

# Neoadjuvant Chemoradiotherapy in Patients With Unresectable Locally Advanced Sigmoid Colon Cancer: Clinical Feasibility and Outcome

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## Research

**Keywords:** Sigmoid colon cancer, Neoadjuvant chemoradiotherapy, Down staging, Pathological complete response, Organ preservation

**Posted Date:** February 13th, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-200191/v1>

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# Abstract

**Background:** Patients with locally advanced sigmoid colon cancer (LASCC) have limited treatment options and a dismal prognosis with poor quality of life. This prospective study aimed to further evaluate the feasibility and efficacy of neoadjuvant chemoradiotherapy (NACRT) followed by surgery as treatment for select patients with unresectable LASCC.

**Methods:** We studied patients with unresectable LASCC who received NACRT between November 2010 and April 2019. The NACRT regimen consisted of intensity modulated radiotherapy (IMRT) of 50 Gy to the gross tumor and positive lymphoma nodes and 45 Gy to the clinical target volume. Capecitabine-based chemotherapy was administered every 3 weeks. Surgery was scheduled 6–8 weeks after radiotherapy.

**Results:** Seventy-two patients were enrolled in this study. Patients had a regular follow-up (median, 41.1 months; range, 8.3–116.5 months). Seventy-one patients completed NACRT, and sixty-five completed surgery. Resection with microscopically negative margins (R0 resection) was achieved in 64 patients (88.9%). Pathologic complete response was observed in 15 patients (23.1%), and multivisceral resection was necessary in 38 patients (58.3%). The cumulative probability of 3-year overall survival and disease-free survival were 75.8% and 70.7%, respectively.

**Conclusion:** For patients with unresectable LASCC, neoadjuvant chemoradiotherapy is feasible, surgery can be performed safely and may result in increased survival and organ preservation rates.

## Background

Colorectal cancer is the third most common malignancy and the third leading cause of cancer-related death worldwide [1]. Approximately 15% of patients present with locally advanced tumor (T4 stage), and if the tumor directly invades other organs or structures, multivisceral resection (MVR) is required [2]. Despite application of multiple treatment strategies, patients with locally advanced colon carcinoma (LACC) still have poor prognoses [3-7].

NACRT has been established as standard therapy for local advanced rectal cancer (LARC) [8] and may reduce local recurrence, but this has not been elucidated in colon cancer. Results of existing series studies of colon cancer show that neo-chemoradiotherapy can be beneficial for selected unresectable LACCs [9-14]. Our previous study[10] also proved that preoperative chemoradiotherapy and surgery can be performed safely and may result in an increased survival rate in patients with locally advanced sigmoid colon cancer (LASCC). In this study, we expand the sample size and prolong the follow-up time, and we described the treatment results of the adoption of neo-CRT for unresectable LASCC patients.

## Methods And Materials

### Patient selection

Patients with pathologically diagnosed and unresectable LASCC in our hospital between November 2010 and April 2019 were enrolled. This was an observational study approved by our institutional medical ethics committee (B2020-174-01). Patients with LASCC (defined as the primary tumor having an inferior margin >15 cm from the anal verge) were selected to undergo neoadjuvant chemoradiotherapy (NACRT) on a case-by-case basis through multidisciplinary team consultation. This study had the following inclusion criteria: 1) curative resection was impossible due to preoperative imaging examinations showing that the tumor extensively involved adjacent organs/structures or involved multiple lymph node metastases, making radical resection difficult to achieve; 2) curative resection was deemed impossible after exploratory laparotomy. Patients with the following criteria were excluded: 1) patients with uncontrolled medical conditions (e.g., hypertension, diabetes, heart failure, or psychiatric disease); 2) prior history of other malignancies. This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. Before treatment, written informed consent was obtained from all patients.

