Prognostic Significance of Lymph Node Metastases and Ratio in Laryngeal Squamous Cell Carcinoma

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Research article

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Abstract

Background

The lymph node metastases (LNM) and the lymph node ratio (LNR) were shown to be prognostic factors in head and neck cancer. The purpose of this study was to investigate the prognostic significance of the LNM and LNR in patients with laryngeal squamous cell carcinoma (LSCC).

Methods

All patients undergoing resection of laryngeal cancer at the First Affiliated Hospital of Chongqing Medical University between March 2011 and December 2018 were reviewed. Univariate and multivariate analyses were performed using log-rank and Cox proportional hazard models, and survival curves estimated using the Kaplan-Meier method.

Results

Of 670 patients with LSCC, the median overall survival (OS) of was 42.2 months, and 3-year and 5-year OS rates were respectively 92.9 ± 1.1% and 86.1 ± 1.7%. 12.69% (85/670) were pathological nodal positive (pN+). LNM was associated with tumor site, T stage and differentiation degree ($p < 0.05$). And the 5-year OS rates in the pathological nodal negative (pN-) and pN + groups were 88.7± 1.7% and 69.9 ± 5.9%, respectively ($p = 0.000$), and the presence of pN + was the most significant prognostic factor for survival. Furthermore, the 5-year OS of patients with 1 to 3 positive LN and 4 or more positive LN were 64.6±8.1% and 44.9 ± 15.2%, respectively ($p = 0.032$). Additionally, LNR examination did not reach significance in our study. However, it demonstrates that increasing LNR was associated with worsening survival.

Conclusion

LNM is an independent prognostic factor in LSCC, and increasing number of positive LN and LNR in patients portend a poor prognosis.

Background

Laryngeal cancer ranks at the fourteenth most universal type of cancer in the world [1]. Laryngeal squamous cell carcinoma (LSCC), which occupies 85–90% of total malignant tumors in the larynx, is the second-largest head and neck epithelial tumor and insensitive to currently used chemotherapeutics[2, 3]. Therefore, surgical resection has been become the preferred treatment for LSCC. In the past 20 years, although there have been advances in term of diagnosis and treatment, it has not been satisfactory in the long-term survival for LSCC patients[4–6]. The postoperative regimens combining chemotherapy and radiation are increasingly being used to decrease radical radiotherapy-induced complication and prolong survival.

The lymph node metastases (LNM) have been identified as one of the most significant prognostic factors in head and neck squamous cell carcinoma (HNSCC)[7–10]. As previous studies showed that the OS rate was significant differences in patients with different numbers of LNM, and a general trend of increasing positive nodes resulted to a worse prognosis[11, 12, 9, 10]. Furthermore, the lymph node ratio (LNR), which is defined as the ratio of the number of positive lymph nodes to the total number of excised lymph nodes, was recently demonstrated as a vital independent prognostic factor for HNSCC[13–20]. However, the LNR is not recommended in any kinds of tumors of the AJCC staging.

Clinical tumor–node–metastasis (TNM) stage as the criterion has been more widely adopted in the therapeutic management of patients with malignant tumor. However, lymph node staging is sometimes not an adequate prognostic factor. A standardized prognostic tool that can distinguish patients at high risk of death would be more beneficial for adjuvant treatment strategy. Therefore, the study focuses in therapeutic outcome and prognostic factors for survival in LSCC. The aim of this study was to examine the prognostic significance of increasing numbers of pathological positive LN and LNR, and to determine whether them can be a useful guide for distinguishing potential candidates for adjuvant treatment strategy.

Methods

Patients

The medical records of 670 patients with LSCC were underwent surgical resection and neck dissection at the First Affiliated Hospital of Chongqing Medical University (Chongqing, China) from March 2011 to December 2018, and their clinical and pathological characteristics were retrospectively reviewed. The staging of patients used the eighth edition of AJCC TNM staging system [21]. All treatment strategy for patients was made at a multidisciplinary team including otorhinolaryngologist, radiologist and radiation oncologists. The therapeutic scheme was based on TNM stage, patient preference, physical condition, radiation-related morbidity, general performance status and so on. All patients in this study were underwent primary surgical tumor resection with or without neck dissection that was performed by the same surgical team. Each neck specimen was divided into levels by the surgeon, then sectioned and examined by the pathologist. Indications for postoperative radiotherapy included advanced stage of the primary tumor and pathological positive nodes. The average dose of irradiation was 56.8 gy (50–65 gy). But chemotherapy was also added to postoperative therapy in the case of extranodal extension.

