Three-Dimensional Length from the Center of the Liver is a Prognostic Factor of Colorectal Cancer with Liver Metastasis: A Retrospective Analysis

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Research

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Abstract

Background Resectability of liver metastasis is important to establish a treatment strategy for colorectal cancer patients. We aimed to evaluate the effect of distance from metastasis to the center of the liver on the resectability and patient outcomes after hepatectomy.

Methods Clinical data of a total of 124 patients who underwent hepatectomy for colorectal cancer with liver metastasis were retrospectively reviewed. We measured the minimal length from metastasis to the bifurcation of the portal vein at the primary branch of the Glissonean tree and defined it as “Centrality”. Predictive effects on positive resection margin and overall survival of centrality were statistically analyzed.

Results The value as a predictive factor for the positive resection margin of centrality was analyzed by the receiver operating characteristic curve (area under the curve = 0.72, $P<0.001$). In multivariate analysis, total number of metastases ≥ 3 and centrality ≤ 1.5 cm were significant risk factors of overall survival. Patients with these two risk factors (n=21) had worse 5-year overall survival (10.7%) than patients with one (n=35, 58.3%) or no risk factor (n=68, 69.2%). In subgroups analysis, neoadjuvant chemotherapy improved overall survival in patients with these two risk factors.

Conclusion Centrality was related with a positive resection margin and had a negative effect on survival. By combining the total number of metastases with centrality, we could determine disease prognosis and neoadjuvant chemotherapy indications for advanced colorectal cancer with liver metastasis.

Introduction

Although curative resection of isolated hepatic metastasis improves long-term survival of patients with colorectal cancer, only 20–30% of colorectal liver metastasis (CRLM) is resectable at the time of diagnosis [1, 2]. Several trials assessing the expansion of liver resectability by staged resection or systemic chemotherapy to convert unresectable metastases into resectable metastases have been conducted [3, 4]. Generally, the tolerable liver remnant volumes are 20% in a normal liver, 30% in a liver with chemotherapy-induced injury, and 40% in cirrhotic liver [5]. Additionally, adequate resection means the removal of a negative margin in all viable tumors with adequate vascular inflow and outflow and biliary drainage [6]. Thus, a multidisciplinary setting is required to establish treatment strategies for CRLM to achieve favorable oncologic outcomes and preserve remnant liver function after curative resection.

Vascular proximity to the central vessels of the liver is an important factor in selecting a proper treatment strategy. With metastasis occasionally observed near the central vessels, a large-volume resection is required, and subsequently, complete resection is considered difficult. Thus, this study aimed to evaluate the effect of distance from metastasis to the center of the liver on the resectability of metastases and to demonstrate its association with patients’ survival.

Materials And Methods

Data collection

We retrospectively reviewed the medical records of patients who underwent hepatectomy for CRLM in our institution from January 2012 to December 2017. Patients who were diagnosed with colorectal adenocarcinoma with liver-only metastasis and underwent resections with curative intent were included. Patients with other liver diseases, including liver cirrhosis or hepatocellular cell carcinoma, were excluded. The clinical characteristics of patients, such as age at diagnosis of the primary cancer, sex, primary cancer location, and TN categories, were investigated. Characteristics associated with liver metastasis, such as carcinoembryonic antigen (CEA) level at the diagnosis of liver metastasis, neoadjuvant chemotherapy (NAC), and the longest diameter, total number, and lobar involvement of liver metastases, were also investigated. Operative factors associated with hepatectomy, such as positive resection margin, length of the closest resection margin, intraoperative radiofrequency ablation (IORFA), and synchronous resection with primary tumor, were investigated. Positive resection margin was defined as the absence of malignant tumor cells on the border of the specimen's resection margin after hepatectomy.

Decision-making in a multidisciplinary team

All the treatment strategies for these patients were established by a multidisciplinary team (MDT) in our institution. The MDT for CRLM comprised a group of experienced specialists from medical oncology, colorectal and hepatobiliary surgery, radiation oncology, pathology, and diagnostic and interventional radiology. The resectability of CRLM was assessed by two experienced hepatobiliary surgeons in MDT.

Centrality

"Centrality" was defined as the minimal length from metastasis to the center of the liver, the bifurcation of the portal vein at the primary branch of the Glissonean tree. To measure the centrality, a process of three-dimensional (3D) interpolation from two-dimensional (2D) computed tomography (CT) or magnetic resonance (MR) images was performed using a 3- or 5-mm slice thickness (a gap between two serial images) of CT or MR images (Fig. 1). For 3D interpolation, three lengths on the X-, Y-, and Z-axes were required. First, the first axial image of a point correlated with the center of the liver was identified. Subsequently, the second axial image where the liver metastasis lesion began to appear was also identified. The length on the Y-axis was measured as the distance between the two images, a multiple (n) of slice thickness. The length on the X- and Z-axes could be measured on one axial image. Thus, centrality was calculated using the Pythagorean theorem as follows:

$$Centrality^2 = x^2 + (slicethickness \times n)^2 + z^2$$

In case of multiple metastatic lesions, centralities were calculated for all lesions close to the hilum, and the minimum value was selected and defined as a final centrality for that case.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 20.0 (International Business Machines Corporation SPSS, Chicago, IL, USA). Discrete values, such as sex, TN categories, and primary tumor locations, were compared using the Pearson's χ^2 test. Student's t-test was used to compare continuous values such as age, CEA level, and total number and longest diameter of liver metastases. To compare the predictive value of centrality for positive resection margin after hepatectomy, the receiver operating characteristic (ROC) curve analysis was used. Overall survival (OS), from diagnosis of liver metastasis to death or the last follow-up, was analyzed using the Kaplan-Meier method and log-rank test. Cox proportional hazards regression analysis was used to evaluate the risk factors for OS. A two-sided P value < 0.05 was considered statistically significant.