### **Treatment procedure details**

Radiotherapy (RT) was delivered using IMRT with 6 MV photon beams, and all plans were calculated using the Eclipse or Monaco system. Median radiation doses were 50 Gy (range: 45.0-54.0 Gy) for gross tumor volume (GTV) and positive lymph nodes and 45 Gy (46.0-56.0 Gy) for clinical target volume (CTV) with conventional segmentation. Gross tumor volume (GTV) was defined as the macroscopic tumor and involved regional lymph nodes shown on imaging studies and physical examination before treatment. CTV as defined as GTV with a cranio-caudal margin of 2–3 cm, sigmoid mesocolon and lymphatic drainage regions. If adjacent structures were involved, a further 1.5 cm isotropic margin into the involved structures and the ischiorectal fossa was included to account for microscopic disease and possible implantation metastases to the pelvic floor. Patients received capecitabine chemotherapy regimens during radiotherapy, and adjuvant chemotherapy consisted of a capecitabine-based regimen. Surgery was scheduled 6–8 weeks after RT. All imaging and blood tests were repeated before surgery. When tumor infiltration or adhesion to adjacent organs was detected intraoperatively, MVR was required.

### **Response, toxicity and complications**

Acute and late adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 4.03). Surgical complications were assessed according to the Clavien-Dindo classification [15].

### **Follow-up**

Outpatient follow-up visits were performed every 3 months during the first 2 years after treatment, semiannually in the subsequent 3 years, and then yearly thereafter. Patients were followed up by outpatient interview or telephone until death or through May 31, 2020.

### **Statistical analysis**

Statistical analysis was performed using Statistical Product and Service Solutions software for Windows (SPSS Inc., Version 25, Chicago, IL). Kaplan–Meier curves were used to calculate overall survival (OS), progression free survival (PFS), and local control (LC). PFS was defined as freedom of local, regional and distant failure from the date of diagnosis with biopsy confirmation to date of first documented relapse. Patients who were alive at last follow-up and progress free were censored. Primary end points were overall survival (OS) and progression-free survival (PFS). Secondary end points included tumor response grade (TRG) and the rate of R0.

## Results

### Characteristics and compliance

Between November 2010 and April 2019, a total of 72 patients were enrolled in this study. The mean age was 56 (range: 29-79) years old, and 75% (n=54) were males. According to the 8th edition of the Union for American Joint Cancer Committee (AJCC) TNM staging system, 9 patients were diagnosed with T3 stage, 5 with T4a and 58 with T4b disease. Three quarters of pathologic diagnoses were moderately differentiated adenocarcinoma. The most commonly involved organs were bladder (62.5%), abdominal/pelvic wall (25.0%), small intestine (12.5%) and ureter (11.1%). Among the 45 patients with bladder involvement, six were proved by cystoscopy and the rest by CT and/or MRI and irritation signs of the bladder (e.g. hematuria, urgent urination, frequent micturition, odynuria). Clinical and treatment characteristics of study patients are presented in Table 1.

### Short-term clinical efficacy

After NACRT, 65 patients with initially unresectable tumors were successfully transformed to operable, while tumors in 7 patients failed to reach this criterion. Among the 65 patients undergoing surgery, 64 (64/72, 88.89%) patients who received radical surgical resection with negative margins (R0), and one exhibited macroscopic residue (R2). Fifteen patents (23.1%) experienced pathological complete remission (pCR) after NACRT. Among the 45 patients with bladder invasion before treatment, only two received complete bladder excision, 21 received partial bladder excision, and 15 patients' bladders were completely preserved (the remains 7 patients abandoned surgery). Surgical results and pathological findings are detailed in Table 2.

Among the 65 patients who received surgery, 64 had R0 resection (64/72, 88.9%), and 15 (20.8%) achieved pathological complete remission after NACRT.

### Long-term survival

Median follow-up of surviving patients was 41.1 months (range, 8.3-116.5 months) in the entire group. The estimated 3-year OS, PFS, RFS and MFS were 75.8%, 70.7%, 89.0%, and 75.2%, respectively (Figure 2).

