Research Square

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Efficacy of upfront hepatectomy without neoadjuvant chemotherapy for resectable colorectal liver metastasis

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Keywords: Beppu score, neoadjuvant chemotherapy, hepatectomy

Posted Date: November 20th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-111307/v1

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Version of Record: A version of this preprint was published at World Journal of Surgical Oncology on April 5th, 2021. See the published version at https://doi.org/10.1186/s12957-021-02210-9.

Abstract

Background

This study evaluated the impact of neoadjuvant chemotherapy on the prognosis of patients with resectable colorectal liver metastasis and assessed the usefulness of Beppu's nomogram for predicting prognosis.

Methods

This retrospective study identified 88 consecutive inpatients who underwent primary hepatic resection for colorectal liver metastasis; 58 received neoadjuvant chemotherapy and 30 underwent upfront surgery. Factors associated with recurrence-free survival were identified via univariate and multivariate analysis. Propensity score analysis using inverse probability of treatment weighting was also performed.

Results

On univariate analysis, poor recurrence-free survival was associated with multiple tumors, advanced primary tumor stage, vascular invasion by the primary tumor, a Beppu score ≥ 6, and neoadjuvant chemotherapy. On multivariate analysis, a Beppu score ≥ 6 and neoadjuvant chemotherapy were independent risk factors for recurrence. Neoadjuvant chemotherapy recipients had a higher incidence of lymph node metastasis and vascular invasion than non-recipients. Propensity score analysis revealed no significant difference in the recurrence-free survival rate between these groups.

Conclusions

Our results show the usefulness of Beppu scores for predicting the prognosis of patients with colorectal liver metastasis, but do not support the use of neoadjuvant chemotherapy in these patients.

Background

Colorectal cancer (CRC) is the third most common cancer, and its incidence is increasing worldwide [1]. Hepatectomy is the gold standard treatment for colorectal liver metastasis (CRLM). Owing to recent advancements in perioperative surgical management, CRLMs once considered unresectable can now be safely resected via staged hepatectomy [2]. However, even if curative resection is performed, the postoperative recurrence rate in the remnant liver is high (approximately 75%) [3] and the 5-year survival rate is dismal (33–61%) [4].

Perioperative chemotherapy is a potential strategy for improving the long-term survival of patients with CRLM. There is evidence supporting the efficacy of postoperative adjuvant chemotherapy [5]. In the

EORTIC 40983 clinical trial, patients with resectable CRLM who received perioperative neoadjuvant chemotherapy (NAC) had a better 3-year progression-free survival rate than those who received surgery alone [6]. Following this trial, the European Society for Medical Oncology recommended perioperative adjuvant chemotherapy for CRLM [7]. However, a subsequent study of the patient groups in the EORTIC 49083 found no significant effect of NAC on the 3- or 5- year overall survival (OS) rate [8]. In addition, a review of chemotherapy treatments for resectable CRLM found no difference in the OS rate in patients who received versus those who did not receive preoperative chemotherapy [9].

Accurate prediction of prognosis is important when considering perioperative chemotherapy strategies. In this study, we used Beppu's nomogram as a prognostic tool. This nomogram consists of 6 preoperative factors, is simple to apply, and has been shown to predict disease-free survival (DFS) rates in CRLM patients after radical resection [10]. Although this nomogram was analyzed based on chemotherapies between 2000 and 2004, it is applicable in cases using newly developed chemotherapies (e.g., oxaliplatin and irinotecan) as demonstrated in recent study by Higuchi et al. [11].

This study examined the efficacy of NAC for CRLM with radical resection and the usefulness of Beppu's nomogram for predicting prognosis.

Methods

Patients

This retrospective study identified 88 consecutive inpatients who underwent primary hepatic resection for CRLM in the Department of Surgery at Onomichi General Hospital between June 2006 and April 2019. It was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study design was approved by our institutional review board (OJH-201509), and all patients provided informed consent for their treatment.