Results

A total of 124 patients were included in this study (Table 1). The median age at diagnosis of primary tumor was 60 years (interquartile range [IQR], 54–70), and the present study predominantly comprised men (n = 77, 62.1%). Left colon and rectal cancer were more frequently observed than right colon cancer (42.7%, 37.9%, and 19.4%, respectively). Eighty-one (65.3%) patients were simultaneously diagnosed with primary cancer and liver metastasis. The median length of liver metastasis was 2 cm (IQR, 1.2–4), and the median number of total liver metastasis was 2 (IQR, 1–4). The median centrality was 4.4 cm (IQR, 2.3–6.0), and 56 (45.2%) patients showed metastasis on both the right and left lobes. Neoadjuvant chemotherapy was performed in 42 (33.9%) patients, and among them, 83.3% received a combination of neoadjuvant chemotherapy with a target agent bevacizumab or cetuximab. Synchronous resections with primary tumor were performed in 73 (58.9%) patients, and 16 (12.9%) patients received IORFA. The median length of the closest resection margin was 0.4 cm (IQR, 0.1–0.8), and the proportion of the liver's negative resection margin was 71.0% (n = 88).

Table 1
Clinicopathologic characteristics of colorectal cancer in patients with liver metastasis

Characteristics	Total N = 124
	No. (%)
Patient characteristics	
Age, years, median (IQR)	60 (54–70)
Sex, male	77 (62.1)
Primary tumor characteristics	
Location	
Right colon	24 (19.4)
Left colon	53 (42.7)
Rectum	47 (37.9)
T categories	
1	3 (2.4)
2	8 (6.5)
3	83 (66.9)
4	26 (21.0)
N categories	
0	36 (29.0)
1	72 (58.1)
2	12 (9.7)
Liver metastasis	
Synchronous	81 (65.3)
CEA, median (IQR)	6 (2.5–28.5)
Diameter, cm, median (IQR)	2 (1.25–4)
Number, median (IQR)	2 (1–4)
Bilobar involvement	56 (45.2)
NAC	42 (33.9)
Target agent	35 (83.3)
Centrality, cm, median (IQR)	4.4 (2.3–6.0)

Characteristics	Total N = 124
	No. (%)
Operative factors	
R0 resection	88 (71.0)
IORFA	16 (12.9)
Resection margin, cm, median (IQR)	0.4 (0.1–0.8)
Synchronous resection	73 (58.9)
Postoperative factors	
Adjuvant chemotherapy	119 (96)
Target agent	78 (65.5)
CEA: carcinoembryonic antigen, NAC: neoadjuvant chemotherapy before liver resection, IORFA: intraoperative radiofrequency ablation	

The distribution of centrality is shown in Fig. 2, and a total of 25 (20.1%) patients had centrality < 1.5 cm. The ability of centrality to predict positive resection margin was analyzed using the ROC curve (area under the curve = 0.72, $P < 0.001$). The characteristics of the two groups, patients with centrality > 1.5 cm (n = 99) and patients with centrality ≤ 1.5 cm (n = 25), were compared, and the results are shown in Table 2. The length of the longest diameter, total number of metastasis, proportion of bilobar involvement, and NAC were higher in patients with centrality ≤ 1.5 cm than those in patients with centrality > 1.5 cm. The proportion of positive resection margin after hepatectomy was also higher in patients with centrality ≤ 1.5 cm than that in patients with centrality > 1.5 cm. Moreover, the resection margin in patients with centrality ≤ 1.5 cm was closer than that in patients with centrality > 1.5 cm.

Table 2
Comparison of characteristics after subgroup classification by centrality

Characteristics	**Centrality > 1.5 cm** **Total N = 99** **No. (%)**	**Centrality ≤ 1.5 cm** **Total N = 25** **No. (%)**	**P**
Patient characteristics			
Age, years, mean ± SD	60.9 ± 11.2	61.5 ± 9.8	0.813[a]
Sex, male	61 (61.6)	16 (64.0)	0.826[b]
Primary tumor characteristics			
Location			0.429[b]
Right colon	19 (19.2)	5 (20.0)	
Left colon	45 (45.5)	8 (32.0)	
Rectum	35 (35.4)	12 (48.0)	
T categories			0.729[b]
1	2 (2.1)	1 (4.0)	
2	7 (7.4)	1 (4.0)	
3	64 (67.4)	19 (76.0)	
4	22 (23.2)	4 (16.0)	
N categories			0.919[b]
0	29 (30.5)	7 (28.0)	
1	57 (60.0)	15 (60.0)	
2	9 (9.5)	3 (12.0)	
Liver metastasis			
Synchronous	61 (61.6)	20 (80.0)	0.084[b]
CEA, mean ± SD	83.7 ± 320.6	79.8 ± 127.4	0.954[a]
Diameter, cm, mean ± SD	2.9 ± 2.5	5.5 ± 4.8	0.015[a]
Number, mean ± SD	2.8 ± 3.4	7.3 ± 6.9	0.004[a]
Bilobar involvement	35 (35.4)	21 (84.0)	< 0.001[b]