Follow-up

Patients underwent a standardized postoperative follow-up schedule (including clinical examinations, electrolaryngendoscope, abdominal ultrasonography, neck and chest contrast-enhanced CT) every 3 months for the first postoperative year and every 6 months thereafter. The follow-up period ranged from

3.1 to 136.4 months (median, 42.2 months). Postoperative follow-up data were available for all patients. The overall survival time was defined as the interval between the date of surgery and the date of the last consultation or date of death.

Statistical analysis

The data collection and statistical analysis were performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). The χ^2 test or Fisher's exact test was used to determine the incidence of metastasis and correlated factors. The overall survival rate was calculated by using the Kaplan-Meier method.

Results

Patient Characteristics

There were 670 LSCC patients consisted of 21 women (3.13%) and 649 men (96.87%) from March 2011 to December 2018, and the median age was 61 years (range 37–88 years). 85 patients were pathological nodal positive. The median follow-up time was 42.2 months (ranged 3.1 to 136.4 months). The clinical and pathological information was presented in Table 1. We found that LNM was significantly correlated with tumor location, T stage and differentiation degree ($p < 0.001$), but not associated with gender, age, drinking and smoking ($p > 0.05$). The risk of LNM increased obviously with the increase of T stage or decrease of differentiation degree (Tables 1 and 2). Furthermore, the total number of LNs examined in pN- and pN + groups were respectively 27.50 ± 16.98 and 34.82 ± 17.87 ($p < 0.001$) (Table 3).

Table 1
Clinicopathological characteristics of patients with LSCC.

Term	**Overall** n = 670	**pN-** n = 585	**pN+** 85	**Metastasis rate (%)** 12.69	χ^2	*P*
Age						
≥ 60	391	341	50	12.79	0.009	0.926
< 60	279	244	35	12.54		
Gender						
Male	649	565	84	12.94	1.229	0.268
Female	21	20	1	4.76		
Smoking						
Yes	599	522	77	12.85	0.144	0.704
No	71	63	8	11.27		
Drinking						
Yes	291	254	37	12.71	0.000	0.985
No	379	331	48	12.66		
Tumor site						
Glottic	559	525	34	6.08	133.081	0.000
Supraglottic	99	53	46	46.46		
Subglottic	12	7	5	41.67		
Differentiation						
Well	404	369	35	8.66	73.674	0.000
Moderately	183	163	20	10.93		
Poor	60	30	30	50.00		
T stage						
T1	282	281	1	0.35	113.682	0.000
T2	188	168	20	10.64		
T3	151	108	43	28.48		
T4	49	28	21	42.86		

Table 2
Correlation between lymph node metastases and T stage.

Term	**Overall** n = 647	**pN-** n = 562	**pN+** 85	**Metastasis rate (%)** 13.14	χ^2	*P*
Well						
T1	7	7	0	0.00	17.940	0.000
T2	20	14	6	30.00		
T3	25	8	17	68.00		
T4	8	1	7	87.50		
Moderately						
T1	78	78	0	0.00	45.002	0.000
T2	52	45	7	13.46		
T3	39	31	8	20.51		
T4	14	9	5	35.71		
Poor						
T1	181	180	1	0.55	52.905	0.000
T2	110	103	7	6.36		
T3	86	168	18	20.93		
T4	27	18	9	33.33		
Glottic						
T1	273	273	0	0.00	71.782	0.000
T2	163	154	9	5.52		
T3	92	77	13	16.30		
T4	31	21	0	32.26		
Supraglottic						
T1	8	7	1	12.5	4.740	0.192
T2	22	12	10	45.45		
T3	52	29	23	44.23		
T4	17	7	10	58.82		

23 patients could not be told the differentiation degree.

