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

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

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36 **AV, PB, UC:** Designed the study

37 **AV, PB, ACF, GS, MV, UC:** Analysed the data

38 **AV, PB, GS, MV, UC:** Wrote the paper

39  
40  
41 I, AV, certify that to have had full access to all of the data in this study and take responsibility for  
42 the integrity of the data and the accuracy of the data analysis.

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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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**Key words:** Hepatocellular carcinoma; Cirrhosis; Liver resection; Loco-regional therapies; Best supportive care; Survival benefit.

## 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:  $(MS \text{ resection} - MS \text{ LRT}) / MS \text{ BSC}$ .

**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  $\leq$  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

1  
2 Prognostic assessment and treatment strategy for patients with hepatocellular carcinoma (HCC) and  
3  
4 liver cirrhosis are extremely complex due to the simultaneous presence of two distinct diseases[1].  
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7 The Barcelona Clinic Liver Cancer (BCLC) classification is the only HCC staging system  
8  
9 accounting for tumor burden, liver function, general conditions (as expression of symptomatic  
10  
11 tumor), able to guide in the treatment decision[1]. The main limit of BCLC is the great prognostic  
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13 heterogeneity within each stage[2]. In last years, some authors proposed a new model for prognostic  
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15 prediction in HCC patients[3], the model to estimate survival in ambulatory HCC patients score  
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17 (MESIAH). The MESIAH score showed a significantly higher predictive power than BCLC [3],but  
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19 its main limit is that it doesn't help clinicians in treatment decision.  
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24 Although the BCLC classification is directly translated into a strict treatment algorithm, assigning  
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26 different therapies to different subgroups of patients[1],there is a great overlap between treatments  
27  
28 and prognostic stages in daily clinical practice. Recent studies demonstrated that radical therapies,  
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30 such as hepatic resection and liver transplantation, are commonly preferred and have a great benefit  
31  
32 even for intermediate and advanced HCC [4, 5], while locoregional therapies, such as  
33  
34 radiofrequency (RF) percutaneous ablation and trans-arterial chemoembolization (TACE), are  
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36 largely used as first line therapy even for early HCC [6].  
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41 With the exception of liver transplantation, which is greatly limited by scarce donor resources [5],  
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43 liver resection is considered the best oncological treatment for HCC[4].  
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46 Only few randomized control trials comparing resection to percutaneous ablation in very selected  
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48 subgroups of patients have been published until now [7]. These studies are often underpowered and  
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50 propose percutaneous ablation as an alternative to resection in BCLC 0 HCC patients [1, 8].  
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53 There is a lack of well-designed large studies comparing resection versus the whole span of  
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55 therapeutic alternatives for each BCLC stage. Moreover, while comparing resection and other  
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57 therapies, the natural history of the disease should be taken into consideration, in order to determine  
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59 the actual benefit/harm ratio of each therapy.  
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1 All this considered, we aimed to compare the net survival benefit of resection over non-surgical  
2 loco-regional-therapies (LRT) and best supportive care (BSC) in a large cohort of HCC patients  
3  
4 with different BCLC stages.  
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## 7 8 9 **Materials and Methods**

### 10 *Patient demographic and clinical data*

11  
12 A total of 2686 patients undergoing surgical or non-surgical treatment for HCC between 2000 and  
13  
14 2012 in the institutions participating in the Italian Liver Cancer (ITA.LI.CA.) database were  
15  
16 identified. Patients with BCLC stage D (n=385), presence of extra-hepatic metastasis (n=114) and  
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18 those treated with liver transplantation (n=77) were excluded from the study. Since only 40 patients  
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20 received Sorafenib (< 2% of the entire cohort), these patients were also excluded from the analysis.  
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22 The study group finally consisted of 2090 patients.  
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29 We considered three main therapeutic subgroups. Firstly we selected all patients undergoing  
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31 liver resection (resection group, n=550) and we followed them from the time of resection onwards.  
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33 These patients were considered in the resection group even if they underwent other HCC non-  
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35 surgical therapies. Then, we selected patients undergoing at least one LRT such as RF or TACE  
36  
37 (LRT group, n= 1046) and we followed them from the time of first LRT onwards, independently  
38  
39 from other non-surgical treatment received during their follow-up. The remnant patients were  
40  
41 considered in the BSC group (n=494).  
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46 Standard patient demographic and clinicopathological data were collected including age,  
47  
48 sex, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status (PST), general  
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50 symptoms, modality of HCC and cirrhosis diagnosis (biopsy/surgical specimen or unequivocal  
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52 clinical and radiological findings), serological parameters (sodium, bilirubin, albumin, INR,  
53  
54 creatinine, platelet count, alfa-fetoprotein (AFP) levels), Child Pugh class, clinically relevant portal  
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56 hypertension (CRPH) and BCLC stage. Tumor characteristics were also collected, including tumor  
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58 location, size, number and vascular invasion.  
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1 CRPH diagnosis was based on unequivocal clinical signs (gastroesophageal varices, ascites,  
2 splenomegaly with a platelet count of less than 100,000/ml) since hepatic venous pressure gradients  
3 were not determined [1].  
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7 The BCLC classification was used to stratify the study population in different prognostic stages,  
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9 after the adoption of the following changes: since recent evidences have re-assessed the role of PST  
10 in the BCLC classification [9], patients with PST=1 and without macroscopic vascular invasion  
11 were included in BCLC stage B; the definition of early HCC according to the BCLC classification  
12 is still debated (i.e. early HCC is single nodule of any size when the tumor is considered resectable,  
13 while it is a single nodule smaller than 5 cm when the tumor is considered unresectable), therefore  
14 we added a separate subgroup of patients (named stage AB) that included patients with a single  
15 nodule larger than 5 cm without vascular invasion, Child Pugh A-B cirrhosis, and PST 0 or 1 [1].  
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26 According to tumor characteristics, liver functional status, and patient will, several therapeutic  
27 strategies were used, such as resection, percutaneous tumor ablation, trans-arterial LRT, systemic  
28 therapy and BSC.  
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### 34 35 36 *Statistical analysis*

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38 Qualitative data were described by frequency and percentage. Quantitative data were described by  
39 median (interquartile range (IQR)). In the comparison among different subgroups, quantitative  
40 variables were compared using Student's *t* or Wilcoxon Rank Sums tests, and categorical variables  
41 using  $\chi^2$  or Fisher's exact tests, as appropriate. Length of follow-up and survival are expressed as  
42 medians (IQR). Overall survival was calculated from the baseline visit until death from any cause  
43 or latest follow-up. Survival curves were estimated using the Kaplan-Meier method, whereas the  
44 statistical significance between survival curves was tested by the Log-Rank test.  
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54 We tested several multivariate survival models (the semi-parametric Cox model, and parametric  
55 exponential, log-normal, Weibull, and log-logistic models) including the following variables:  
56 patient-related covariates (age, and PST), liver function-related (MELD score, Child Pugh class,  
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1 CRPH); and tumor-related (diameter, number of nodules, AFP values, and macroscopic vascular  
2 invasion). The selection of these variables was based on recent literature reports [1, 2, 4, 5, 8].  
3