Surgery

The initial surgery was performed using a laparoscopic or open method. The extent of resection was determined by the location of the tumor. Partial resection was selected if possible; if not, segment resection or lobectomy was selected to preserve liver function. The Pringle method was used as much as possible to control bleeding.

Neoadjuvant chemotherapy

Fifty-eight patients received NAC. The regimens were as follows: 1) 5-fluorouracil (5FU), leucovorin (LV), and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) (n = 34); 2) 5FU, LV, and irinotecan (FOLFILI, n = 10); and 3) tegafur/gimeracil/oteracil (TS-1) or tegafur/uracil with either LV (UFT/UZEL) or capecitabine (n = 14). The FOLFOX and FOLFILLI regimens also included a molecularly targeted agent (bevacizumab, cetuximab, or panitumumab) if needed. the standard treatment at our facility has been NAC. The administration period depends on the case and regimen, but usually includes six treatment

courses. Upfront hepatectomy was performed in the patients who refused to undergo NAC and in those whose general condition contraindicated NAC.

Complications and morbidity

Complications were classified as described by Dindo et al [12]. Postoperative complications were defined as complications of grade IIIa or greater and postoperative mortality was defined as any death that occurred within 30 days after surgery. Survival values were calculated from the date of surgery.

Follow-up strategy

All patients were followed until death and underwent annual follow-ups consisting of abdominal ultrasonography and laboratory tests for tumor markers, namely, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen. Dynamic computed tomography (CT) was performed every 6 months. If a definitive diagnosis of recurrence could not be established based on tumor marker data, ultrasonography-guided biopsy imaging (CT, magnetic resonance imaging, endoscopic ultrasonography, or fluorodeoxyglucose-positron emission tomography) was performed.

Beppu's nomogram

The following six preoperative factors were used to create the nomogram for DFS: synchronous metastasis (3 points); positive primary lymph node (3 points); tumor number, (4 points for 2–4 tumors and 9 points for ≥5 tumors); largest tumor diameter >5 cm (2 points); extrahepatic metastasis at hepatectomy (4 points); and preoperative CA19-9 level >100 (4 points). Zero, 5, 10, and >10 points corresponded to estimated median DFS times of >8.4 years, 1.9 years, 1 year, and <0.6 years, respectively. The total preoperative Beppu scores ranged from 0 to 25 points.

Statistical analyses

Recurrence-free survival (RFS) rates were determined using the Kaplan-Meier method and the log-rank test. Multivariate analyses for RFS were performed using Cox's regression model. Appropriate calibration of the model was indicated by a P value of 0.620 in the Hosmer-Lemeshow test, and good discrimination was indicated by a C-statistic of 0.773 with a 95% confidence interval (CI) of 0.662–0.884 and a P value <0.001. Propensity score analysis using inverse probability of treatment weighting (IPTW) was performed to overcome bias related to the different distributions of the covariates between NAC recipients and non-recipients. After IPTW processing, differences in RFS between these groups were tested using Cox regression and multiple logistic regression analyses. Two-tailed P-values <0.05 were considered statistically significant, and all analyses were performed using SPSS software (version 24; IBM, Armonk, NY, USA).

Results

Patients

Of the 88 patients in our study, 63 (72%) were men and 25 (28%) were women, and the median age was 70 years (Table 1). The primary tumor was located in the colon in 47 (53%) cases and the rectum in 41 (47%) cases; it was left-sided in 67 (76%) cases and right-sided in 12 (14%) cases. Synchronous liver metastasis, metachronous CRLM, and synchronous lung metastasis were detected in 42 (48%), 46 (52%), and five (6%) cases, respectively. Forty-six (52%) patients had one liver metastasis, 28 (32%) had 2–4 liver metastases, and 14 (16%) had ≥5 liver metastases. The median tumor number was one (range: 1–15), and the median tumor size was 17 mm. Forty-two (48%) patients were TNM classification stage I–III and 46 (52%) were stage IV.