In univariate analysis, non-R0 resection, non-downstaging T, postsurgical pathology N stage (N1), postsurgical pathology N stage (T4a-T4b), low differentiation and perineurium invasion (PNI) were significantly associated with poorer OS, while non-R0 resection, no pathological complete remission (no-PCR), non-downstaging T, postsurgical pathology N stage (T4a-T4b) and PNI were associated with reduced PFS ( $p<0.05$ ) (Table 3). In multivariate analysis, differentiation remained an independent prognostic factor for overall survival rates (Figure 3A). Meanwhile, downstaging T was an independent prognostic factor for PFS (Figure 3B).

### **Treatment-related toxicity**

Treatment toxicities were assessed according to CTCAE criteria version 4.03 as shown in Table 4. The most common NACRT-related toxicities were grade 1 to 2 myelosuppression (88.9%), mucositis/dermatitis (97.2%) and gastrointestinal (GI) toxicities (93.1%). Four patients developed intestinal obstruction during NACRT. Only one patient failed to complete the radiation course due to tumor rupture and underwent emergency surgery. Among the 65 patients who underwent surgery, grade 3/4 Clavien-Dindo postsurgical complications were observed in 5 cases (7.7%).

## **Discussion**

Although NACRT is the standard treatment for local advanced rectal cancer, its place in the management of sigmoid colon cancer has yet to be defined. There are several single or very small sample size case reports about utilizing NACRT for sigmoid colon cancer [12, 16-18]. M Cukier et al [18] retrospectively reviewed 33 patients with potentially resectable, non-metastatic primary LACC who received neoadjuvant CRT, and all patients had R0 resection. The rates of pCR and 3-year OS were 3% and 85.9%, respectively. Our previous work [10] also revealed promising clinical outcomes and mild side effects in response to NACRT in LASCC, in which all 21 LASCC patients (100%) with locally unresectable disease attained resectable disease, including 14 patients (66.7%) who received a simple colectomy and 7 patients (22.2%) who were in need of MVR. The rates of pCR and 3-year OS were 38.1% and 95.2%, respectively.

MVR is the recommended surgical treatment for LACC [19]. Mohan et al [20] found MVR to be associated with the best chance of long term survival when clear margins are achieved, and R0 resection was the strongest factor associated with long-term survival when analyzing 22 studies comprising 1575 patients from 1995 to 2012. Therefore, whether LACC patients could be successfully transformed from unresectable to resectable status is crucial for the goal of cure. NACRT provides patients with unresectable LASCC a choice to improve resectability and survival. Ideal treatment results were also seen in our study in 65 patients (90.3%) who successfully transformed to resectable status, with R0 resection achieved in 64 patients (88.9%). After a median follow-up of 41.1 months, patients presented with an OS of 75.8%.

In our study, NACRT achieved satisfactory clinical outcomes. Sixty-five patients received surgical resection after NACRT. According to postoperative pathological results, 62 patients experienced downstaging, and the pCR rate was as high as 23.1%. T stage was down-graded in 54 patients (75.0%), and the

N stage was down-graded in 63 cases (87.5%). In fact, when followed up for a median period of 41.1 months, the 3-year OS and PFS were 75.8% and 70.7%, respectively, which is comparable to results recorded in the literature [9, 10, 21].

In addition to improving the prognosis, NACRT ameliorates organ preservation during surgery. The bladder and small intestine are the most commonly affected organs in LASCC, which are most commonly removed in MVR. In this study, 45 patients (62.5%) exhibited bladder invasion before treatment. Among the 65 patients receiving surgery, only 21 cases (32.3%) received partial cystectomy, while two received total cystectomy. Owing to NACRT, 36 patients (36/45, 80%) retained bladder function. Therefore, NACRT improved quality of life in these patients by preserving important organs.