Table 3 The number of LNs examined in pN- and pN+

	n (Mean±SD)	*P* value
pN-	27.50±16.98	
pN+	34.82±17.87	0.0008

Lnm Was Associated With Os

All 670 LSCC patients were included in the survival analysis. Kaplan-Meier curves were used to assess the prognosis of LSCC patients. The 3-year and 5-year OS rates for patients with LSCC were respectively 92.9 ± 1.1% and 86.1 ± 1.7% (Fig. 1A). According to the differentiate degree, the 5-year OS rate was: 87.1 ± 1.8% at moderately and well group, 81.1 ± 6.3% at poor group ($p = 0.028$) (Fig. 1B). And the 5-year OS rate according to pathological T stage was: 91.4 ± 2.6% at T1 stage, 84.8 ± 3.1% at T2 stage, 84.4 ± 3.4% at T3 stage, 82.9 ± 6.0% at T4 stage ($p = 0.018$) (Fig. 1C). A multivariable analysis indicated that LNM was an independent prognostic factor for LSCC patients. When classified into the pN- and pN + groups, the 5 year OS rate was 88.7 ± 1.7% and 69.9±5.9%, respectively ($p < 0.001$) (Fig. 2A). Furthermore, we surveyed the association between the number of pathological positive LNs and the risk of LSCC death, and found that patients with 1 to 3 positive LNs had a 5-year survival of 64.6 ± 8.1%, while the 5-year OS decreased to 44.9 ± 15.2% in patients with 4 or more positive LNs ($p = 0.032$) (Fig. 2B). The relationship between the number of positive LNs and prognosis was presented by the manner of Kaplan-Meier survival curves (Fig. 2B).

The hazard of death according to LNM is shown in Tables 4 and 5. In the multivariable analysis adjusted for confounding variables, the hazard of death of patients with pN + was associated with more than triple compared with pN- group (HR = 3.397; 95% CI: 2.107–5.476) ($p < 0.001$). In addition, compared to patients with 1–3 positive LNs, patients with ≥ 4 positive LNs was associated with more than twice the hazard of death (HR = 2.484; 95% CI: 1.049–5.884) ($p = 0.032$).

Table 4
Mutually adjusted hazard ratios for LNM among all cases.

	n (%)	HR (95% CI)	*P* value
pN-	585 (87.3)	1.00	
pN+	85 (12.7)	3.397 (2.107,5.476)	0.000
CI = confidence interval; HR = hazardratio.			

Table 5
Mutually adjusted hazard ratios for the number of positive LNs among pN+.

	n (%)	HR (95% CI)	*P* value
0 < positive LNs < 4	69 (81.2)	1.00	
positive LNs ≥ 4	16 (18.8)	2.484 (1.049,5.884)	0.032
CI = confidence interval; HR = hazard ratio.			

Lnr Was Associated With Os

Recent studies indicated that LNR was an important prognostic factor in head and neck cancer patients[22, 23, 12, 24]. Therefore, we next examined the impact of an increasing LNR on survival. The mean value of LNR for pN + patients was 0.1 (range 0.01 to 0.8). Therefore, we divided all pN + patients into three groups including LNR < 0.05, 0.05 ≤ LNR < 0.1 and LNR ≥ 0.1, and their 5-year OS were 74.6 ± 9.8%, 69.2 ± 9.6% and 66.4 ± 11.6%, respectively ($p = 0.491$). The difference in survival among these three groups was not significant, but the 5-year OS decreased obviously with the increase of LNR. Corresponding KaplanMeier survival curves are shown in Fig. 3.

Discussion

Surgical resection remains the preferred treatment because of LSCC is insensitive to currently used chemotherapeutics. Despite improvements in operative and diagnostic technique, the long-term overall survival is still dissatisfactory [4–6]. The postoperative adjuvant treatment including radiotherapy or chemoradiotherapy is used to decrease recurrence and improve the long-term survival. However, which patients should be received the postoperative adjuvant treatment has been a subject of debate.

