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Original Article

A new LNR surgical staging system in non HIV-related cervical tuberculosis lymphadenitis

Zhi Wang[1], Jincheng Liu[1], Qiliang Chen[1], Qianhong Wu[2], Junxiao Li[1]

Departments of [1]Surgery, [2]Internal Medicine, Shaanxi Tuberculosis Hospital, Xi'an, China

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Abstract: The objective of this study was to propose a new simple and reproducible staging system for assessing prognosis and preventing potential complications. Patients (n=167) diagnosed with cervical tuberculosis lymphadenitis and had undergone surgical treatment from November 2012 - June 2015 in the Shaanxi Tuberculosis Hospital were included as participants. Risk factors were identified using a logistic regression model. The proposed staging system was designed by integrating a variety of identified risk factors. The results showed that lesion size, lymph node involvement areas and multi-drug resistance were identified as independent risk factors of surgical prognosis. The following is a summary of the LNR surgical staging system: The system was based on lesion (L), node (N) and multi-drug resistance (R). The lesion size < 3 cm was defined as L_1 and the lesion size ≥ 3 cm was defined as L_2. lymph node involvement < 2 areas was defined as N_1 while the rest was defined as N_2. Multidrug-resistance negative was defined as R_0 while the rest was defined as R_1. Stage I: $L_1N_1R_0$, $L_1N_2R_0$. Stage II: $L_2N_1R_0$, $L_2N_2R_0$, $L_1N_1R_1$, $L_1N_2R_1$. Stage III: $L_2N_1R_1$, $L_2N_2R_1$. A significant difference among stages in complications was found by χ^2 test. In conclusion, lesion size, nodal involvement level and multi-drug resistance are risk factors to postoperative complications in CTL patients, which could be the elements of a new staging system. The LNR surgical staging system is a simple and reproducible method for screening high-risk patients for surgical prognosis and selecting suitable treatments.

Keywords: Cervical tuberculosis lymphadenitis, risk factors, staging system, complications, surgical prognosis, LNR

Introduction

Cervical tuberculous lymphadenitis (CTL) is one of the most common sites of extrapulmonary tuberculosis [1]. Research shows that CTL accounts for 60-90% of all extrapulmonary tuberculosis cases [2]. CTL remains both a diagnostic and therapeutic challenge because it mimics other pathologic characteristics and has inconsistent physical and laboratory findings.

Surgery plays an important role in the diagnosis and treatment stage of CTL [3]. A diagnostic surgery contributes to a bacteriologic and pathological confirmation when other scientific examinations cannot make a clear diagnosis. A therapeutic surgery is sufficient in the presence of a cold abscess, an inexhaustible fistula, lymphadenitis with atypical mycobacterium, and a large and calcified lymph-node mass for which medical treatment will not be sufficient. Secondary surgery is alsoan effective supplement in the event of a failure in medical treatment or in the case of residual adenopathy at the end of a full course medical treatment.

However, the prognosis and postoperative complications of CTL is unsatisfactory, because they significantly increase inpatient time and trauma. Staging system has played an important role in predicting prognosis and planning personalized treatment for cancer and other diseases. In the present study, we aimed to propose a new simple and reproducible staging system for assessing prognosis and preventing potential complications.

Participants and methods

Participants

Clinical data from 167 consecutive patients treated at the Shaanxi Tuberculosis Hospital Department of Surgery have been recorded ret-

Table 1. Medical records of 167 patients before surgery

Medical records	Numbers	(%)
Age (years)		
14~39	117	71.3
≥ 40	47	28.7
Gender		
Male	86	52.4
Female	78	47.6
BMI		
< 24 Kg/m^2	106	64.6
≥ 24 Kg/m^2	58	35.4
Lesion size		
< 3 cm	56	34.1
≥ 3 cm	108	65.9
Nodal involvement level		
I	6	3.7
II	46	28
III	65	39.6
IV	83	50.6
V	99	60.3
VI	7	4.3
VII	3	1.8 56 34.1
1 level	89	54.2
≥ 2 levels	75	45.7
MDR		
(+)	11	6.7
(-)	153	93.3
Diabetes		
(+)	6	3.7
(-)	158	96.3