Characteristics	Centrality > 1.5 cm Total N = 99	Centrality ≤ 1.5 cm Total N = 25	P
	No. (%)	No. (%)	
NAC	26 (26.3)	16 (64.0)	< 0.001[b]
Operative factors			
Positive resection margin	22 (22.2)	13 (54.2)	0.002[b]
Resection margin, cm, mean ± SD	0.7 ± 0.8	0.2 ± 0.2	< 0.001[a]
IORFA	11 (11.1)	5 (20.0)	0.236[b]
Synchronous resection	56 (56.6)	17 (68.0)	0.299[b]
Postoperative factors			
Adjuvant chemotherapy	95 (96.0)	24 (96.0)	0.993[b]

CEA: carcinoembryonic antigen, NAC: neoadjuvant chemotherapy before liver resection, IORFA: intraoperative radiofrequency ablation, SD: standard deviation, a: analyzed by Student's t-test method, b: analyzed by Pearson's χ^2 test method

The median follow-up period of all patients was 39.2 months (min: 5.9, max: 145.8). According to a multivariate analysis, risk factors related with OS were the number of liver metastasis > 3 and centrality < 1.5 cm (Table 3). All patients were classified based on the number of the risk factors observed, and the distribution of patients is shown in Fig. 3. Z0 (zone 0) represents patients with no risk factor (centrality > 1.5 cm and total number of metastasis < 3 [n = 68]). Z1 represents patients with single risk factor (centrality ≤ 1.5 cm or total number of metastasis ≥ 3 [n = 35]), and Z2 represents patients with both risk factors (centrality ≤ 1.5 cm and total number of metastasis ≥ 3 [n = 21]). Figure 4 presents the Kaplan-Meier curves of OS of Z0, Z1, and Z2 (5-year OS: Z0, 69.2%; Z1, 58.3%; Z2, 10.7%). Z2 showed worst OS among the three groups, and statistically significant differences in OS among the three groups were observed (Z0 and Z1, P = 0.026; Z1 and Z2, P = 0.016; Z0 and Z2, P < 0.001). Additionally, patients in Z0–Z2 were stratified based on NAC, and their differences in OS between subgroups were analyzed (Fig. 5). After performing a subgroup analysis, patients receiving NAC in Z2 showed better OS than patients not receiving NAC in Z2 (3-year OS: 65.3% vs. 0%, P = 0.017). However, there was no statistically significant difference in OS between subgroups of Z0 and Z1 (Z0: 5-year OS, 70.2% vs. 72.9%, P = 0.166; Z1: 5-year OS, 65.0% vs. 51.5%, P = 0.396).

Table 3
Univariate and multivariate analyses of overall survival

Factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age, years						
< 65	1					
≥ 65	1.092	0.570, 2.091	0.791			
Sex						
Female	1					
Male	1.808	0.851, 3.841	0.123			
Location of primary tumor						
Right colon	1		0.433			
Left colon	0.668	0.299, 1.493				
Rectum	0.559	0.227, 1.381				
T categories						
1,2	1		0.228			
3,4	1.48	0.782, 2.799				
N categories						
0	1		0.692			
1,2	1.154	0.569, 2.342				
Synchronous metastasis						
No	1					
Yes	1.235	0.627, 2.431	1.235			
CEA						
< 5	1					
≥ 5	1.908	0.953, 3.818	0.068			
Size						
< 5 cm	1					
≥ 5 cm	1.667	0.829, 3.354	0.152			
Number						

Factors	Univariate analysis			Multivariate analysis		
	HR	**95% CI**	**P**	**HR**	**95% CI**	**P**
< 3	1					
≥ 3	3.49	1.775, 6.865	< 0.001	2.688	1.290, 5.602	0.008
Lobar involvement						
Unilobar	1					
Bilobar	2.979	1.524, 5.822	0.001	1.336	0.462, 3.864	0.593
Centrality						
> 1.5 cm	1					
≤ 1.5 cm	3.713	1.815, 7.595	< 0.001	2.272	1.033, 4.999	0.041
Resection margin						
Negative						
Positive	2.243	1.060, 4.746	0.035	1.428	0.646, 3.154	0.379
Combined resection of primary tumor						
No	1					
Yes	1.433	0.736, 2.791	0.29			
Adjuvant chemotherapy						
No		1				
Yes	1.514	0.207, 11.071	0.683			
CEA: carcinoembryonic antigen						

Discussion

This study is considered significant considering that centrality, which is defined as the vascular proximity of liver metastasis, was proven to be another morphologic factor in deciding the resectability of CRLM. During the resection of liver metastasis, how to optimally solve two conflicting issues of preserving maximum liver function and securing sufficient resection margin after hepatectomy should be significantly considered. Traditionally, volumetric parameters such as tumor size and number of CRLM have been shown to be significant factors associated with resectability and prognosis after resection [7, 8]. However, the concept of resectability of CRLM has been changed over the last decade with the introduction of several treatments. Surgical techniques, such as portal vein embolism (PVE) or two-stage hepatectomy (TSH) are proven to be safe and curative in selective cases of advanced CRLM with inadequate future liver remnant (FLR) or underlying liver diseases [9, 10]. Combined resection with IORFA is beneficial in preserving FLR with favorable oncologic outcomes [11, 12]. Additionally, NAC with a target agent and rescue surgery for unresectable CRLM results in tumor downsizing with survival benefits [13]. Considering that the benefits of these treatments have been proven, active resections have been widely performed, and the criteria for resectability have focused on how to perform R0 resection with sufficient liver function [7]. Thus, factors associated with positive resection margin should be comprehensively studied to define the resectability of CRLM.