4 Treatment (resection vs. LRT vs. BSC) was used as stratifying covariate.  
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6  
7 The log-logistic model was finally chosen among semi-parametric and parametric ones since it the  
8 showed the lowest Akaike Information Criterion (AIC) and the highest Harrell C-index values.[10]  
9

10 This multivariate survival model was used to investigate the impact of patient-, liver-, and tumor-  
11 related variables on survival after each treatment. To overcome biases owing to the different  
12 distribution of covariates among patients undergoing resection and those undergoing LRT or BSC,  
13 we calculated three individual median survival predictions -after resection, after LRT therapies or  
14 after BSC- independently from therapy actually received. Subgroup analyses were then performed  
15 based on BCLC staging, Child Pugh class, MELD score, and presence of CRPH. Since MELD  
16 score in HCC patients undergoing loco-regional therapies is mainly used as dichotomous variable,  
17 MELD > 9 was used in the subgroup analysis [11]. In order to weight the benefit/harm ratio of  
18 therapy in each patient we calculated the net benefit of resection over LRT with the following  
19 formula: (median survival with resection – median survival with LRT) / median survival with BSC.  
20  
21 The net benefit of resection over LRT represents a simple novel endpoint based on the commonly  
22 used concept of survival benefit (expressed as gain in survived months) adjusted for the median  
23 survival of patients not receiving any anti-cancer therapy (natural history of the disease). This  
24 measure gives an estimation of the net proportion (%) of survival in months gained or lost using  
25 resection instead of LRT in each patient. Net benefit results were presented as medians  
26 (interquartile range).  
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50 A boosting forest tree method (partition modelling) was finally used to measure the contribution of  
51 each covariate to resection net benefit over LRT [12]. Partition trees were constructed using a  
52 training set (corresponding to 70% of the entire cohort) and a validation set (corresponding to 30%  
53 of the entire cohort) and the final model was that with the highest R square in both training and  
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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  $\pm$  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.

1 As expected, patients who received BSC had a more impaired liver function and a higher rate of  
2 advanced tumors compared to the other two groups. (Table 1) The 20% of them were classified as  
3  
4 BCLC stages 0 and A.  
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7 In supplementary table 1 we described patient-, liver function -, and tumor- characteristics in  
8  
9 different BCLC stages. Interestingly, a considerable proportion of patients with MELD > 9 were  
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11 identified in each BCLC stage. Among patients undergoing LRT, 617 (30%) underwent RF ±  
12  
13 TACE as main therapy, while 429 (21%) had only trans-arterial therapies. These two subgroups  
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15 among LRT patients were differently distributed in each BCLC stage (Supplementary table 1).  
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### 21 *Survival analysis*

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24 An unmatched comparison of survival profile of patients in the three different treatment subgroups  
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26 (Figure 1) and in different BCLC stages, showed that liver resection had higher long-term survival  
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28 than LRT and BSC in early and intermediate stages. Differently, LRT had the highest long-term  
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30 survival in advanced stages. All differences between resection, LRT, and BSC were statistically  
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32 significant using Log Rank test.  
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36 Table 2 shows the prognostic impact of patient-, liver function-, and tumor-related variables on  
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38 survival in the three different treatment groups based on a log-logistic parametric survival model.  
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40 Interestingly, tumor variables, such as size, number of nodules and vascular invasion, had a higher  
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42 discrimination power in non-surgical compared to surgical ones. Conversely, some patient- and  
43  
44 liver function- variables, such as PST = 2, MELD score, and Child Pugh class B, were stronger  
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46 survival predictors in patients who underwent liver resection. Conversely, MELD score and PST=2  
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48 had a low discrimination power in the LRT group.  
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51 The multivariate models obtained for each treatment subgroup showed a higher discrimination  
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53 ability (lower AIC and higher C-index) than the same models calculated by semi-parametric Cox  
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55 proportional hazard analysis, and than consolidated prognostic models for HCC patients such as the  
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57 BCLC staging and the MESIAH score (Table 2).  
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### *Survival benefit of liver resection*

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2 Median net survival benefit of resection over LRT according to BCLC stage was: BCLC 0 = 62%  
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4 (40%, 82%), A = 45% (13%, 65%), AB= 38% (3%, 60%), B = 49% (9%, 79%), C = -16% (-55%,  
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6 33%) (Figure 2A and 2B).  
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9  
10 The different prognostic impact of patient-, liver function-, and tumor-related covariates in the three  
11  
12 treatment groups (Table 2) corresponded to a different contribution of these variables on net  
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14 survival benefit of resection. MELD score > 9, Child B class, and PST = 2 proved to be the  
15  
16 strongest predictors of low net resection benefit (Figure 3). Conversely, tumor characteristics were  
17  
18 negligible predictors of net resection benefit.  
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21  
22 Based on these results, we inquired the impact of BCLC on net survival benefit of resection. We  
23  
24 stratified the population in two subgroups, 1181 patients (57%) with a favorable profile for liver  
25  
26 resection (MELD  $\leq$  9, Child A, and PST <2) and 909 (43%) with an unfavorable profile (MELD >  
27  
28 9, Child B, or PST = 2). Patients in the first subgroup always had a large positive net survival  
29  
30 benefit of resection over LRT independently from BCLC stage. (Figure 4A and 4B). Among  
31  
32 patients in the second group, liver resection did not prove any survival benefit over LRT. (Figure  
33  
34 4C and 4D).  
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39 A separate analysis comparing the outcome of patients undergoing resection, RFA  $\pm$  TACE, TACE  
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41 alone, or BSC was performed (Supplementary Table 2). Liver resection confirmed higher median  
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43 survivals than both RFA and TACE in BCLC stages 0, A, AB, and B. Interestingly, RFA proved to  
44  
45 be clearly superior to TACE in BCLC 0 and AB stages patients (Supplementary figure 1).  
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### *Propensity score analysis.*

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52 To validate and confirm our findings we performed a propensity score analysis among patients  
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54 undergoing resection and those undergoing LRT. We selected 318 patients in the resection group  
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56 and in the LRT group with similar patient -, liver function -, and tumor characteristics  
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60 (Supplementary Table 3). We showed a relevant trend of better results in patients treated with  
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1 resection versus LRT both in early and advanced BCLC stages, when a positive resection profile  
2 was maintained (Supplementary figures 2A and C). Conversely, a negative resection profile  
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5 contraindicated liver resection in these candidates (Supplementary figures 2B and D).  
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## 9 **Discussion**