Table 2. The surgical prognosis in 167 patients with CTL

Complications	Numbers	(%)
Subcutaneous abscess formation	17	9.2
Major vascular injury	4	2.3
Chylous fistula	1	0.6
Neck disorders	5	2.9
Recurrence	9	5.2
Total	36	20.2

rospectively in a computerized database between December 1, 2012 and June 31, 2015 (**Table 1**). All patients were bacteriologically or histologically diagnosed as CTL and met one of the following surgical indications: i) Lymph nodes did not shrink or expand after 3 to 4 weeks of anti-tuberculosis chemotherapy; ii) Skin ulcers or sinuses had formed; iii) Patient complained about significant compression symptoms; iv) Multi-drug resistance was detected; v) No contraindication for patient was identified; vi) No HIV infection and immunodeficiency disorder cases were detected in the patients. There were 90 men and 77 women recruited, with a median age of 28.9 years and a range between 14-76 years.

Risk factors

The following 7 factors were found to be associated with postoperative complications and prognosis: age, gender, body mass index (BMI), size of the lesions, nodal involvement level, complication of diabetes and the presence of multi-drug resistance (MDR). Each factor was divided into two categories in order to determine the significance of risk. Age was divided into a youth group (14~39 years old) and an elderly group (40 years or older). BMI was divided into BMI < 23 kg/m^2 (low and average group) and ≥ 23 kg/m^2 (overweight and obese group) according to the WHO Asia standard [4]. Lesion size was divided into < 3 cm group and ≥ 3 cm group. The largest cross-sectional diameter on the CT scan was recorded to evaluate lesion size. Affected lymph node level was divided into 1 level and ≥ 2 levels, determined by CT scans and ultrasound before and during operation. MDR status was divided according to the WHO standards, that is, at least both resistant to isoniazid and rifampicin (refer to other paper, I addressed the same thing). The surgical staging system was designed on the basis of integrating identified risk factors and validated through retrospection of patients.

Treatment protocol

At least 3-4 weeks of anti-tuberculosis treatment was administrated before surgery. Large subcutaneous abscess and ulcer was treated by either decompression or incision drainage. Patients underwent focal cleaning or selective neck dissection according to the involvement of lymph node level. Anti-tuberculosis protocol was adjusted according to the result of first and second line drug susceptibility tests. The follow-up period ranged from 15 to 40 months with a median of 33 months. The study protocol was approved by the ethical committee of Shaanxi Tuberculosis Hospital.

Table 3. Univiarate logistic regression analysis of preoperative medical records and the incidence of postoperative complications

Medical records	Complications rate	*P* value	OR	(95% CI)
Age (Years)		0.479	1.137	(0.451-2.886)
14~39	24/117			
≥ 40	11/47			
Gender		0.292	1.447	(0.697-3.642)
Male	21/86			
Female	14/78			
BMI		0.867	1.022	(0.379-2.712)
< 24 Kg/m^2	26/106			
≥ 24 Kg/m^2	9/58			
Lesion size		0.014	2.723	(1.221-6.075)
< 3 cm	12/56			
≥ 3 cm	23/108			
Nodal involvement level		0.005	3.289	(1.477-7.528)
1 level	11/89			
≥ 2 levels	24/75			
MDR		0.001	7.920	(2.083-30.109)
(+)	9/11			
(-)	26/159			
Diabetes		0.271	2.896	(0.511-17.749)
(+)	2/6			
(-)	33/158			

P < 0.05 was considered statically significant. OR: Odds ratio. CI: confidence interval.