Histologically, 46 (52%) primary tumors were well-differentiated adenocarcinomas; the remainder were of various types. Lymphatic invasion was negative in 29 (33%) cases and positive in 59 (67%) cases. Venous invasion was negative in 59 (67%) cases and positive in 29 (33%) cases (positive). Regional lymph node metastasis around the primary tumor was negative in 27 (31%) cases. The Beppu score was >6 points in 54 (61%) patients and >10 in 31 (39%) patients. NAC was administered to 58 (67%) patients, and postoperative complications were observed in 14 of the 88 patients (16%).

Univariate and multivariate analyses for factors associated with the 3-year RFS rate of patients with resectable CRLM

On univariate analysis, the following five factors were significantly associated with a low RFS rate: tumor number ≥5 (P = 0.03), TNM stage IV at the time of surgery (P = 0.041), liver metastasis classification H2–3 (P = 0.013), prognosis grade classification B–C (P = 0.005), vascular invasion (P = 0.021), Beppu score ≥6 (P = 0.027), and NAC (P = 0.029) (Table 1). On multivariate analysis, a Beppu score ≥6 (hazard ratio: 1.994, P = 0.027) and NAC (hazard ratio: 1.962, P = 0.024) were independent risk factors for RFS (Fig. 1).

Clinicopathological characteristics of the NAC+ and NAC- groups

Table 2 compares the characteristics of the patients who received NAC (NAC+ group) and those who did not (NAC- group). There were no significant differences in the general conditions of the groups at the time of hepatectomy. However, values related to the primary tumor, including the incidence of lymph node metastasis (P = 0.012) and vascular invasion (P = 0.009), were higher in the NAC+ group than in the NAC- group. Significantly more patients in the NAC+ group had a Beppu score ≥10.

Prognostic impact of NAC after IPTW

After IPTW, there was no significant difference in the RFS rate between the NAC+ and NAC- groups (P = 0.724) (Table 3, Fig. 2).

Discussion

This study shows the following for patients with resectable CRLM: 1) NAC does not improve RFS, even when radical resection is performed; 2) low Beppu scores are strongly associated with favorable long-

term prognosis; and 3) upfront hepatectomy is an efficacious treatment strategy. The aims of NAC include preservation of the remnant liver volume by tumor shrinkage and securing of the surgical margin. Neoadjuvant chemotherapy is an early treatment for micro-metastases, and determination of its efficacy is important. Although evidence of NAC efficacy in various cancers is increasing [13, 14], there are no data supporting its use in CRLM.

In this study, lymph node metastasis, lymphatic invasion, and high Beppu scores were more likely in patients who received NAC than in those who did not. However, NAC did not improve prognosis, even after the background characteristics of the two groups were aligned via IPTW.

The 2016 revised ESMO guideline recommend upfront hepatectomy for patients with clearly resectable CRLM and favorable prognostic indicators [15]. However, in advanced cases with high hepatic tumor loads and multiple tumors, perioperative systemic chemotherapy is essential for down-staging unresectable CRLM. Moreover, shortening the interval between NAC and hepatectomy improves the outcome in advanced CRLM cases [16]. Along with advances in surgical technology such as 2-stage hepatectomy (e.g., liver partition and portal vein ligation for staged hepatectomy), the use of NAC has increased the number of cases in which conversion surgery is possible [17].

Another interesting result in this study is the significant correlation between the Beppu score and prognosis. This relatively simple nomogram was easily applied to the patients in our study. In agreement with the findings of Higuchi et al. [18], it effectively predicted the prognosis of patients with resectable CRLM despite our use of different NAC regimens, as necessitated by differences in the patients' medical histories. Others demonstrated the usefulness of the nomogram as a recurrence prediction tool [18] and hence it may be useful for selecting patients most likely to benefit from NAC optimally.