10  
11 Hepatocellular carcinoma has shown an extremely heterogeneous biological behavior [1], in  
12 fact, if in a relevant proportion of patients it has a relatively slow progression [14, 15], in other  
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14 patients it presents an extremely aggressive behavior. In this setting, surgical and loco-regional  
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16 therapies risk to not improve patient outcome and, more importantly, to negatively impact on  
17  
18 overall survival and quality of life. Different staging systems have been proposed to predict survival  
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20 of patients with HCC [16]. One of the most widely staging system used for its ability to account for  
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22 tumor burden, liver function and general conditions, is the BCLC [1]. Nonetheless, in daily clinical  
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24 practice, there is a great overlap between BCLC and the subsequent treatment. For this reason we  
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26 aimed to compare the survival benefit of different therapeutic strategies in a large cohort of HCC  
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28 patients assigned to different BCLC stages.  
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36 The availability of a large database of HCC patients allowed to calculate individual survival rates  
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38 after resection, LRT, and BSC in each BCLC stage, and to introduce the concept of net survival  
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40 benefit after liver resection. This novel measure takes into consideration: 1) the benefit/harm ratio  
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42 of each patient after surgical and non-surgical therapies; 2) the survival gain based on the disease  
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44 stage. This new net benefit formula could seem quite artificial. However, we think that this is a  
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46 useful method to measure the benefit of liver resection over alternative therapies adjusted for the  
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48 natural history of the disease (i.e. without anticancer therapy). Absolute differences in median  
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50 survivals, in fact, don't consider the aggressiveness of the disease. For example, a gain in 3 months  
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52 in BCLC stage 0 is quite irrelevant, while the same gain in advanced stages (BCLC C) may be more  
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54 clinically relevant [17]. The concept of net benefit clearly captured these two different clinical  
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56 situations: the net benefit would be 7% (3/46 months) for BCLC 0 patients and 20% (3/15 months)  
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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

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

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10 These findings may radically change the prognostic evaluation and management of HCC  
11 patients, suggesting that BCLC stage does not influence the prognostic impact of different  
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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  $\leq 9$ , 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  $\leq 9$ , Child A and PST  $< 2$ ), where the risk of post-operative liver failure is very low. These results reinforce the impact of cirrhosis

1 stage and clinical conditions on the therapeutic management of HCC patients. In case of advanced  
2 cirrhosis and high PST a non-surgical approach should be preferred.  
3

4 In the supplementary figure 1 and supplementary Table 2 we performed a separate analysis  
5 to compare the outcome after RFA ± TACE and TACE alone. In this context, our study supports  
6 current guidelines indicating RFA as the best alternative to resection in BCLC 0 patients.  
7

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

25 In the absence of adequately powered randomized clinical trials (RCT), we think that the  
26 statistical methodology used in this study has the highest potential to simulate a RCT. The  
27 availability of three independent prognostic models (Table 2), one for resection, one for LRT, and  
28 one for BSC, allows individual predictions for three possible therapeutic scenarios in each enrolled  
29 patient simulating a three-arms RCT. The prognostic performance of our models was significantly  
30



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

4 To validate and confirm our findings we performed a propensity score analysis  
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6 (Supplementary table 3 and Supplementary figure 2). Although propensity score intrinsically  
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8 decreased sample size and thus the possibility to find significant differences, we proved a relevant  
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10 trend of better results with resection versus LRT both in early and advanced BCLC stages, when a  
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12 positive resection profile was maintained. Conversely, a negative resection profile contraindicated  
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14 liver resection in these candidates.  
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19 In conclusion, we are proposing a novel measure to weight the liver resection over the  
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21 natural history of the disease for any HCC BCLC stage, and we showed that this therapeutic  
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23 approach has a higher net survival benefit compared with non-surgical treatments, regardless of the  
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25 BCLC stage in well selected HCC patients (MELD  $\leq$  9, Child A, and PST 0-1). These findings  
26  
27 suggest that an interdisciplinary approach to patients with HCC is critical in managing this complex  
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29 entity. Independently from the BCLC stage, different treatment options should be investigated for  
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31 their feasibility and potential oncological radicality.  
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## 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

<i>Variables</i>	<i>Resection group (n = 550)</i>	<i>LRT group (n=1046)</i>	<i>BSC group (n=494)</i>
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%)
Macrovascular invasion§	57 (10%)	115 (11%)	218 (44%)
BCLC stage*§	43 (8%)	62 (6%)	174 (35%)
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
<b>AIC and C-index of the whole Log-logistic parametric model ± standard error</b>	<b>2904</b> 0.670 ± 0.019	<b>6378</b> 0.660 ± 0.013	<b>2772</b> 0.723 ± 0.018
<b>AIC and C-index of the whole Cox model ± standard error</b>	<b>3056</b> 0.652 ± 0.019	<b>7968</b> 0.649 ± 0.013	<b>3742</b> 0.716 ± 0.018
<b>AIC and C-index of the MESIAH score ± standard error</b>	<b>3010</b> 0.653 ± 0.020	<b>7568</b> 0.651 ± 0.013	<b>3598</b> 0.664 ± 0.019
<b>AIC and C-index of the BCLC staging ± standard error</b>	<b>3110</b> 0.596 ± 0.018	<b>8044</b> 0.583 ± 0.012	<b>3830</b> 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