Acute toxicities in response to NACRT were mild. Myelosuppression and radiodermatitis/mucositis were the most common adverse events. For myelosuppression, grade 1-2 incidence was 88.9%, and grade 3-4 was 11.1%. The incidences of grade 1-2 and grade 3-4 mucositis and dermatitis were 97.2% and 2.8%, respectively. Only two patients experienced grade 3-4 gastrointestinal reactions. Therefore, according to the results of this study, NACRT for LASCC is both safe and tolerable.

There are several limitations to this study. First, the sample size was small, and the median follow-up period of 41.1 months was rather short. Second, this study was non-randomized.

## Conclusions

NACRT is feasible in patients with unresectable LASCC, and surgery can be performed safely and may result in increased survival and organ preservation rates.

## Declarations

- Ethics approval and consent to participate This was an observational study was performed in accordance with the Declaration of Helsinki and approved by Sun Yat-sen University cancer center medical ethics committee (B2020-174-01). This study was approved by the Institutional Review Board of Sun Yat-sen University Cancer Center. Before treatment, written informed consent was obtained from all patients.
- Consent for publication: Not applicable, because our manuscript does not contain data from any individual person.
- Availability of data and material: The datasets analyzed during the current study available from the corresponding author on reasonable request.
- Competing interests The authors report no competing interests in this work.
- Funding This work was supported by the Grants from National Natural Science Foundation of China [81672987, 82073329] and Natural Science Foundation of Guangdong Province [2020A1515011286].

- Authors' contributions—Shao-Qing Niu, Rong-Zhen Li and Yan Yuan drafted the manuscript; Wei-Hao Xie, Qiao-Xuan Wang and Hui Chang performed the statistic analysis; Zhen-Hai Lu, Pei-Rong Ding, Li-Ren Li and Xiao-Jun Wu were members of the research group and participated in the treatment of patients and data collection; Zhi-Fan Zeng revised the draft; Wei-Wei Xiao and Yuan-Hong Gao conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.
- Acknowledgements—Not applicable.

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## Tables

**Table 1.** Baseline clinicopathologic characteristics of the 72 patients with unresectable sigmoid colon cancer (LASCC).

Characteristic	No. (%)
Age	
≤65	58(80.6)
>65	14(19.4)
Gender	
Male	54(75.0)
Female	18(25.0)
cT stage	
T3	9(12.5)
T4a	5(6.9)
T4b	58(80.6)
cN stage	
N0	1(1.4)
N1	25(34.7)
N2	46(63.9)
Clinical stage	
IIc	1(1.4)
IIIb	15(20.8)
IIIc	55(76.4)
IV	1(1.4)
Tumor differentiation	
High	15(20.8)
Moderate	54(75.0)
Low	3(4.2)
Involved organ	
Bladder	45(62.5)
Ureter	8(11.1)
Abdominal/Pelvic wall	18(25.0)
Small intestine	9(12.5)

CEA	
≤5 ng/ml	30/41.7%
>5 ng/ml	35/48.6%
unknown	7/9.7%
Bladder fistula/perforation	
Yes	14/19.4%
No	58/80.6%
Intestinal obstruction	
Yes	13/18.1%
No	59/81.9%
Family history	
Yes	12/16.7%
No	60/83.3%
MMR	
dMMR	6/8.3%
pMMR	40/55.6%
Unknown	26/36.1%
KPS	
≥90	58/80.6%
<90	14/19.4%

Abbreviations: KPS, Karnofsky Performance Status; BMI, Body Mass Index; cT stage, clinical T stage; cN stage, clinical N stage; MMR, mismatch repair phenotype.