The status of neck lymph nodes, which include the size, number and level of LNM and the presence of extranodal extension, have a significant impact on regional control and survival in HNSCC[25–28]. In the current study, LNM was found to be an independent factor in determining the survival rate in LSCC, and the hazard of death in patient with pN + was associated with more than threefold compared with pN-. Furthermore, the increasing number of positive LNs significantly decreased the OS rate. The 5-year OS in patients with 4 or more metastatic LNs was worse than 3 or fewer according to our findings. As previous study showed that a change point at four metastatic LNs was identified in oral cavity cancer[13]. This similarity may reflect comparability in the biological behavior between LSCC and oral cavity cancer. As similar with the reported data, the number of LNM was proved to be an independent prognostic factor in head and neck cancer[12, 13]. In addition, we found that LNM was significantly associated with tumor location, T stage and differentiation degree. These results based on prior studies evaluating metastatic LN number on head and neck cancer prognosis[29, 30].

As limited lymph node dissection may result in pathological understaging, a growing number of studies show that LNR is superior to the traditional nodal staging in term of estimating survival, and some researchers have suggested a modified TNM staging system based on LNR[22, 31–33]. Therefore, we next investigated the impact of LNR on survival. We divided all pN + patients into LNR < 0.05, 0.05 ≤ LNR < 0.1 and LNR ≥ 0.1 groups. Although the LNR did not reach significance in our study, the 5-year OS decreased obviously with the increase of LNR. Künzel et al reported a similar finding: LNR only became significant if it was the range of 0.08–0.1, and the LNR seems to be of limited value for the decision-making process in the treatment of patients with LSCC[14]. Zhang *et al* reported that the LNR was confirmed as a more reliable indicator for evaluating the prognosis in LSCC[15], but the object of study was the pN0 and pN + LSCC, the prognostic factor of LNR on survival should be further investigated in pN + LSCC.

In addition, when considering the prognostic significance of the LNR, we need to know that the LNR is a mathematical figure that is affected by kinds of conditions. For example, the extent of neck dissection and the number of resected LNs are not unified standards in global. Furthermore, the pathologist examined the number of LNs in the specimen, which can also result to bias. Although the LNR did not reach statistical significance in our study, it was most likely due to the small number of patients with pN+, and prospective studies will be required in order to support the decision-making process based on the LNR in the treatment of patients with LSCC.

Conclusions

Our findings demonstrate that lymph node metastases is an independent prognostic factor in LSCC, and increasing number of positive LN and LNR in patients portend a poor prognosis, therefore, they may be a helpful guide for defining potential candidates for adjuvant treatment strategy. In addition, the postoperative chemoradiotherapy may be necessary for patients with 4 or more pathological positive LNs.

Abbreviations

LNs: positive lymph nodes; LSCC: laryngeal squamous cell carcinoma; pN+: pathological nodal positive; pN-: pathological nodal negative; LNR: lymph node ratio; LNM: lymph node metastases; TNM: Clinical tumor–node–metastasis; HNSCC: head and neck squamous cell carcinoma; OS: over survival; AJCC: American Joint Committee on Cancer.

Declarations

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Author contributions

ZW have been involved in drafting the manuscript. YL performed subsequent data analysis. TL, CL and above researchers together completed experiment part of this research. ZW and GH revised the manuscript for important intellectual content. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study protocol was approved by the institutional review board of Institutional Animal Care Committee at Chongqing Medical University (Chongqing, China). As this study was a retrospective analysis of routine clinical data, the informed consent of participants was waived by the institutional review board.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