Figure 1A

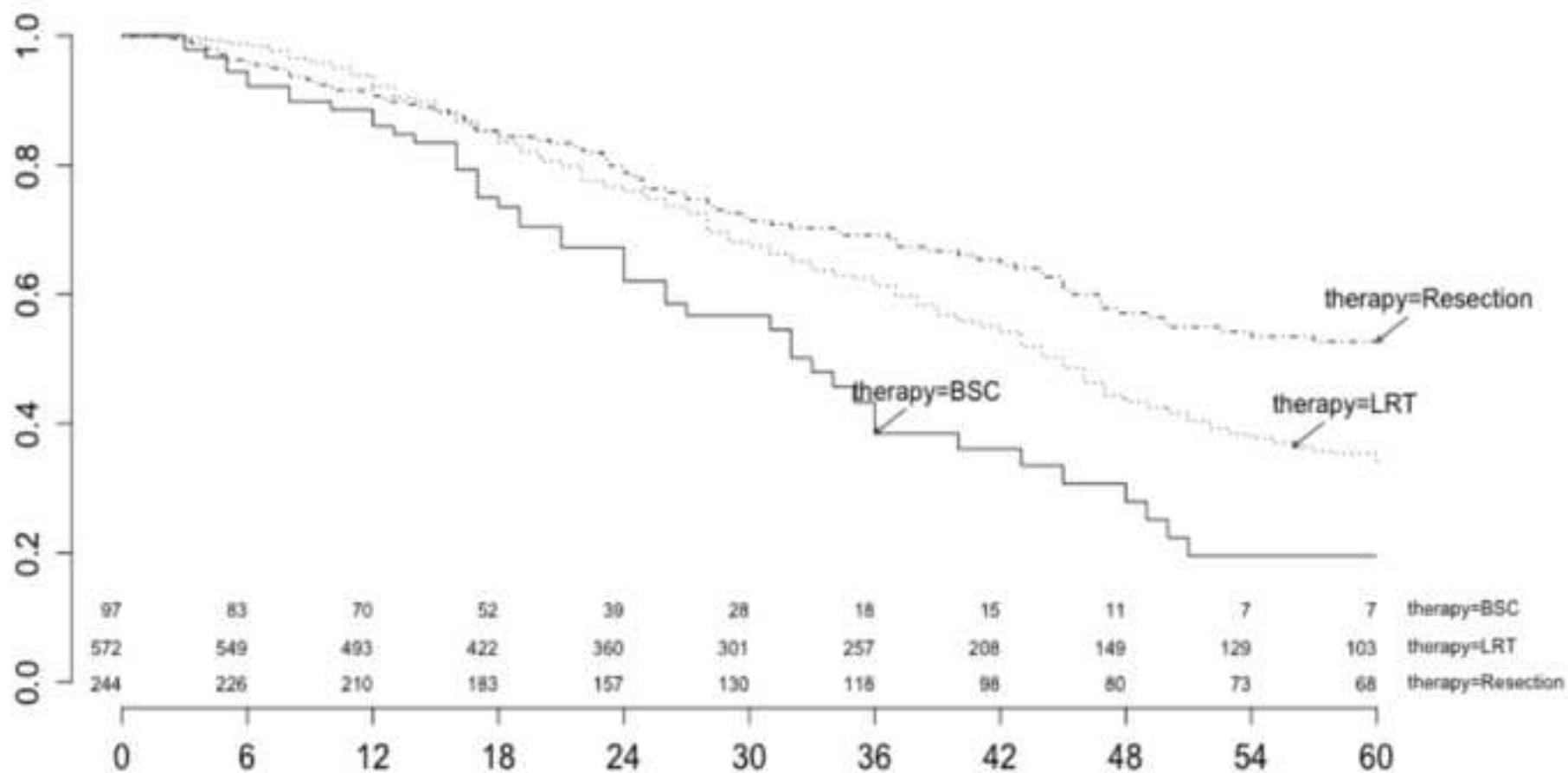


Figure 1B

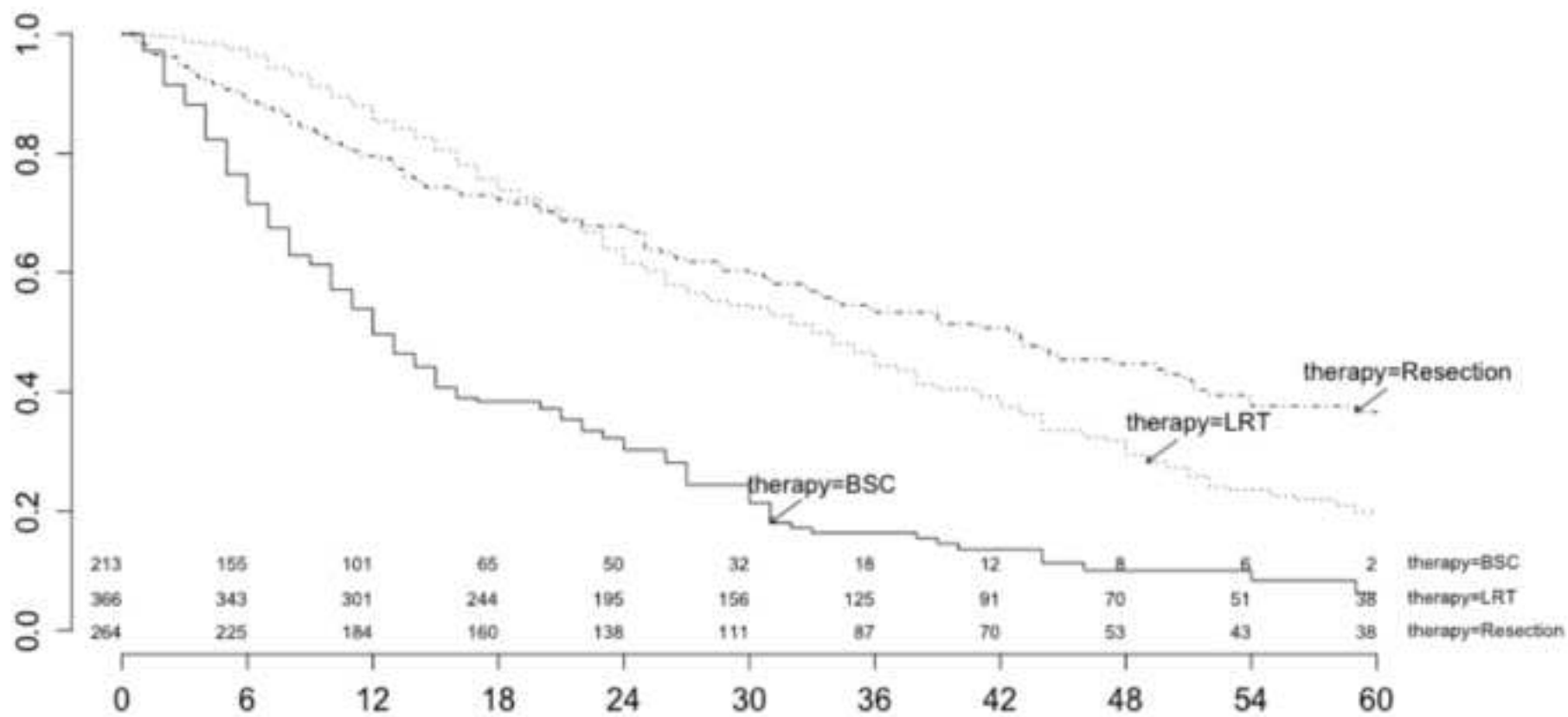


Figure 1C