Complications defined

Prognoses were composed of early complications and recurrence. Early complications were defined as complications during surgery or within 30 days of surgery, including traumatic complications and infectious complications. Traumatic complications were composed of major vascular injury, chyle leakage and affected neck-side disorders. Major vascular injury was defined as injury to internal jugular, subclavian vein or carotid artery. Chyle leakage was attributed to the injury of the thoracic duct or the right lymphatic duct. Affected neck disorders were caused by the injury of the accessory nerve, laryngeal recurrent nerve and facial nerve. Infectious complications were subcutaneous abscess or ulcer formation, culture positive in exudate for tuberculosis, and incision rupture, which requires secondary debridement and suturing. Various complications that occurred in one patient were recorded only once. The recurrence of all patients during the follow-up was also recorded.

Statistical analysis

Univariate and multivariate logistic regression models were carried out to identify the risk factors of postoperative complications. The staging system was designed using χ^2 test to determine their capacity to stratify CTL. Data was collated and filtered using Excel (Microsoft, Redmond, Washington), and the statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Illinois). $P < 0.05$ was considered statistically significant.

Results

Risk factors identified

Early complications and recurrence were listed in **Table 2**. A total of 27 (16.2%) patients experienced early complications while 9 patients experienced reoccurring complications during a follow-up. Univariate analysis showed that lesion size was significantly related to surgical prognosis (OR=2.723; 95% CI=1.221-6.075; P=0.014). Affected lymph node level was also identified as a potential independent risk factor to surgical prognosis (OR=3.289; 95% CI=1.477-7.528; P=0.005). MDR was most significantly related to surgical prognosis (OR=7.920; 95% CI=2.083-30.109; P=0.001) (**Table 3**). We used multivariate logistic analysis to identify independent risk factors for CTL patients. Among all the potential risk factors such as age, gender, body mass index (BMI), the size of the lesions, nodal involvement level, complication of diabetes and the presence of MDR, we found lesion size ≥ 3 cm was an independent risk factor for surgical prognosis (OR=2.761; 95% CI=1.123-7.331; P=0.034). Affected lymph node level ≥ 2 groups was also a risk factor to surgical prognosis (OR=3.315; 95% CI=1.185-7.001; P=0.019). The presence of the MDR was risk factor to surgical prog-

Table 4. Multivariate logistic regression analysis of preoperative medical records and theincidence of postoperative complications

Medical records	*P* value	OR	(95% CI)
Age ≥ 40 years	0.693	1.211	(0.468-3.031)
Male	0.278	1.706	(0.674-4.613)
BMI ≥ 23 Kg/m^2	0.580	0.741	(0.243-2.018)
Lesion ≥ 3 cm	0.028	2.761	(1.119-7.299)
Nodal involvement ≥ 2 levels	0.019	3.315	(1.136-8.199)
MDR (+)	0.0002	9.959	(2.168-45.753)
Diabetes (+)	0.989	0.985	(0.124-7.820)

P < 0.05 was considered statically significant. OR: Odds ratio. CI: confidence interval.

Table 5. The core of LNR surgical staging system for CTL patients

Stage classification	L	N	R
Stage I	L1	N1-2	R0
Stage II	L2	N1-2	R0
	L1	N1-2	R1
Stage III	L2	N1-2	R1

Table 6. χ^2 test of all 167 patients on postoperative complications among different Stages

Stage	Numbers (n)	Complications (n)		χ^2	*P* value
		Occurred	Not occurred		
Stage I	99	12	87	9.348	0.006
Stage II	61	15	46		
Stage III	7	4	3		
Total	167	31	136		

P < 0.05 was considered statically significant.

nosis (OR=10.108; 95% CI=2.083-30.109; P= 0.0002) as well (**Table 4**).