In recent years, several reports have identified potential biomarkers for predicting recurrence. These include circulating tumor DNA (ctDNA) for the prediction of CRC recurrence [19] and circulating tumor cells (CTCs) [20] for the prediction of CRLM recurrence after radical resection. Because NAC does not improve the outcomes of patients with CRLM, it is important to administer the necessary amounts of adjuvant chemotherapeutic agents to selected patients based on their Beppu scores and/or levels of biomarkers such as ctDNA and CTCs. Postoperative adjuvant chemotherapy might prolong long-term survival [21].

There are some limitations to this study. First, it was retrospective and based on a single-center experience. Second, the relatively small sample size made it difficult to draw statistical inferences. Finally, the NAC regimens varied considerably. The optimal regimen for perioperative chemotherapy is still under investigation; however, some regimens may worsen the prognosis. In the new EPOC clinical trial, DFS was significantly lower in patients with resectable CRLM who perioperatively received a molecular targeting drug (cetuximab) than in those who did not [22]. It should be kept in mind that differences in regimens and administration periods can influence the study results.

In conclusion, upfront surgery without neoadjuvant systemic chemotherapy should be considered in cases of resectable CRLM. After IPTW, NAC had no effect on RFS. In cases with high Beppu scores, surveillance requires close attention.

Abbreviations

CRC
Colorectal cancer
CRLM
Colorectal liver metastasis
NAC
Neoadjuvant chemotherapy
DFS
Disease-free survival
5FU
5-fluorouracil
LV
Leucovorin
CA19-9
Carbohydrate antigen 19 – 9
CT
Computed tomography
RFS
Recurrence-free survival
CI
Confidence interval
IPTW
Inverse probability of treatment weighting
ctDNA
Circulating tumor DNA
CTC
Circulating tumor cell

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The study design was approved by our institutional review board (OJH-201509), and all patients provided informed consent for their treatment.

Consent for bublication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request

Competing interests: The authors declare that they have no competing interests.

Funding

None

Author's contributions

All authors participated in the operation or management of the patient in this case report. KO and TA drafted and revised the manuscript. TN is the chairperson of our department and supervised the writing of the manuscript. All authors read and approved the final manuscript.

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Acknowledgments:

None

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Tables

Table 1. Results of univariate and multivariate analyses of the clinicopathological factors for recurrence-free survival rates.

Factors	Univariate analysis			Multivariate analysis
	N	3 yrs (%)	P-value	
Gender				
Male	63	32.6	-	
Female	25	40.9	0.361	
BMI				
<23	39	35.9	-	
≥23	49	34.4	0.910	
Location				
Colon	47	34.8	-	
Rectum	41	34.6	0.853	
Location				
Right side	12	15.0		
Left side	67	37.2		
Transverse	9	44.4	0.125	
Timing of liver metastasis				
Metachronous	46	39.4		
Synchronous	42	30.7	0.190	
Synchronous lung metastasis				
Absent	83	35.0		
Present	5	40.0	0.590	
Number of tumors				
1	46	49.0		
2-4	28	20.8		
≥5	14	19.2	**0.030**	
Largest tumor diameter				
<5 cm	73	34.1		
≥5 cm	15	37.0	0.999	

CEA level (before hepatectomy)			
<5 ng/ml	35	27.9	
≥5 ng/mL	52	38.5	0.438
CA19-9 level (before hepatectomy)			
<38 U/mL	63	29.6	
≥38 U/mL	24	49.7	0.759
Stage (primary tumor)			
□-□	42	43.7	
□	46	27.3	**0.041**
Liver metastasis classification			
H1	55	47.6	
H2-3	28	19.9	**0.013**
Prognosis grade classification			
Grade A	50	48.7	
Grade B, C	32	17.3	**0.005**
Primary tumor differentiation			
Well-differentiated	46	35.5	
Others	42	34.5	0.775
ly (primary tumor)			
Negative	29	41.5	
Positive	59	31.6	0.161
v (primary tumor)			
Negative	59	43.1	
Positive	29	19.9	**0.021**
N			
Negative	27	42.3	0.057
Positive	61	31.3	