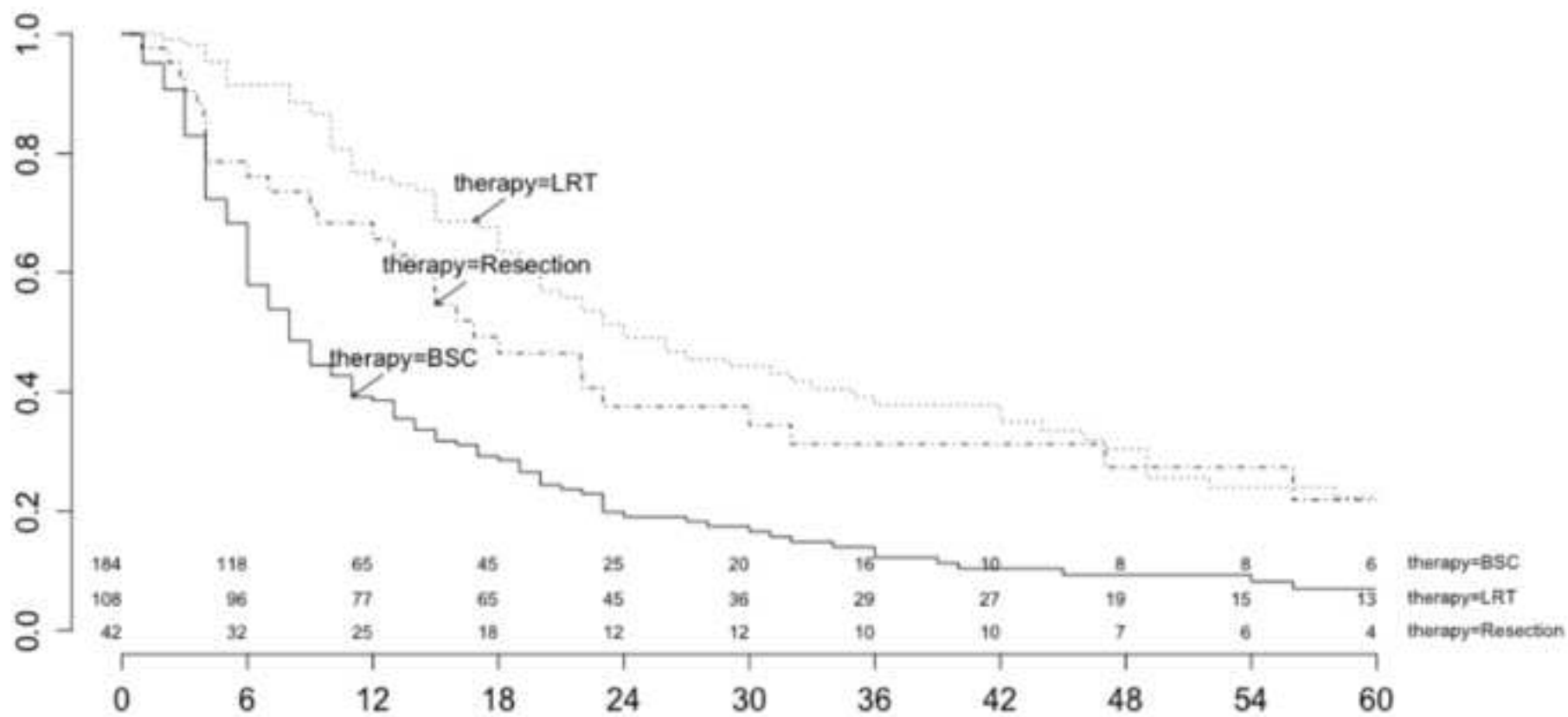


Figure 2A

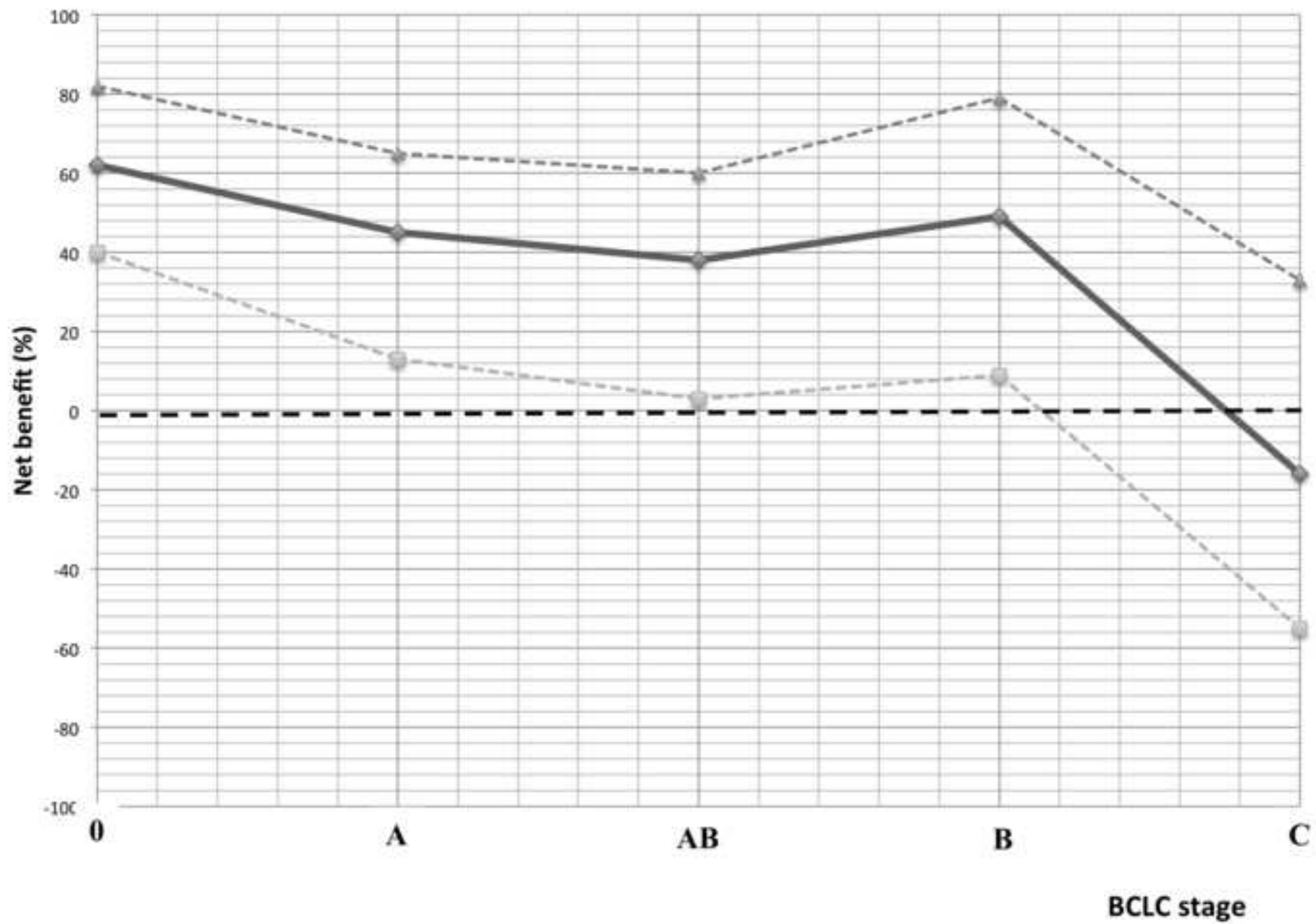


Figure 2B

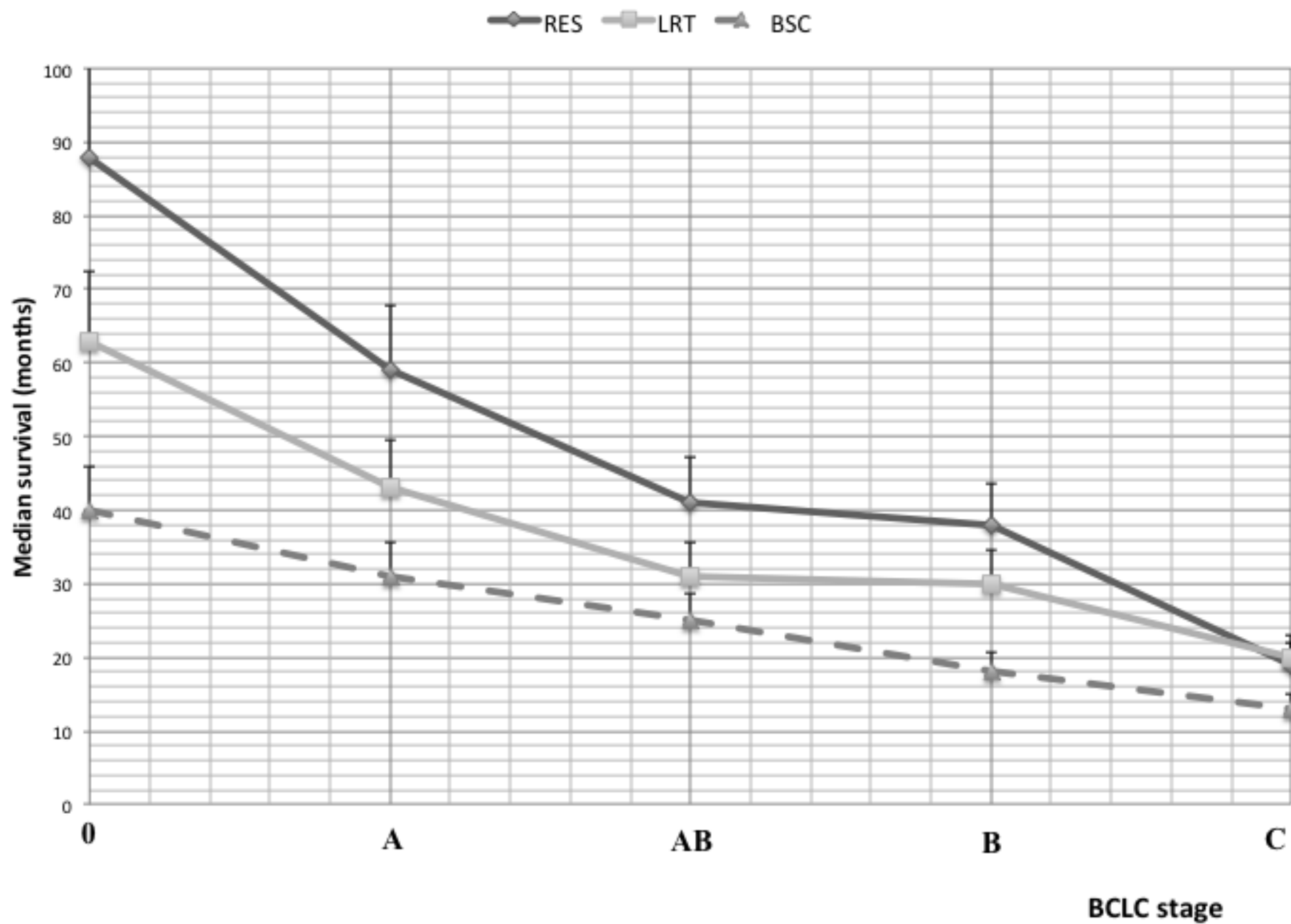