Surgical staging system

According to the independent risk factors identified, the lesion size (L), lymph node involvement area (N) and multi-drug resistant (R) were chosen as the core of the system, thus named as the LNR surgical staging system. The lesion size < 3 cm was defined as L_1 while the lesion size ≥ 3 cm was defined as L_2. Lymph node involvement < 2 levels was defined as N_1, while the rest was define as N_2. Multidrug-resistant negative was defined as R_0, while the rest was defined as R_1. Stage I: $L_1N_1R_0$, $L_1N_2R_0$. Stage II: $L_2N_{1\text{-}2}R_0$, $L_2N_{1\text{-}2}R_0$, $L_1N_1R_1$. Stage III: $L_2N_2R_1$ (**Table 5**). On χ^2 test, discrimination was offered among stages in surgical prognosis (P=0.006, **Table 6**).

Discussion

Surgery on cervical lymph nodes have higher incidence of postoperative complications and unsatisfactory prognosis [5-7]. Identifying and controlling the risk factor before the operation may provide more information for appropriate and effective treatment. However, estimating the risk of surgical prognosis in an individual patient is challenging because of limited research and absent standard.

Some researchers have tried to predict the risk of developing complications during or after surgery. Mahmoud *et al*. reported that BMI, comorbidity status, preoperative white blood cell count, preoperative hematocrit, planned neck dissection, and planned tracheotomy have higher predictive value to major complication after surgery for oral cavity squamous cell carcinoma [8]. Other researchers reported that Level IIB nodes could be omitted when performing neck dissection as it provides significant decrease in spinal accessory nerve trauma-related complications [9].

The staging system is often used to predict postoperative complications and plan personalized treatment. In many diseases, a staging system is widely used to predict prognosis and complications [10-12]. However, to this day there is still no widely accepted or adopted surgical staging system for patients with CTL.

To design the staging system, the first step of this study was to determine the risk factors that significantly influence surgical prognosis following surgery. It was reported that the size of lymph node in CTL cases was associated with the role of surgery [13]. In CTL patients, lymph nodes often merged or formed cold abscess so that it is hard to calculate the involved lymph node numbers accurately. Therefore, we calculated the affected cervical lymph nodes level to analyze its correlation to surgical prognosis. Many studies have confirmed the problem of poor prognosis for MDR patients [14-16]. Our

results showed significant correlation between MDR and surgical prognosis, particularly in recurrence (6 cases). From univariate and multivariate logistic regression, we identified the lesion size, lymph node involvement level and MDR as independent risk factors.

The second step of this study was to design a surgical staging system. LNR stage I patients were defined as those with a lesion size of < 3 cm and were MDR negative. The postoperative complication and reoccurrence in this stage were 12.1%, which is the lowest among all stages. LNR stage II was defined as patients who lesion size ≥ 3 cm, MDR positive and lesion size < 3 cm and were MDR negative. In this stage, postoperative complication and reoccurrence were up to 24.6%, which were more than 2 times than stage I. Stage III patients had a lesion size ≥ 3 cm and were MDR positive. The highest complication rate, up to 57.1% occurred is in this stage. 5 recurrence patients were in this stage altogether. The result showed that surgery alone lead to unfavorable clinical outcome for LNR Stage III CTL patients. This result suggests that surgery alone may not be a suitable treatment for Stage III CTL patients. Multimodality therapy and a longer preoperational chemotherapy may be required for MDR-CTL patients.

In our study, when the proposed surgical staging system was validated back to patients, the significant differences were confirmed by statistic analysis. The LNR surgical staging system offered discrimination among 3 different stages. Therefore, we believe it could be used in surgical clinical practice and trial design.

HIV-infection was not detected in our research. We will increase the sample size and research centers to verify the association between HIV-infection and surgical prognosis in CTL.

In conclusion, we have found that lesion size, nodal involvement level and MDR are major risk factors associated to surgical prognosis in CTL patients. The LNR surgical staging system is based on these factors. It is a simple and reproducible method for screening high-risk patients for surgical prognosis and selecting personalized treatment.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhi Wang, Departments of Surgery, Shaanxi Tuberculosis Hospital, Taiyigong, Xi'an, China. Tel: 86-029-85899082; Fax: 86-029-85899987; E-mail: wanngzhi@hotmail.com

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