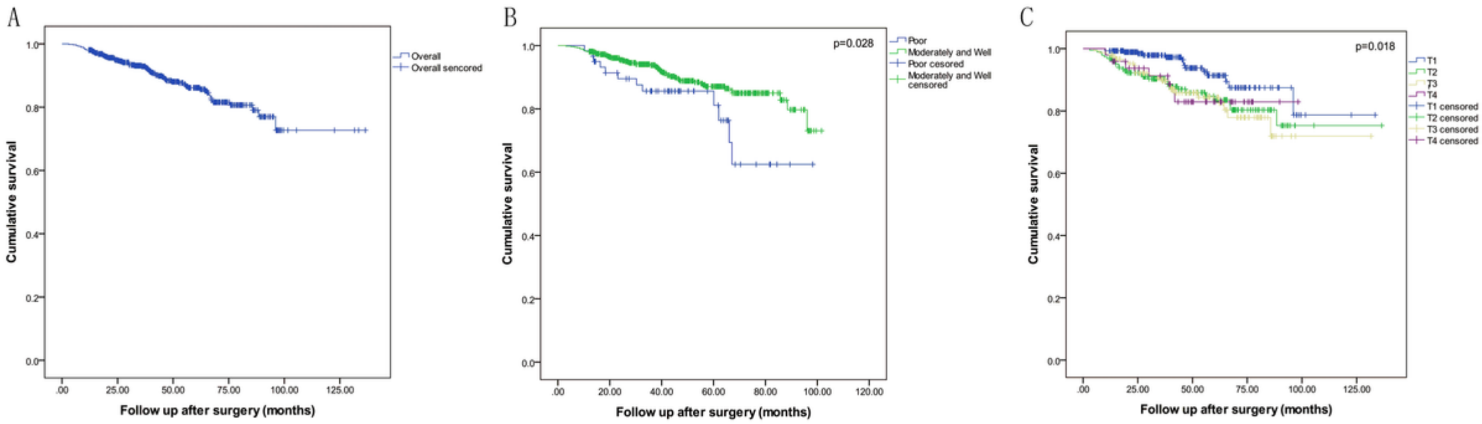

Figure 1

Kaplan−Meier overall survival curves based on the differentiation degree and T stage.

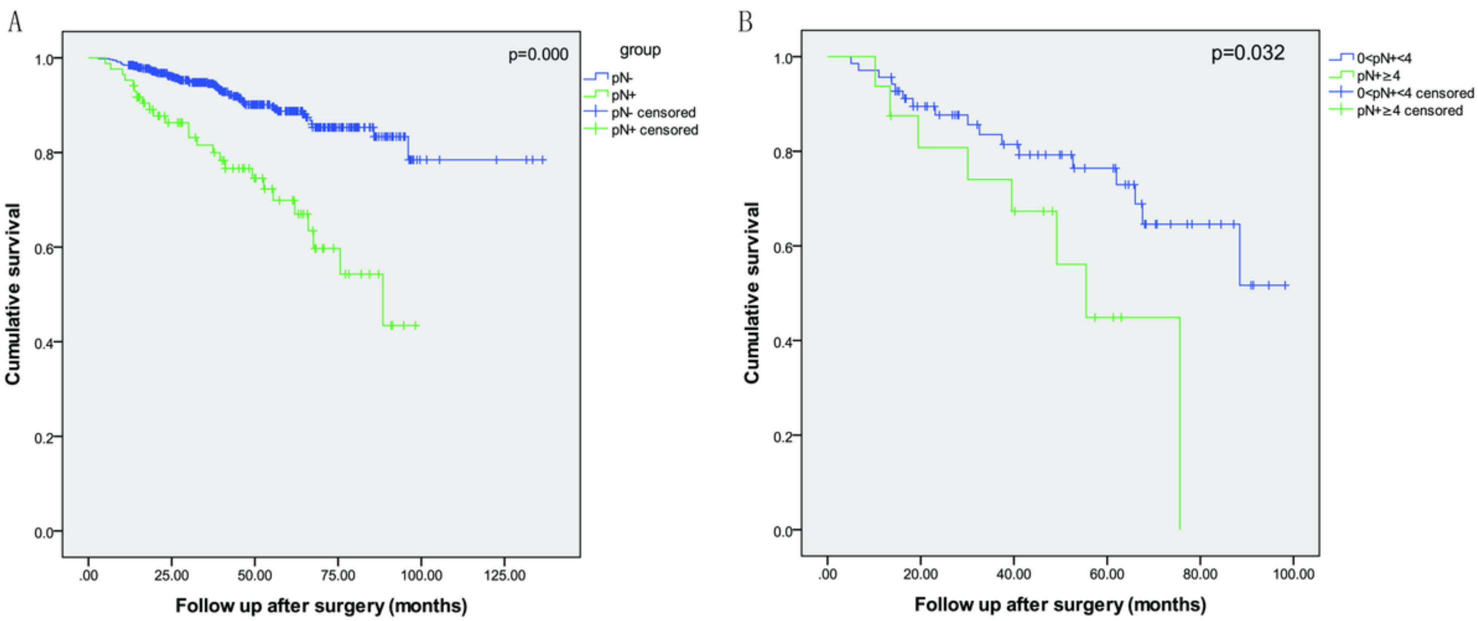

Figure 2

Kaplan−Meier overall survival curves based on the status of pathological nodal.