Figure 3

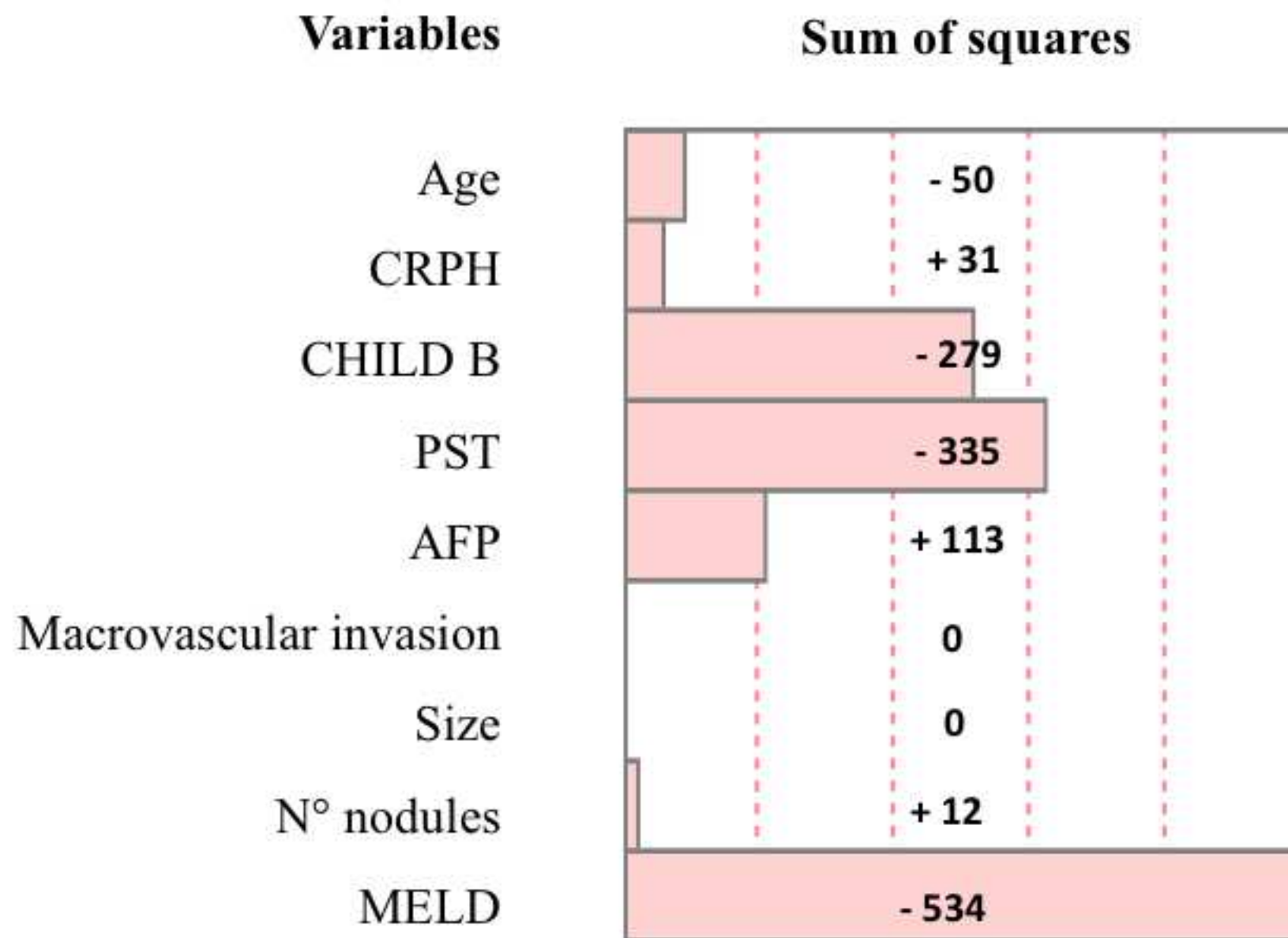


Figure 4A

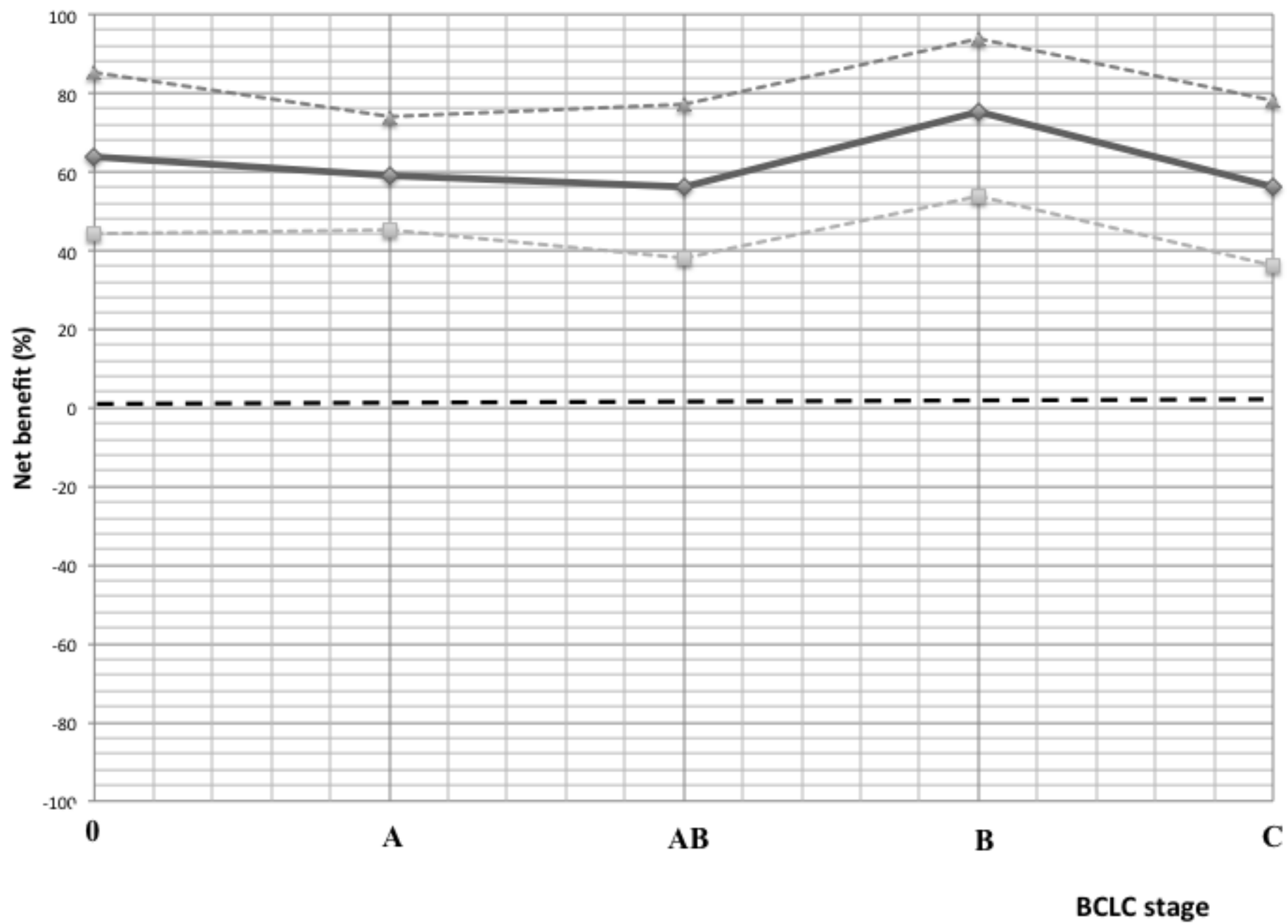