Although the standard width of the resection margin of CRLM remains unknown, traditionally, resection margin of 1 cm has been accepted as a minimal margin to obtain favorable oncologic outcomes [14]. Certainly, R1 resection, i.e., microscopic identification of malignant cells on the resection margin, is a negative factor for survival after resection based on previous reports [15]. However, other studies reported that the width of surgical margin, even < 1 cm, does not affect survival in patients with R0 resection [16]. Thus, hepatic resection tends to be actively performed even when the length of the resection margin is < 1 cm on imaging modality. However, in this study, when the centrality was high (< 1.5 cm), the rate of R0 resection was low. Additionally, OS was also worse in patients with high centrality than in patients with low centrality.

Daisuke et al. suggested several factors in indicating hepatectomy, such as previous hepatectomy, disease type (hepatocellular carcinoma, benign or metastatic lesion), liver function, and tumor size and number [17]. They also reported that performing hepatectomy is highly difficult when the tumor is located in deeper layers or proximal to the branch of the Glissonean tree. As the tumor is closer to the primary branch of the Glissonean tree, the hilar dissection or anatomical resection is required to completely resect the tumor. The centrality in this study was at the bifurcation of the primary Glissonean branch; thus, we could assume that the centrality was a factor indicating the difficulty of hepatectomy to secure sufficient resection margin near the center of the liver.

Subsequently, how should we approach CRLM with high centrality? Attempts to secure sufficient resection margin at the central side of the liver, such as anatomical resections, should be made to achieve favorable oncologic outcomes. Additionally, treatments to increase or preserve hepatic reserve (such as PVE or TSH) should be considered to compensate largely reduced liver volume after resection. Volume-saving therapy, such as IORFA, may also be a promising treatment option for lesions observed at the opposite lobe of the liver. Additionally, recent studies reported a greater conversion rate of initially unresectable CRLM after NAC with regimens of oxaliplatin, irinotecan, and other target agents [18]. Thus, NAC should be considered in patients with high centrality, so that hepatectomy can be performed after securing sufficient resection margin at the central side. However, prolonged chemotherapy may also have a detrimental effect on the hepatic parenchyma due to oxaliplatin-induced sinusoidal obstruction or irinotecan-induced steatosis [19, 20]. Hence, liver function and remnant liver volume should be carefully monitored during chemotherapy. Taken together, various treatment tools should be considered when establishing appropriate strategies for CRLM with high centrality, and treatments should be customized based on patient’s condition.

This study has several limitations. First, the definition of the center of the liver, bifurcation of the portal vein at the first branch of the Glissonean tree, was subjective and did not include other important structures in the liver. For example, proximity to the inferior vena cava is an important factor in deciding treatment strategy of CRLM, but it was not considered in this study. Second, the factor of centrality ≤ 1.5 cm was selected empirically according to the opinion of hepatobiliary surgeons in our MDT team. According to the ROC curve analysis, the specificity for positive resection margin of centrality ≤ 1.5 cm was 91.0%. However, the sensitivity was only 31.4%, suggesting that factors other than centrality should be considered when deciding the positive resection margin of CRLM. Third, this study was retrospectively conducted based on previous pathologic reports, which contained only the shortest length of resection margin of specimens and did not indicate whether the resection margin was of the central side. Fourth, the result of a subgroup analysis in Fig. 5 might not be sufficient to support the idea that NAC was effective in Z2 due to the small volume of subgroups. Although the OS of the subgroup in Z2 was statistically different, additional large-scale studies are required to confirm the association between NAC and centrality.

Conclusion

Centrality, proximity to the central vessels of liver metastasis, had a potency in predicting the positive resection margin after hepatectomy for CRLM and was a significant risk factor for overall survival. With the combination of another volumetric parameters (the number of metastases), it might be beneficial in predicting resectability and survival of patients with advanced CRLM.

Abbreviations

CT: computed tomography; MR: magnetic resonance; CRLM: colorectal cancer with liver metastasis; CEA: carcinoembryonic antigen; NAC: neoadjuvant chemotherpay; IORFA: intraoperative radiofrequency ablation; MDT: multidisciplinary team; 3D: 3-dimensional; 2D: 2-dimensional; ROC: receiver operating characteristic; OS: overall survival; IQR: interquartile range ratio; Z1: zone1; Z2: zone2; Z3: zone3; PVE: portal vein embolization; TSH: two-stage hepatectomy; FLR: future liver remnant

Declarations

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Authors' contributions

Jun Woo Bong: collection, analysis and interpretation of data, writing paper; Sun Il Lee: final approval of the manuscript version; Yeonuk Ju, Jihyun Seo and Sang Hee Kang: drafting of the work for intellectual content; Pyoung-Jae Park, Sae-Byeol Choi, Sang Cheul Oh and Byung Wook Min: design and conception of the work.

Ethics approval and consent to participate

The Institutional Review Board of Korea University Guro Hospital approved this study with a waiver of informed consent (Approval Number: 2018GR0395).

Consent for publication

Not applicable

Conflict of interest

There is no conflict of interest in this study.