**Table 2.** Treatment outcomes of surgeries and pathological findings in 72 surgical patients with LASCC.

	Outcomes	No. (%)
Surgery situation		
	R0	64 88.9
	R2	1 1.4
	Abandoned	7 9.7
pT stage		
	T0	10 13.9
	T1	2 2.8
	T2	7 9.7
	T3	26 36.1
	T4a	6 8.3
	T4b	14 19.4
pN stage		
	N0	62 86.1
	N1	3 4.2
	N2	0
Downstage T		
	yes	54 75.0
	no	11 15.3
Downstage N		
	yes	63 87.5
	no	2 2.8
Downstage		
	yes	62 95.4
	no	3 4.6
MVR		
	yes	38 58.5
	No	27 41.5
pCR		

	yes	15 (23.1%)
	No	50 (76.9%)
TRG		
	1	11 (25.6%)
	2	12 (27.9%)
	3	13 (30.2%)
	4	7 (16.3%)

Abbreviations: pT stage, postoperative pathology T stage; pN stage, postoperative pathology N stage; MVR, multivisceral resection; pCR, Pathologic complete remission; NA: not available; TRG: tumor regression grading.

Notes: \$ exploratory laparotomy;

\* Four patients who underwent exploratory laparotomy were included in this group.

**Table 3.** Univariate and multivariable Cox analysis of prognostic factors for overall survival and progression free survival in 72 patients with unresectable sigmoid colon cancer (LASCC) treated with neoadjuvant chemoradiotherapy and surgery.

	<i>p</i>	HR (95%CI)	<i>p</i>	HR (95%CI)
overall survival variable				
R0 resection R0 vs No-R0	<0.001	0.2920.184-0.465	0.973	0.9370.020-42.855
pCR pCR vs No pCR	0.172	2.3420.690-7.946	0.339	0.1940.007-5.597
Down T stage Yes vs No	0.044	3.0311.033-8.894	0.426	2.0210.358-11.419
pN Stage group (pN0 vs pN1)	0.037	5.2341.105-24.800	0.601	2.8450.057-142.977
pT Stage group (pT0-T3 vs pT4a-4b)	0.023	2.6781.144-6.272	0.634	0.6590.118-3.664
Differentiation	0.001	0.0620.012-0.319	0.003	36.4433.500-379.429
PNYes vs No	0.011	4.1381.377-12.435	0.875	1.2050.119-12.166
	<i>p</i>	HR (95%CI)	<i>p</i>	HR (95%CI)
progress free survival variable				
R0 resection R0 vs No-R0	<0.001	0.3430.219-0.538	0.232	0.0910.002-4.629
pCR Yes vs No	0.035	3.6970.865-15.806	0.991	497046.0930.000-
Down T stage	0.006	4.1091.490-11.333	0.027	6.0951.228-30.253
pT Stage group (pT0-T3 vs pT4a-4b)	0.0101	2.9881.293-6.907	0.797	0.8180.177-3.786
Differentiation	0.111	2.2920.827-6.356	0.130	4.2460.653-27.599
PNYes vs No	0.015	3.8831.300-11.597	0.251	3.1080.448-21.581

**Table 4.** NACRT toxicities and surgical complications in the 72 patients with unresectable sigmoid colon cancer (LASCC).