Figure 4B

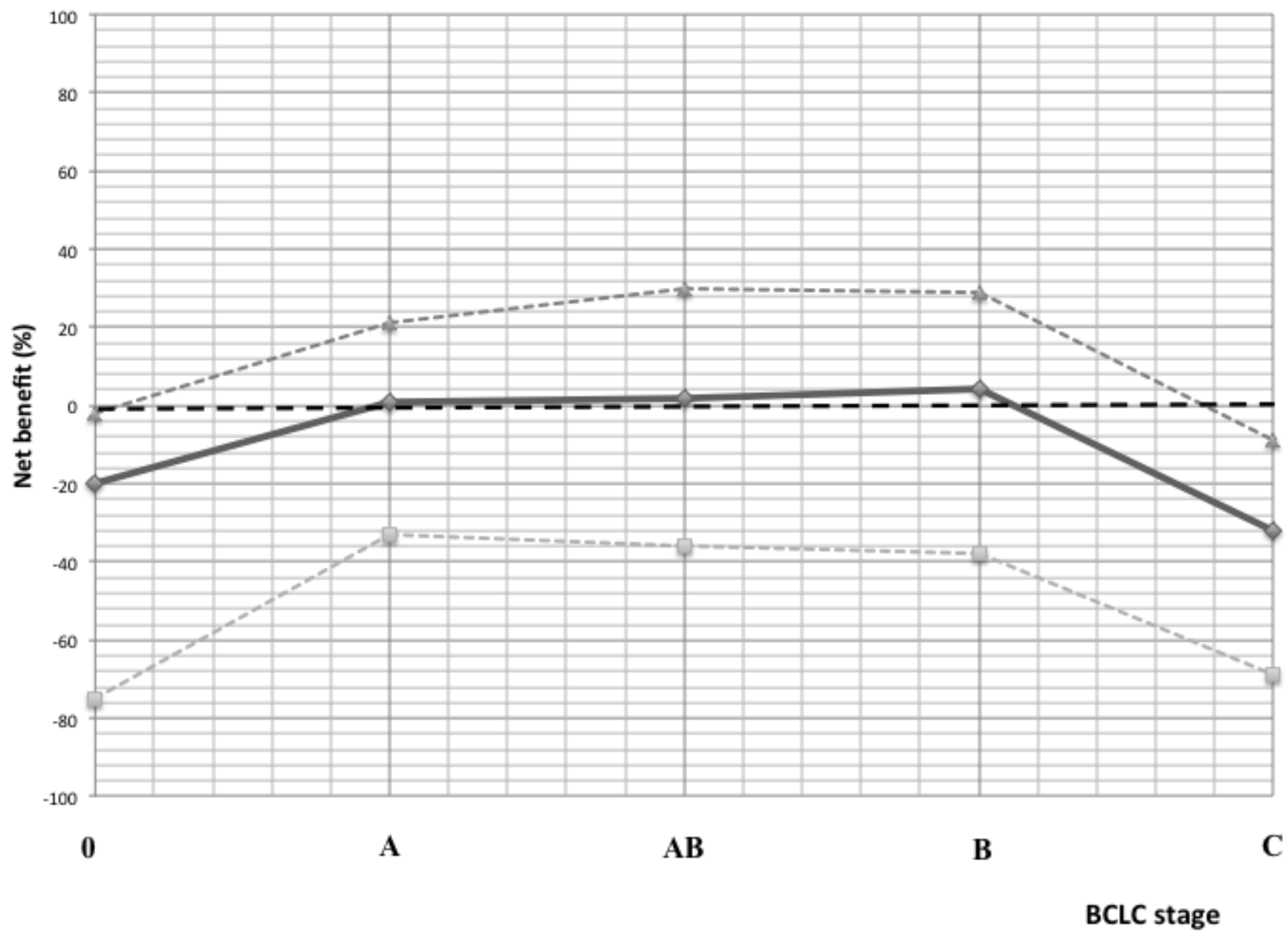




Figure 4C

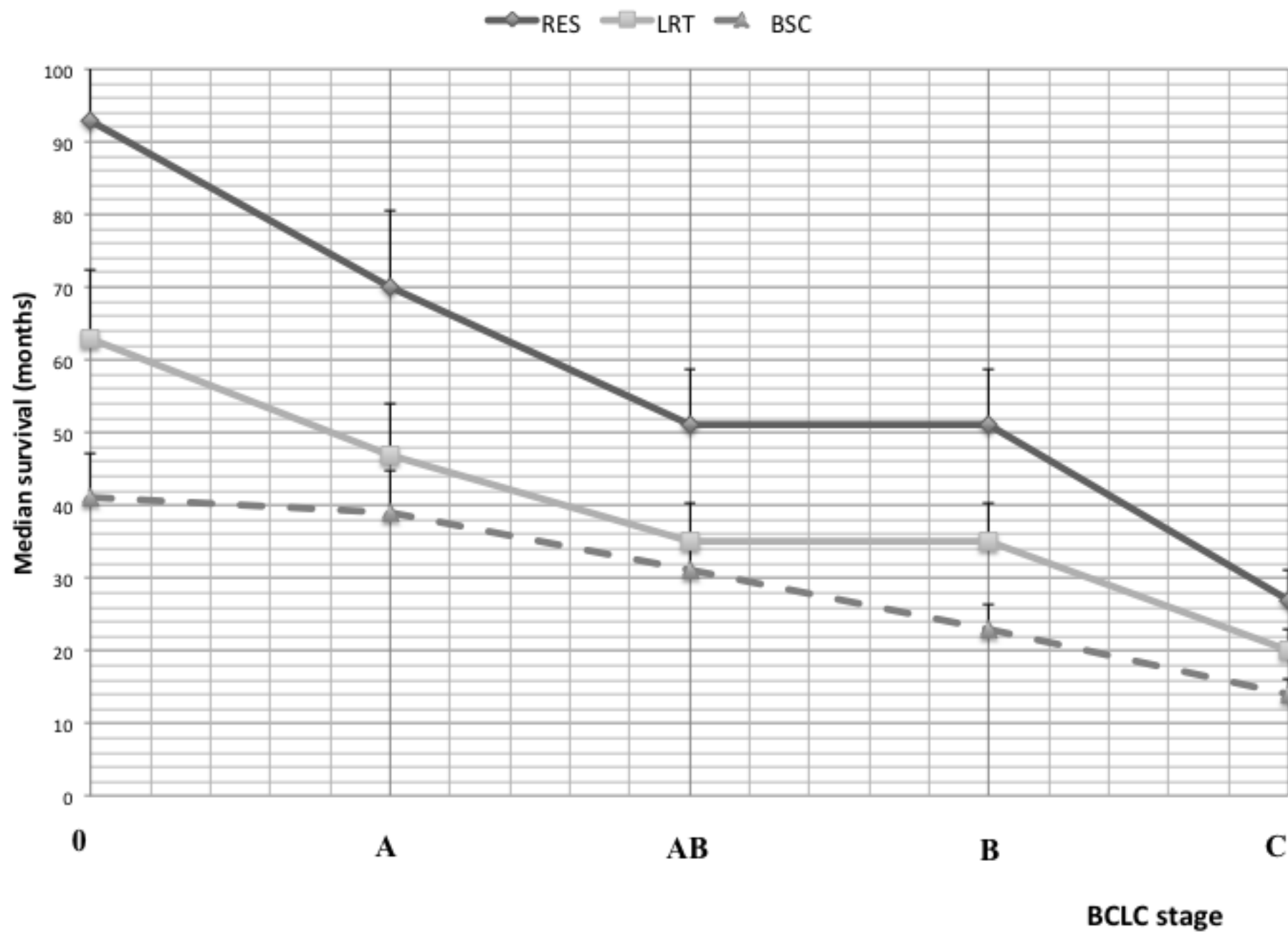