Beppu score				
<6	34	49.2		
≥6	54	26.5	**0.027**	**1.994 (1.083-3.672) 0.027**
Chemotherapy before hepatectomy				
Absent	30	46.8		
Present	58	29.4	**0.029**	**1.962 (1.092-3.524) 0.024**
Clavien-dindo classification				
<3a	74	36.2		
≥3a	14	28.8	0.555	

BMI: Body mass index, mGPS: modified Glasgow prognostic score, NLR: Neutorophil lymphocyte ratio, PNI: Prognostic nutrition index, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9

Table 2. Comparison of patients' characteristics between patients with neoadjuvant chemotherapy and without neoadjuvant chemotherapy

	NAC (-) (n= 30)	NAC (+) (n=58)	*P*-value
Male sex	21 (72%)	42 (71%)	0.904
Age (years)	73.5 (35-86)	69 (48-85)	0.026
BMI (kg/m^2)	22 (16-34)	23 (15-30)	0.940
Location (colon)	11 (38%)	30 (51%)	0.254
Location (right side)	3 (10%)	9 (16%)	0.585
Timing of liver metastasis (synchronous)	13 (43%)	29 (50%)	0.703
Synchronous lung metastasis	0	5 (9%)	0.128
Tumor number (multiple)	14 (47%)	29 (50%)	0.938
Tumor number	1.5 (1-7)	1 (1-15)	0.521
CEA	**13.9 (2-1224)**	**5.25 (1.2-111.1)**	**0.011**
CA19-9	12.5 (2-642)	10.5 (2-2587.8)	0.989
Primary tumor differentiation (well)			
N 1	**15 (50%)**	**46 (79%)**	**0.012**
Ly 1	**14 (47%)**	**45 (78%)**	**0.009**
Beppu score 6<	16 (53%)	38 (66%)	0.403
Beppu score >10	**5 (17%)**	**26 (45%)**	**0.013**
Beppu score			0.092
Clavien-dindo classification	3	11	0.372
Operation time	322 (86-596)	356 (127-727)	0.253
Intraoperative bleeding	205 (20-4000)	290 (20-3020)	0.379
PNI	46 (28-81)	46 (34-61)	0.605
NLR	2.5 (0.3-9.4)	1.9 (0.6-6.2)	0.154
GPS	6	13	0.949
mGPS	3	10	0.356

Variables in bold are statistically significant (*P*□0.05). Continuous variables are expressed as median (range). Qualitative variables are expressed as number (%). Abbreviations: BMI, Body mass index; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index; GPS, Glasgow prognostic score; CEA; CA19-9

Table 3 Unadjusted and adjusted hazard ratios for resection in patients with resectable colorectal liver metastases without neoadjuvant chemotherapy versus neoadjuvant chemotherapy

Endpoint	Crude			Adjusted a			IPTW b		
	HR	95% CI	P Value	HR	95% CI	P Value	HR	95% CI	P value
RFS	1.942	1.057-3.568	0.032	1.616	0.831-3.144	0.157	1.141	0.547-2.380	0.724

a: Adjusted for variables, such as those significant in the univariate analysis.

b: Adjusted by IPTW

HR, hazard ratio; IPTW, inverse probability of treatment weighing; 95% CI, 95% confidence interval; RFS, recurrence-free survival.