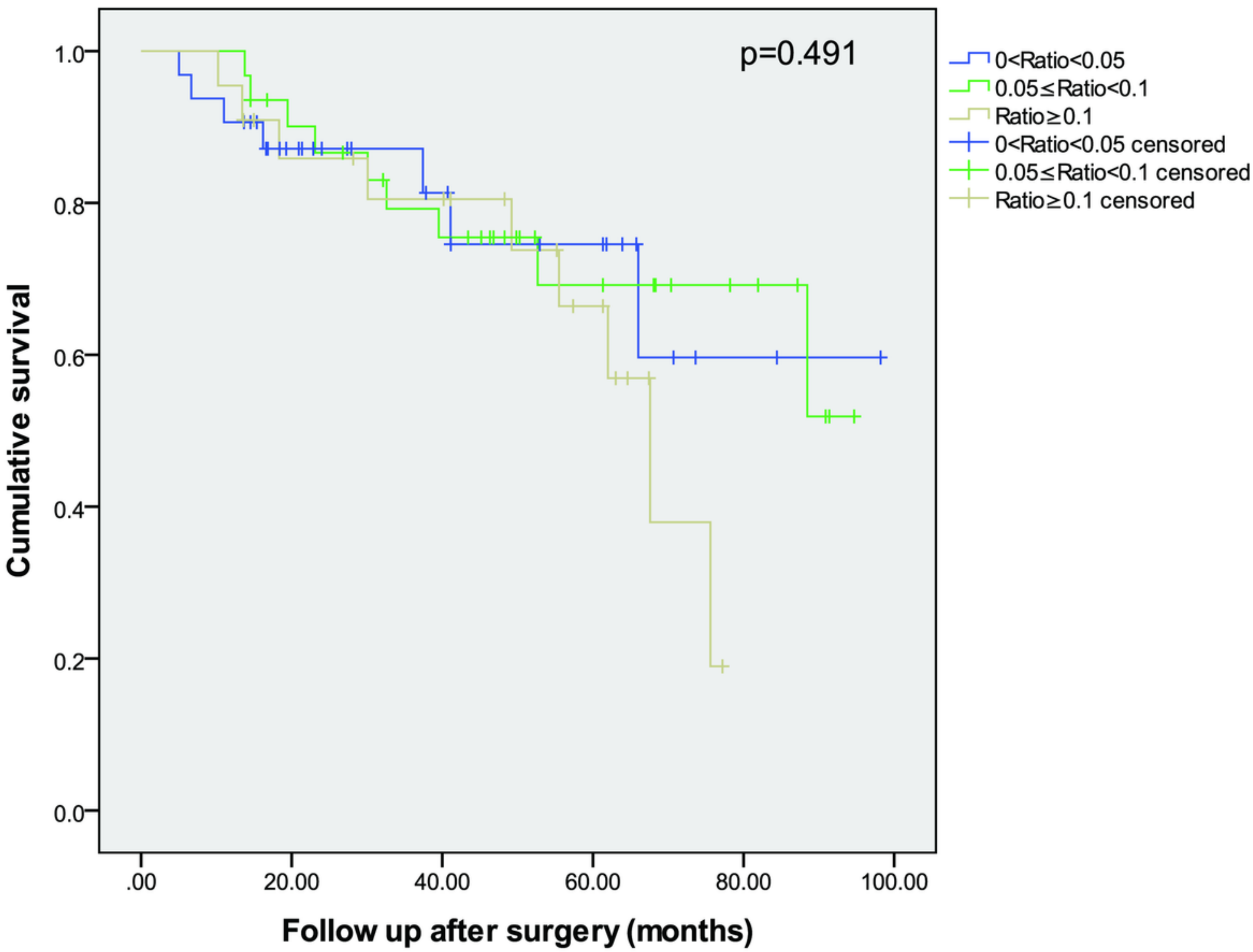

Figure 3

Kaplan−Meier overall survival curves based on LNR.