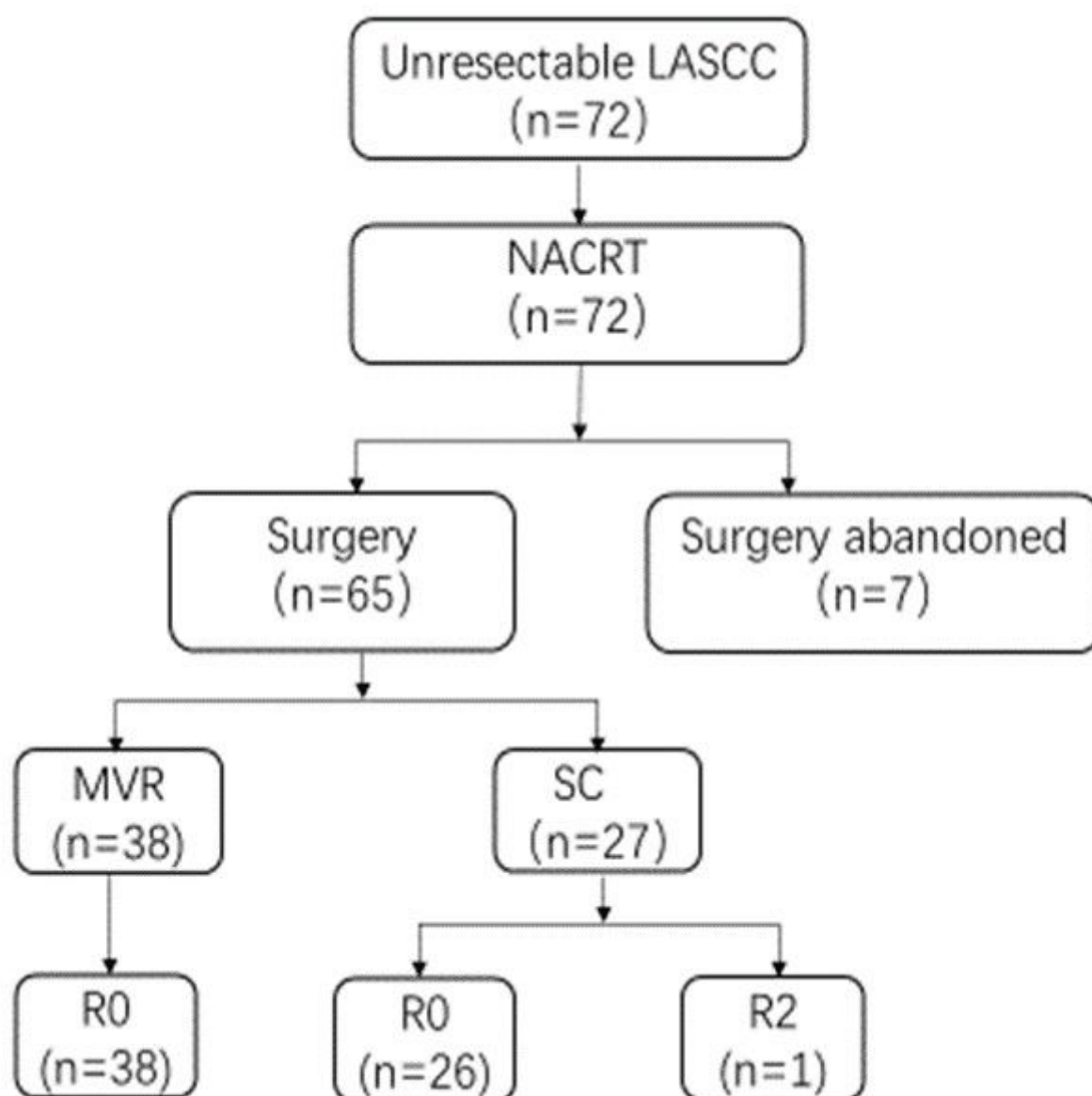
Adverse effects	No. (%)
Myelosuppression	
grade 0–2	64 (88.9)
grade 3–4	8 (11.1)
Mucositis/dermatitis	
grade 0–2	70 (97.2)
grade 3–4	2 (2.8)
GI toxicities	
grade 0–2	67 (93.1)
grade 3–4	5 (6.9)
Intestinal obstruction	
yes	4 (5.6)
no	68 (94.4)
Anastomotic leakage	
yes	9 (12.5)
no	63 (87.5)
Nonresectable surgery #	7

Abbreviations: GI, gastrointestinal.

Notes: # Including 7 cases who abandoned surgery.