Figures

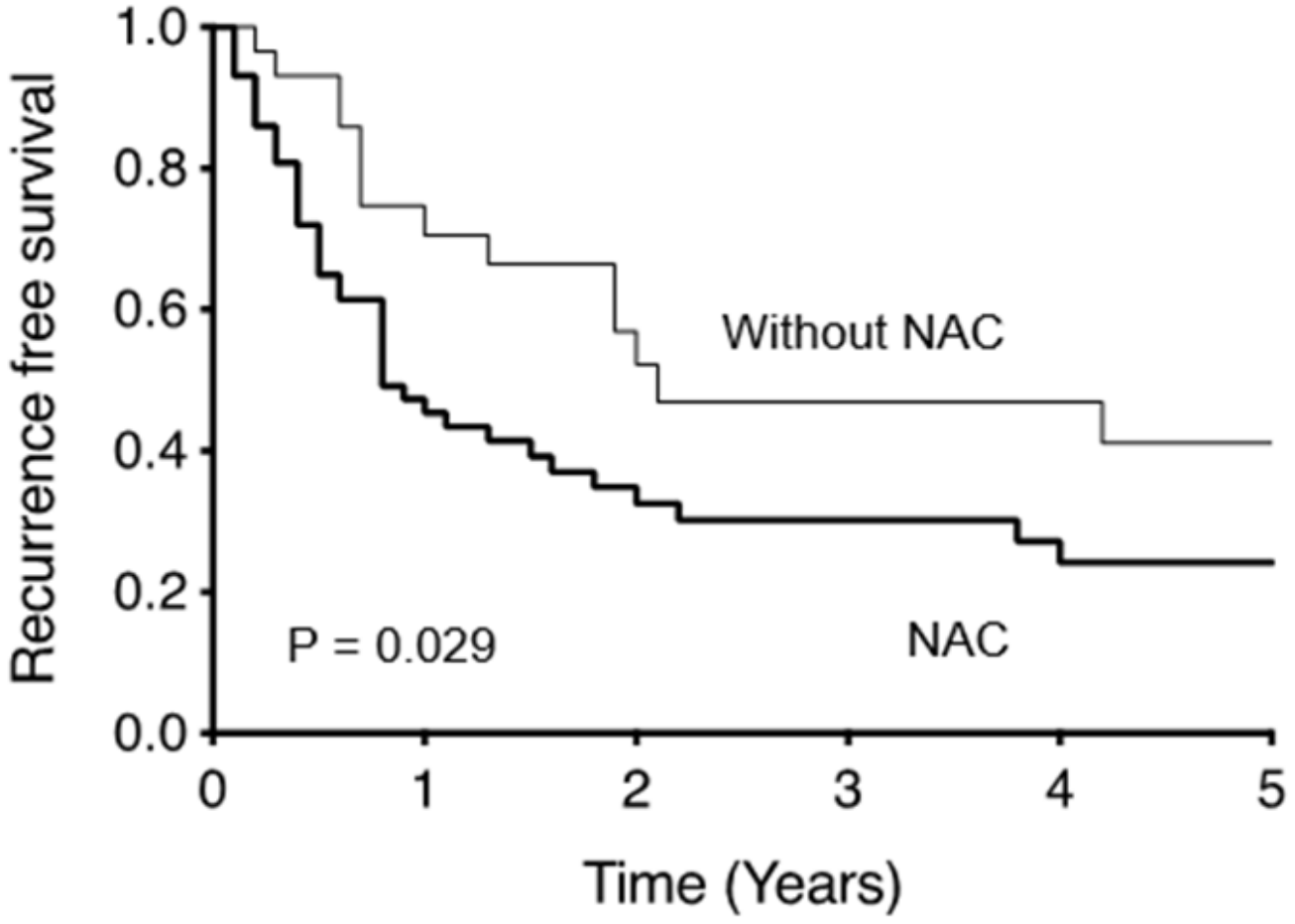

Figure 1

Recurrence-free survival (RFS) after initial treatment for colorectal liver metastasis in patients who received neoadjuvant chemotherapy (the NAC+ group) and those who did not (the NAC- group). The RFS rate was significantly better in the NAC- group than in the NAC+ group (P = 0.029).