Data Availability Statement

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

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Figures

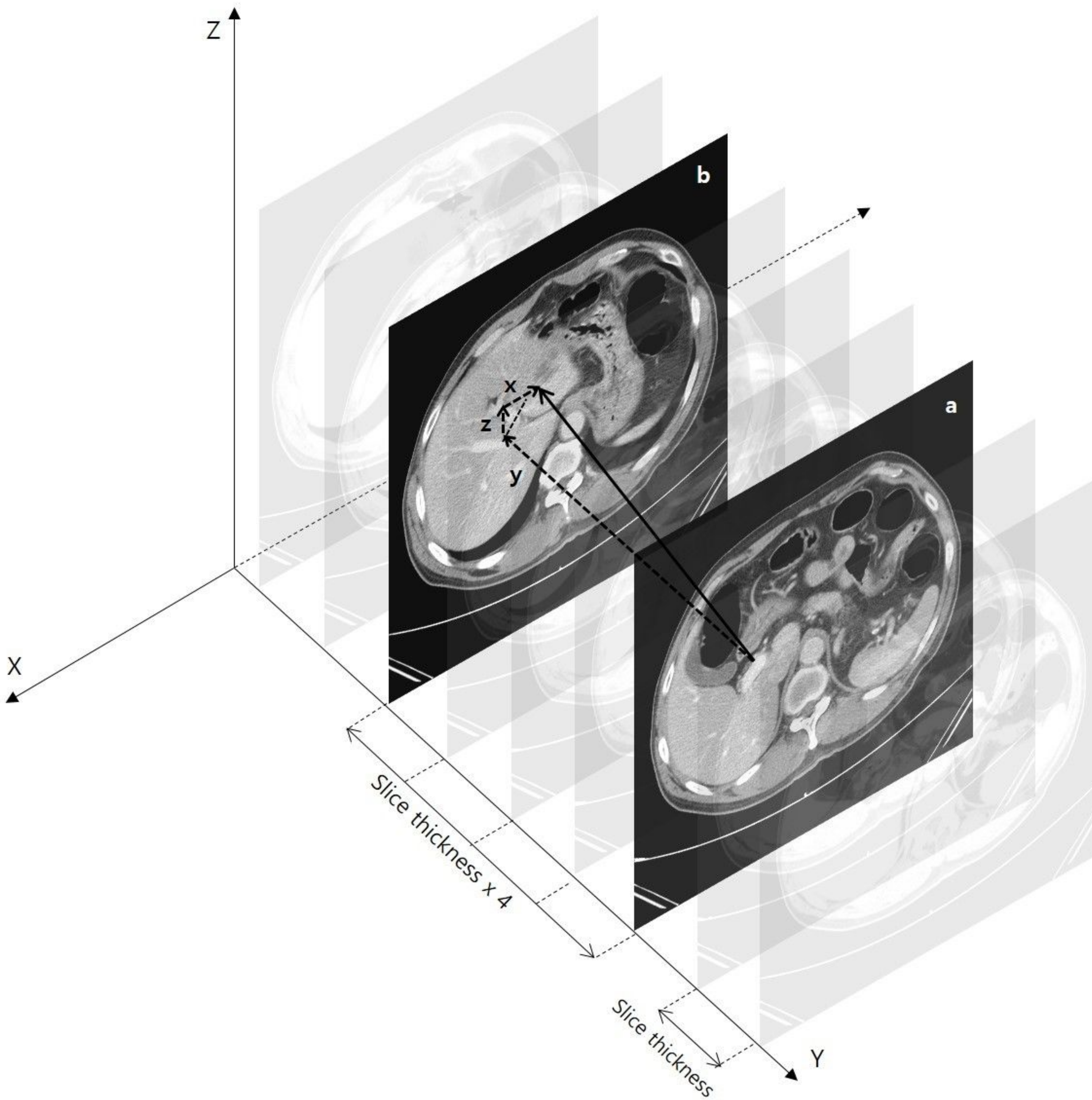

Figure 1

Measurement of centrality using three-dimensional interpolation from two-dimensional images of liver metastasis. Centrality was defined as the minimal length from liver metastasis to the center of the liver to the bifurcation of the portal vein at the primary branch of the Glissonian tree. 〖Centrality〗^2 〖= x〗^2+

(slice thickness×n)^2+z^2, (n = [number of axial images between a and b] + 1), a = the axial image of the center of the liver, b = the first axial image where the liver metastasis lesion began to appear