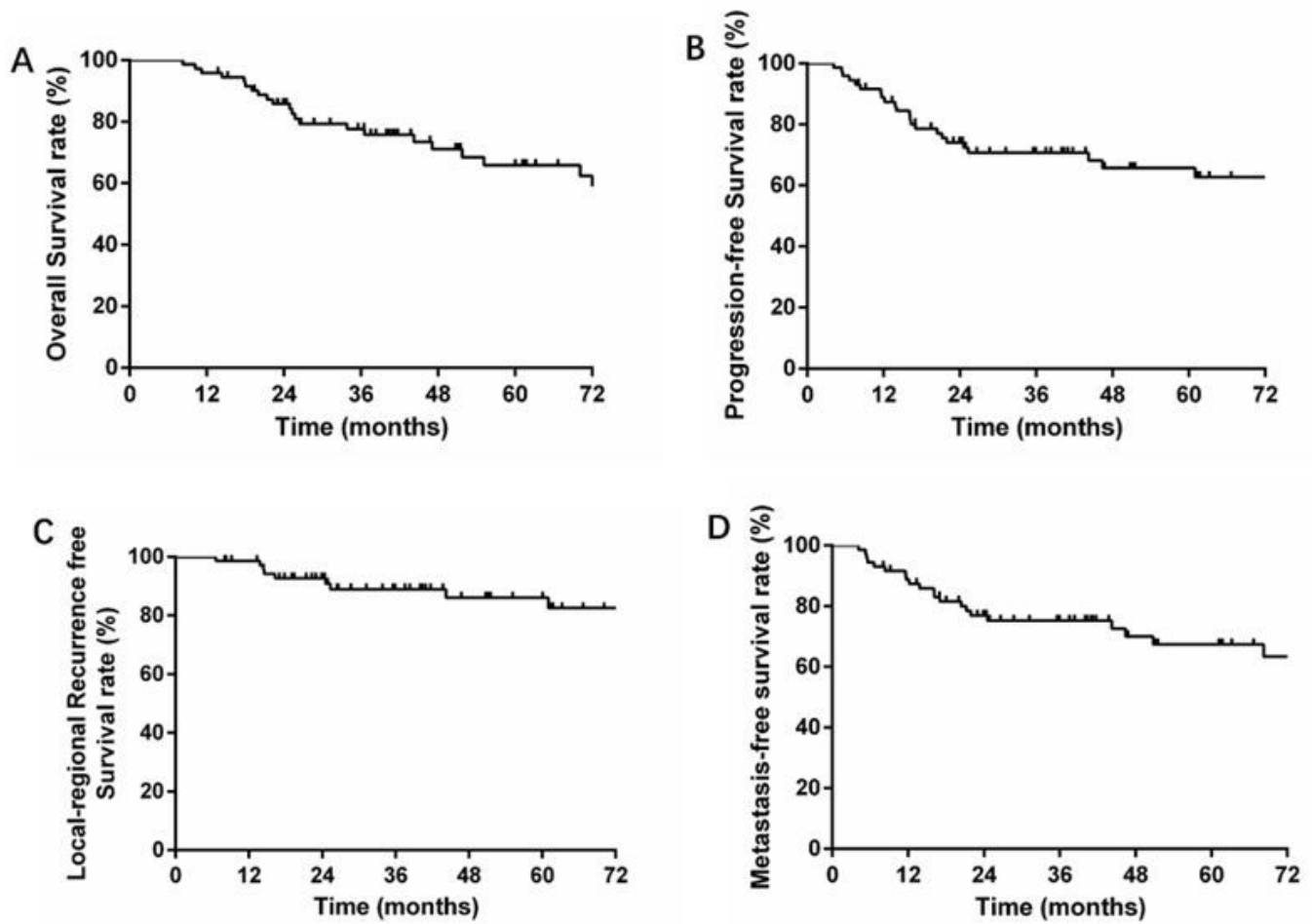
Figures





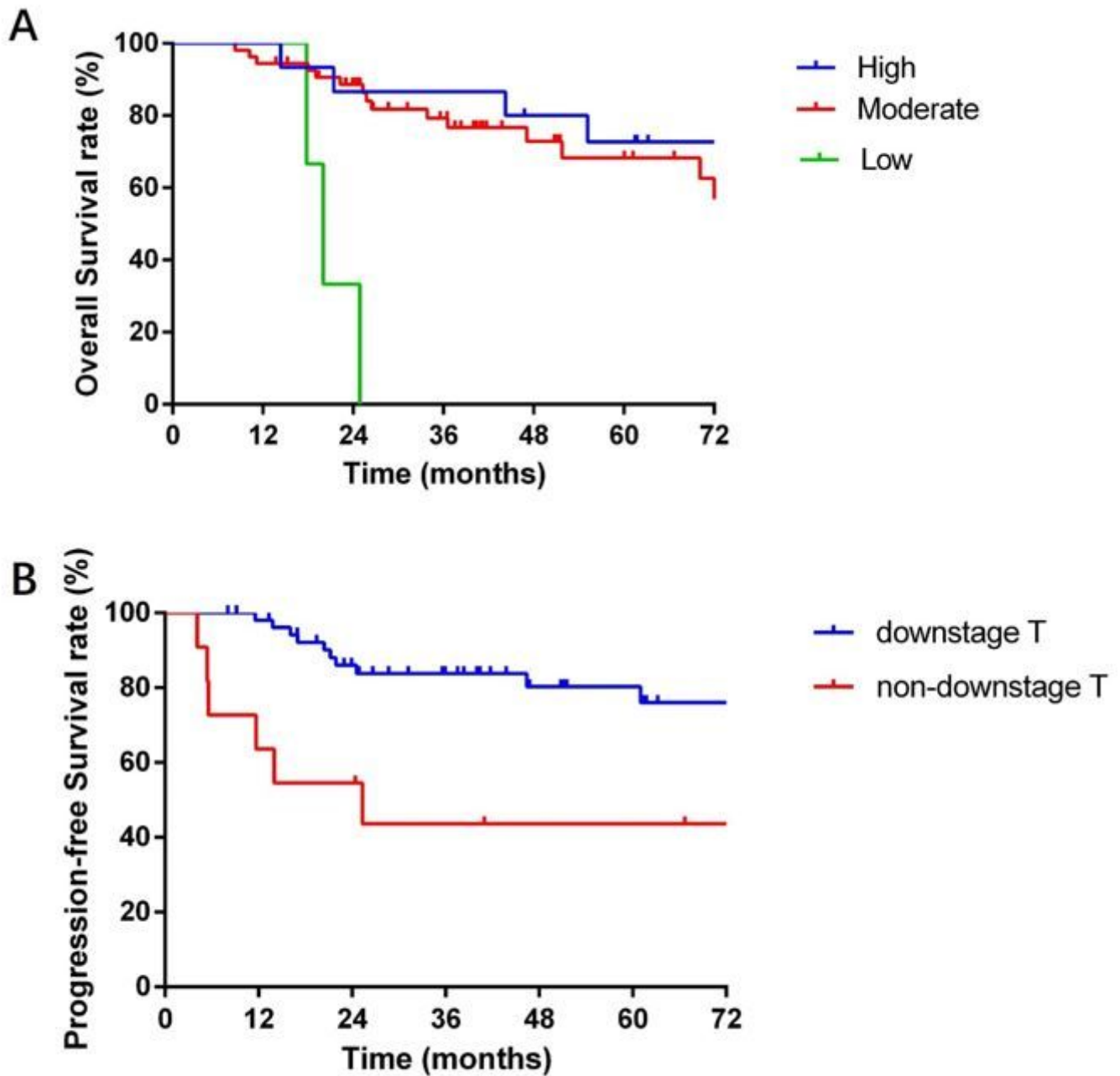
**Figure 1**

Treatment flow chart.



**Figure 2**

Survival curves. Overall survival (A) Progression-free survival. (B) Local-regional recurrence-free survival. (C) Metastasis-free survival. (D) Survival curves of the 72 patients with unresectable LASCC.



**Figure 3**

Subgroup analysis of survival. Overall survival by tumor differentiation (A) ( $p=0.003$ ) and progression-free survival by downstaging T (B) ( $p=0.027$ ) in patients with unresectable LASCc with neoadjuvant chemoradiotherapy and surgery.