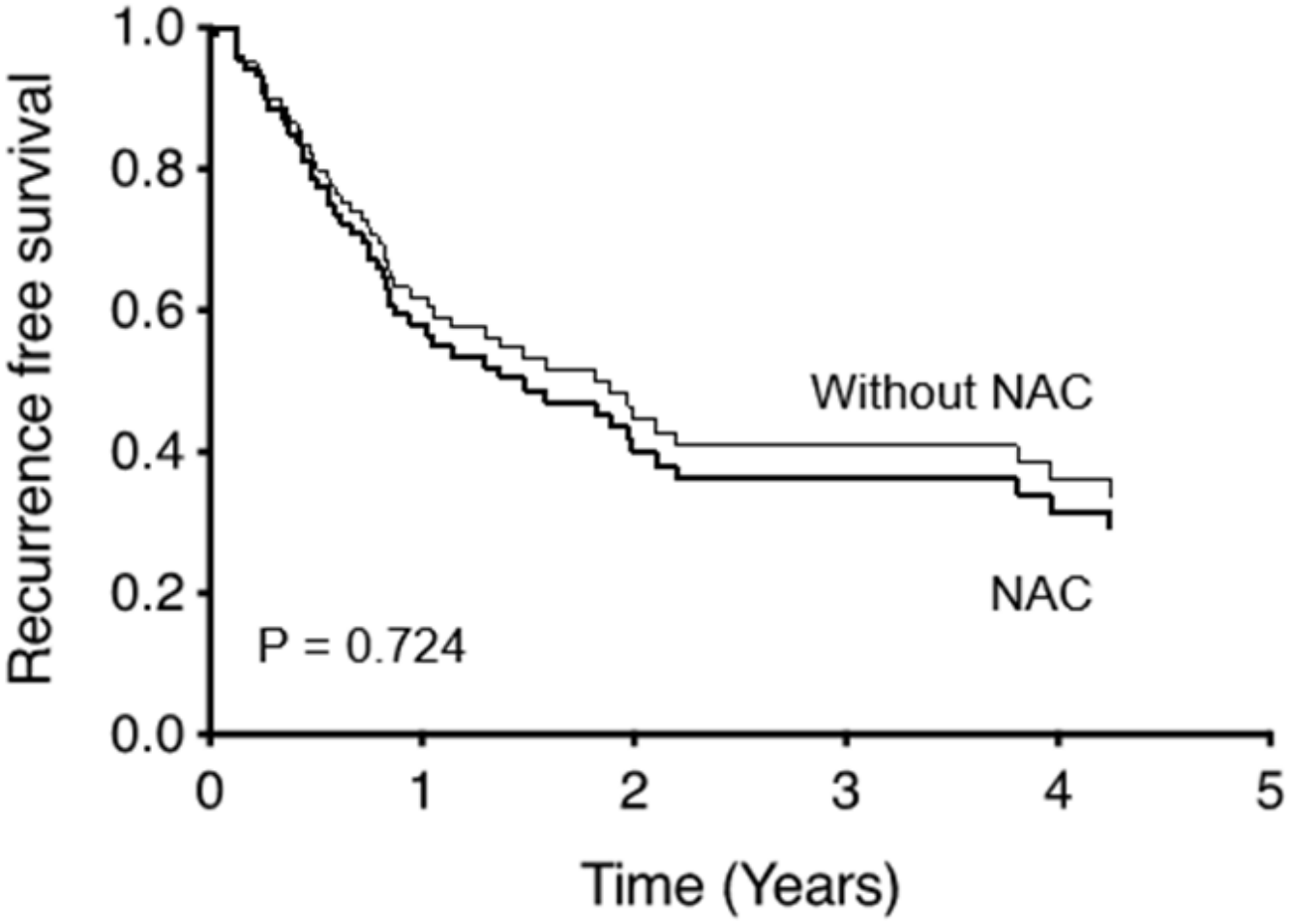

Figure 2

Inverse probability of treatment weighting hows that there is no significant difference in the recurrence-free survival (RFS) rate between the patients who received neoadjuvant chemotherapy (the NAC+ group) and those who did not (the NAC- group) (P = 0.724).