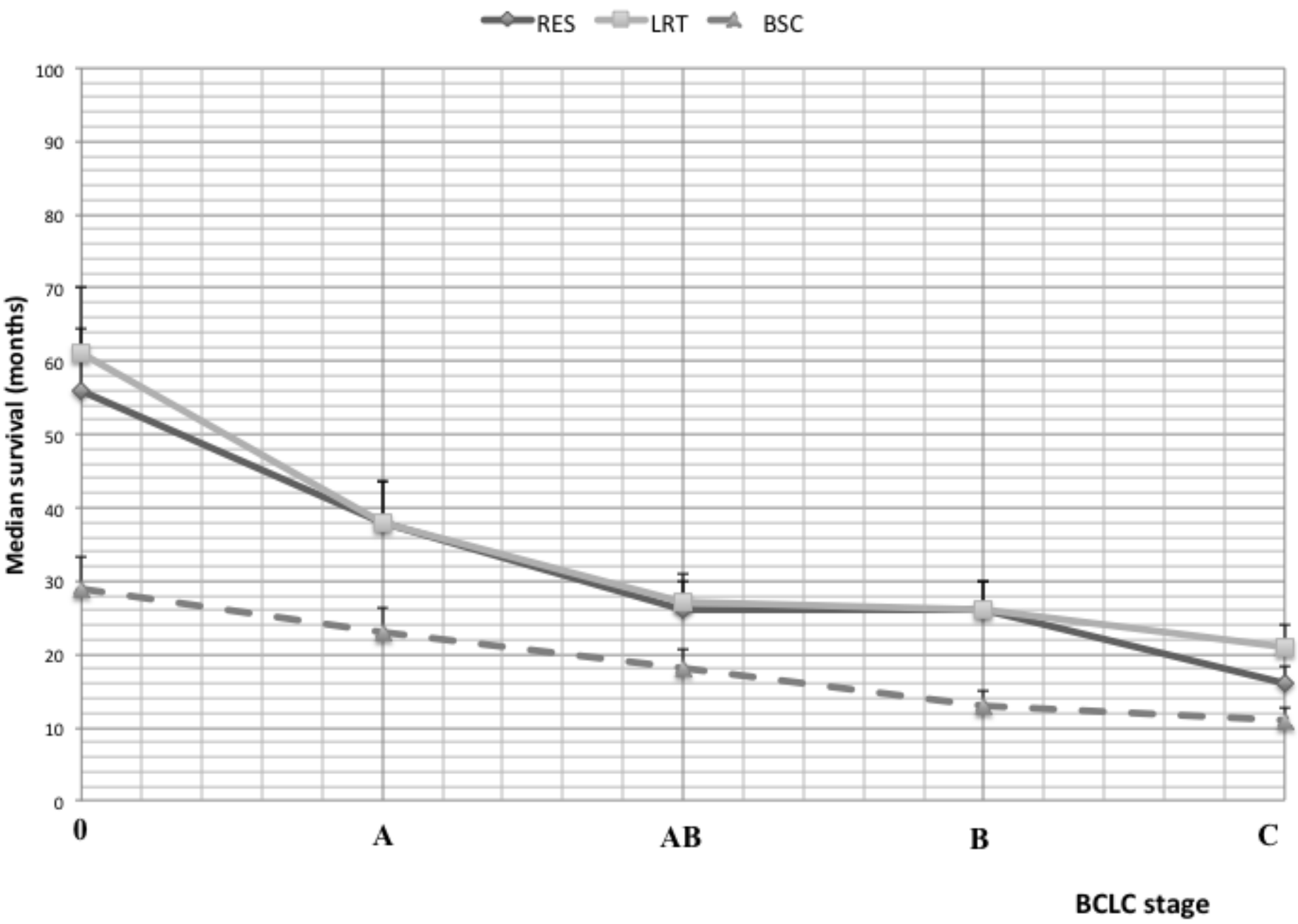

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