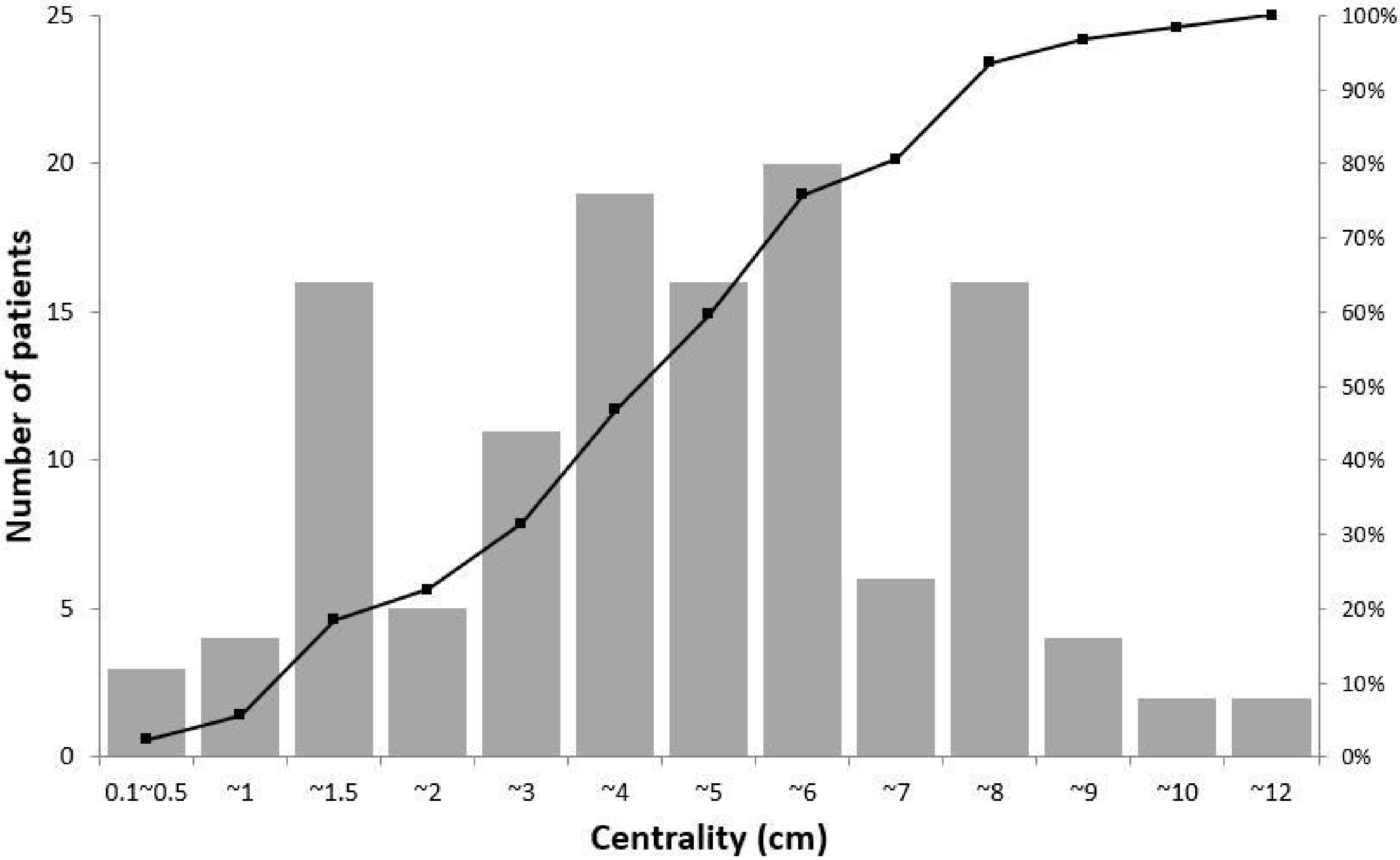

Figure 2

2(a) Distribution of centralities of all patients

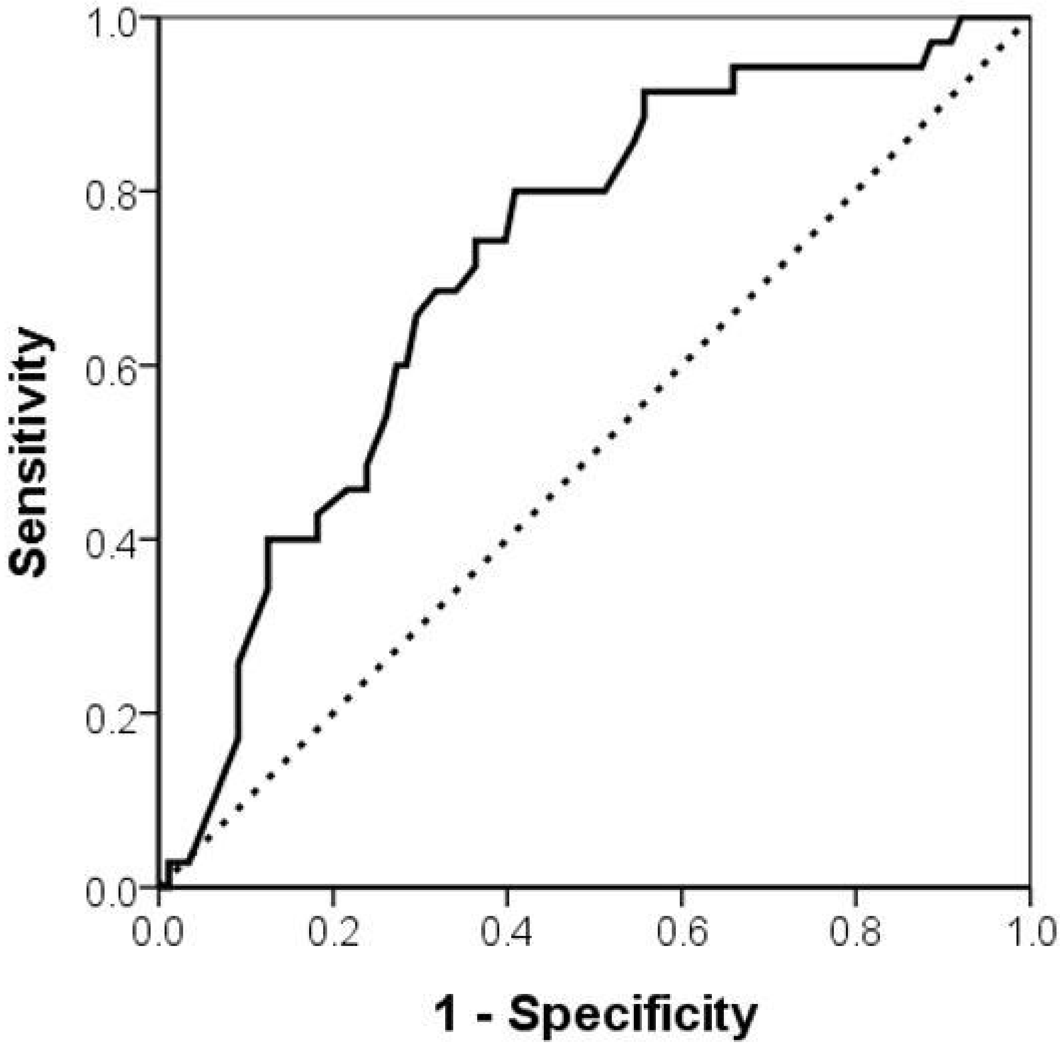

Figure 3

2(b) Receiver operating characteristic curve analysis of centrality for positive resection margin. AUC =0.720, P<0.001, AUC: area under the curve