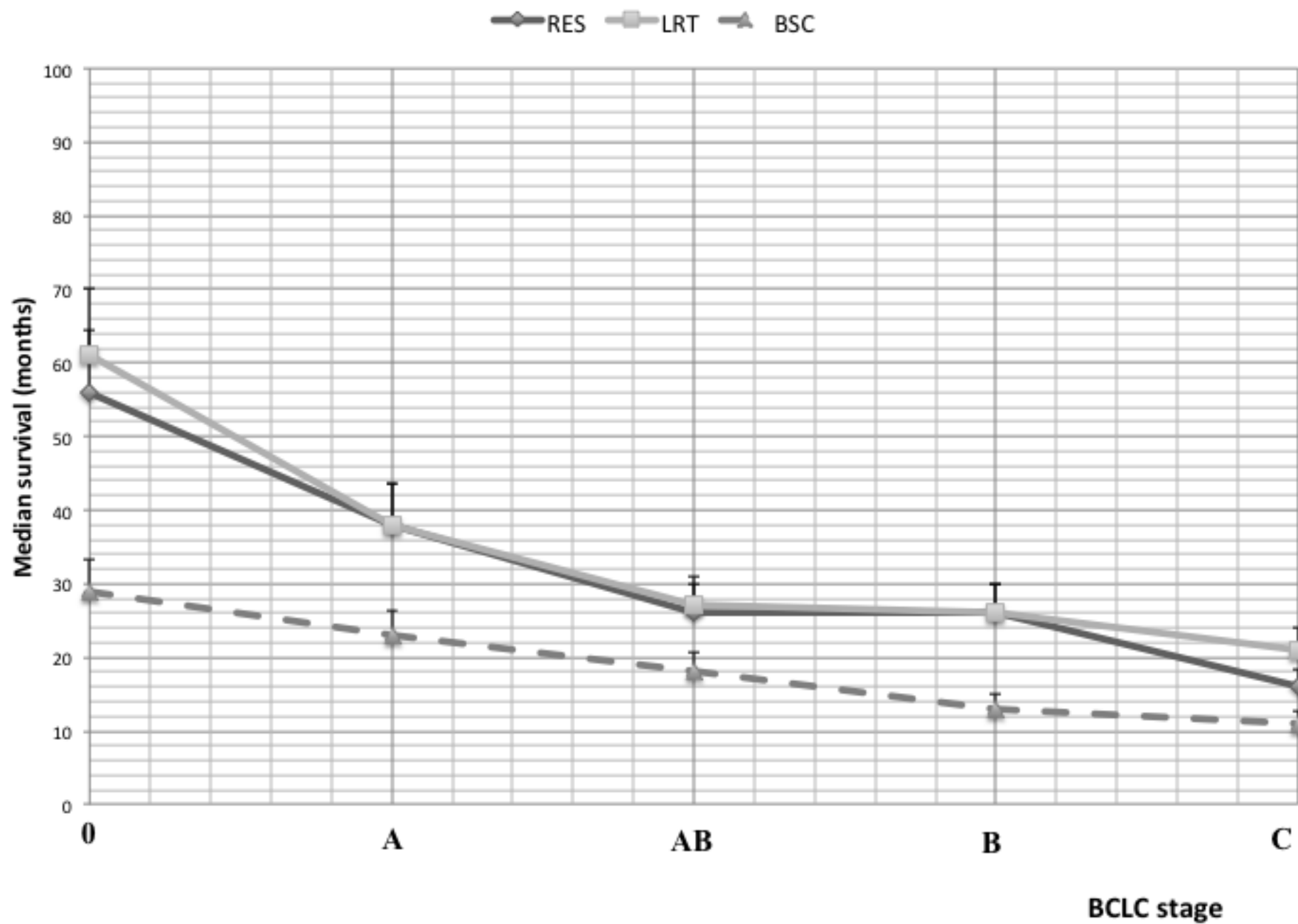


Figure 4D



**Supplementary material**

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