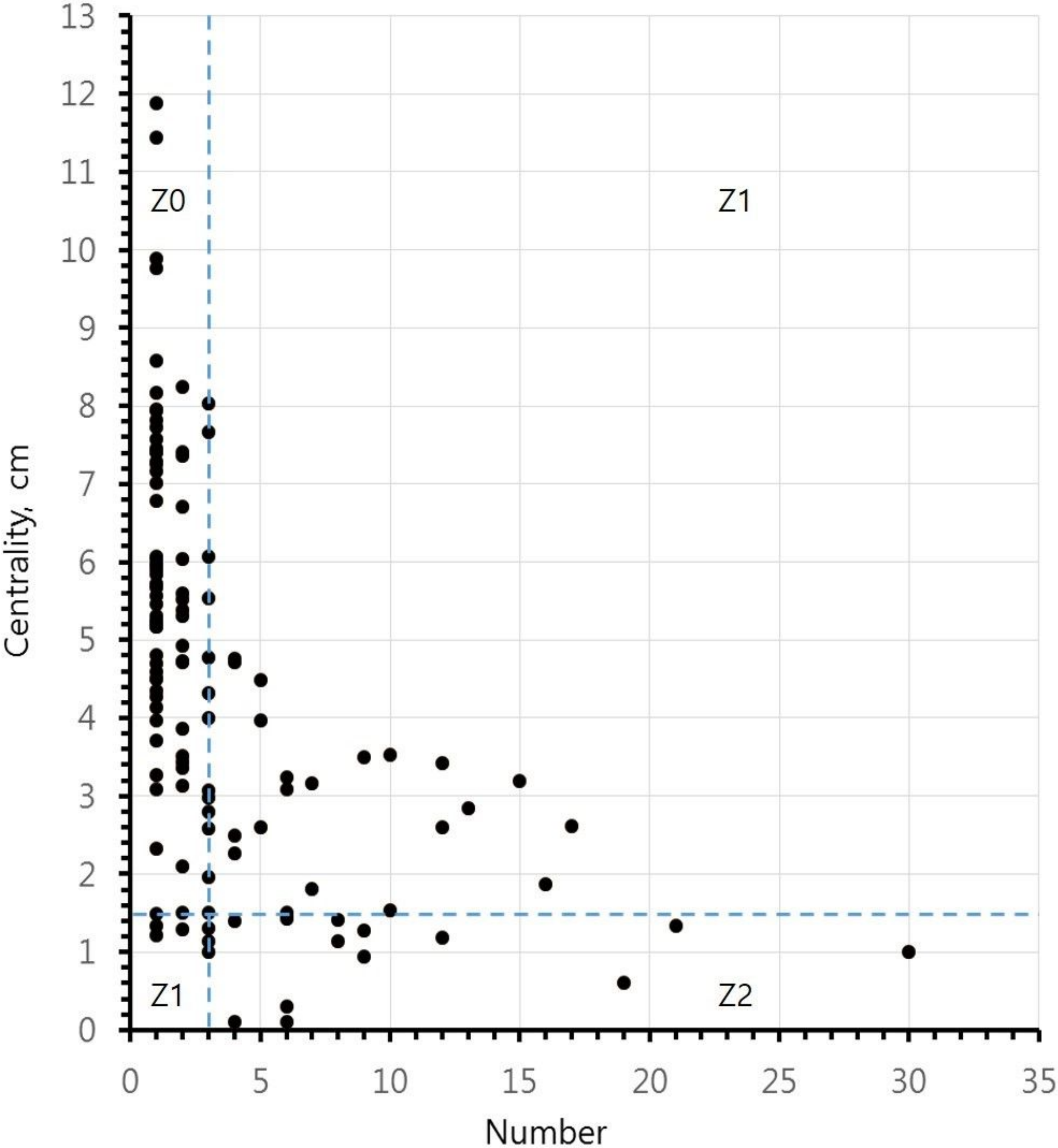

Figure 4

Distribution of patients according to centrality and number of liver metastases Z0: centrality > 1.5 cm and total number of metastases < 3, n = 68, Z1: centrality ≤ 1.5 cm or total number of metastases ≥ 3, n = 35, Z2: centrality ≤ 1.5 cm and total number of metastases ≥ 3, n = 21

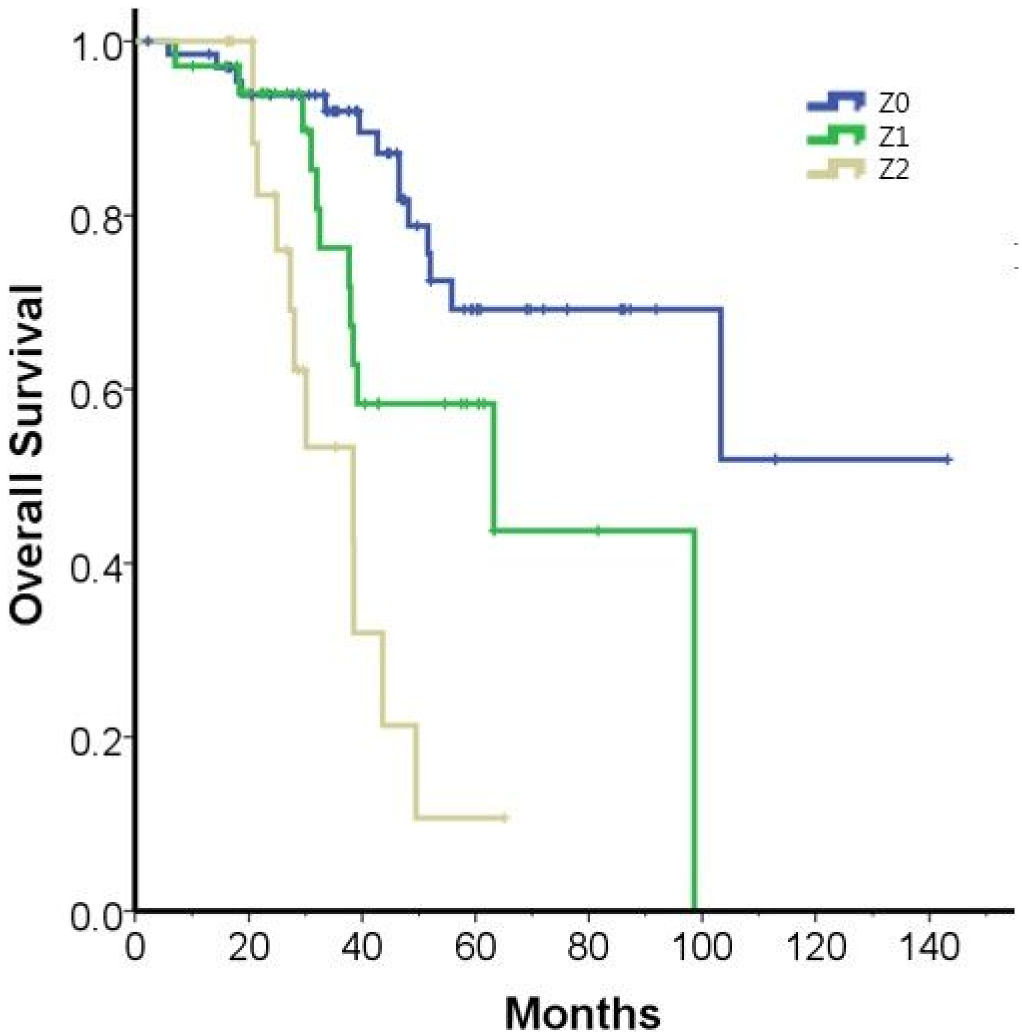

Figure 5

Kaplan-Meier curves of overall survival of patients stratified by the number of risk factors observed. Significant differences in OS among the three groups were observed and Z2 showed worst OS (Z0 and Z1, P=0.026; Z1 and Z2, P=0.016; Z0 and Z2, P<0.001)

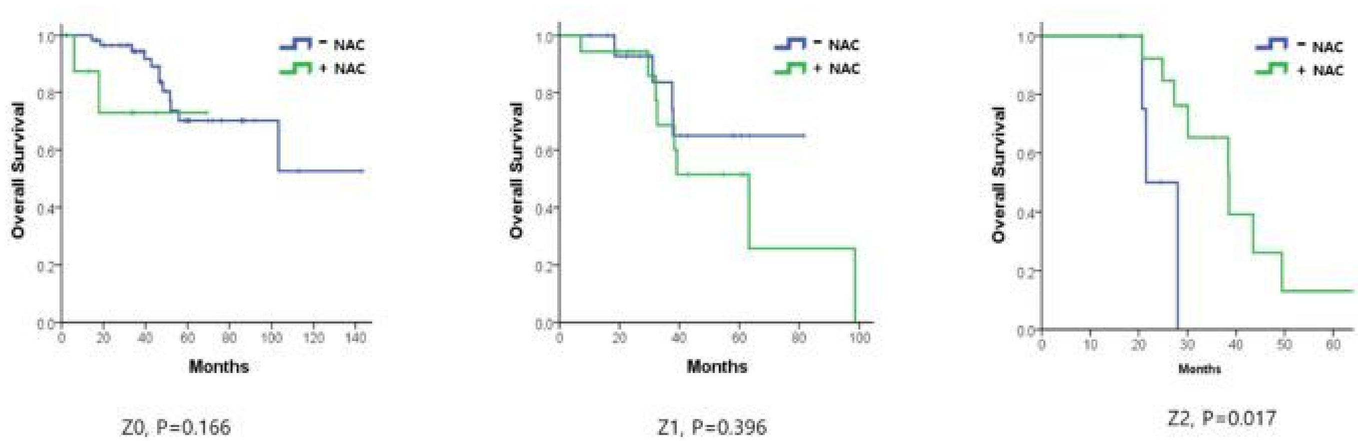

Figure 6

Kaplan-Meier curves of overall survival of subgroups stratified by neoadjuvant chemotherapy. Overall survival was statistically different only in Z2. P=0.166 in Z0, P=0.396 in Z1, and P=0.017 in Z2