RESEARCH ARTICLE

Comparative Effectiveness of Risk-adapted Surveillance *vs* Retroperitoneal Lymph Node Dissection in Clinical Stage I Nonseminomatous Germ Cell Testicular Cancer: A Retrospective Follow-up Study of 81 Patients

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Abstract

Purpose: To retrospective assess the potential predictors for relapse and create an effective clinical mode for surveillance after orchidectomy in clinical stage I non-seminomatous germ cell testicular tumors (CSI-NSGCTs). Materials and Methods: We analyzed data for CSI-NSGCTs patients with non-lymphatic vascular invasion, %ECa < 50% (percentage of embryonal carcinoma < 50%), and negative or declining tumor markers to their half-life following orchidectomy (defined as low-risk patients); these patients were recruited from four Chinese centers between January 1999 and October 2013. Patients were divided into active surveillance group and retroperitoneal lymph node dissection (RPLND) group according to different therapeutic methods after radical orchidectomy was performed. The disease-free survival rates (DFSR) and overall survival rates (OSR) of the two groups were compared by Kaplan-Meier analysis. Results: A total of 121 patients with CSI-NSGCT were collected from four centers, and 81 low-risk patients, including 54 with active surveillance and 27 with RPLND, were enrolled at last. The median follow-up duration was 66.2 (range 6-164) months in the RPLND group and 65.9 (range 8-179) months in the surveillance group. OSR was 100% in active surveillance and RPLND groups, and DFSR was 89.8% and 87.0%, respectively. No significant difference was observed between these two groups (X_2=0.108, *P*=0.743). No significant difference was observed between the patients with a low percentage of embryonal carcinoma (<50%) and those without embryonal carcinoma (87.0% and 91.9%, X_2=0.154, *P*=0.645). No treatment-related complications were observed in the active surveillance group whereas minor and major complications were observed in 13.0% and 26.1% of the RPLND group, respectively. Conclusions: Active surveillance resulted in similar DFSR and OSR compared with RPLND in our trial. Patients with low-risk CSI-NSGCTs could benefit from risk-adapted surveillance after these patients were subjected to radical orchidectomy.

Keywords: Non-seminomatous germ cell testicular cancer - surveillance; retroperitoneal lymph node dissection

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Introduction

Testicular non-seminomatous germ cell tumors (NSGCTs) is a relatively rare cancer type in young men between ages 25 and 39 years (Fossa et al., 2011). An estimated 1/105 diagnoses of testicular cancer was reported in China in 2012, that accounts for about 0.42% of male cancers and mainly affects younger men in the second or third decade of life (Hao et al., 2012). As such, a suitable treatment regimen based on relative risk factors of relapse should be established for patients with NSGCTs (Albers et al., 2011). Retroperitoneal lymph node dissection (RPLND), active surveillance, and primary chemotherapy are available for CSI-NSGCTs patients; RPLND has been suggested as a gold standard method for NSGCTs because of its excellent cure rate. However, some reports have indicated that 67% of low-risk NSGCTs are overtreated because of negative pathological results of retroperitoneal lymph node in 73% to 75% of patients (Roeleveld et al., 2001). A series of institutional reports and guidelines have also been recommended; however, options for CSI-NSGCTs were often misunderstood or misapplied, with active surveillance particularly underutilized (Nichols et al., 2013).

This study aimed to investigate predictors and to create clearly defined and easy-to-use clinical mode for effective

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surveillance following orchidectomy of CS-I NSGCTs.

Materials and Methods

Patients

We retrospectively analyzed an initial study group that included 121 patients who underwent radical orchidectomy for CSI-NSGCT at the Affiliated Cancer Hospital of Xiangya Medical College (between January 1999 and October 2013), the Second Xiangya Hospital (between January 2001 and December 2012), the Third Xiangya Hospital (between January 2001 and December 2012), and Hunan Provincial People's Hospital (between January 2004 and December 2012). The patients were divided into surveillance group and RPLND group according to different therapeutic methods after these patients underwent radical orchidectomy.

Data collection

Clinical and pathological data were retrospectively obtained from the electronic medical records system of the participating centers. These data were encoded in an information collection table.

To be included in the CSI-NSGCT group, all the patients should be diagnosed and confirmed by radiology and pathology; the clinical and pathological stages were determined based on these available data according to the 2009 UICC TNM classification (Sobin et al., 2011).

The candidates, who met all of the following criteria: non-lymphatic vascular invasion (non-LVI), percentage of embryonal carcinoma is <50% (%ECa <50%), and negative or declining tumor markers (AFP: a-fetoprotein; hCG: human chorionic gonadotropin) to their half-life following orchidectomy, were defined as low-risk NSGCT patients and enrolled in our study. The candidates who did not meet the criteria were excluded for high-risk NSGCT.

Procedure

Radical orchidectomy was initially performed. Surveillance or RPLND pros and cons were recommended before subsequent treatments were administered. RPLND was performed by using an open approach or by a laparoscopic approach. Active surveillance was supervised according to the follow-up schedules that were without any therapeutic measures after orchidectomy (neither RPLND nor chemotherapy). Follow-up procedures included physical examination, blood tests for tumor markers, chest X-ray, and abdominopelvic CT or B ultrasound. The detailed schedules are described in Table 1.

Study endpoint and statistical analyses

We clinically assessed several parameters, including disease-free survival rates (DFSR) and overall survival rates (OSR), to determine efficacy. The primary endpoint is disease-free survival defined as the time from post-operation to the first confirmation of disease recurrence or death due to any cause, whichever occurred first.

We used survival analysis methods, including Kaplan-Meier method and log-rank tests, to compare disease-free survival and overall survival between the two treatment groups. The occurrence of relapse was compared between different groups using the χ^2 test. P values were two-sided, and statistical significance was set at 0.05. All statistical analyses were conducted with Review Manager version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results

Patients

A total of 121 patients with low-risk CSI-NSGCT coming from four centers in Hunan (China) between January 1999 and October 2013 were enrolled in our retrospective study. Approximately 49.4% of men were diagnosed between the ages of 20-29 years and 28.4% were diagnosed between the ages of 30-44 years (figure 1). Out of 81 patients, 54 (66.7%) underwent surveillance after radical orchidectomy, and 27 patients (33.3%) elected RPLND. The baseline demographic and clinical characteristics of all the patients are summarized in table

Table 1. Follow-up Schedules for Surveillance and after Retroperitoneal Lymph Node Dissection

Procedure	Year 1	Year 2	≥Year 3
Follow-up schedules for surveillance			
Physical examination	4 times	4 times	Biannual
Tumor markers	4 times	4 times	Biannual
Chest X-ray	3 times	Twice	
Abdominopelvic CT/B ultrasound	3 times	Twice	
Follow-up schedules for RPLND			
Physical examination	4 times	4 times	Biannual
Tumor markers	4 times	4 times	Biannual
Chest X-ray	Twice	Twice	
Abdominopelvic CT/B ultrasound	Once	Once	

CT=computed tomography scan; RPLND = retroperitoneal lymph node dissection

Table 2. Baseline Demographic and Clinical Characteristics

	Surveillance (n=54)	RPLND (n=27)
Age (yr)		
Median (range)	22.3 (1.5-64)	27.2(16~37)
Tumor Location		
Left/Right	23/31	11/16/14
Duration (month)		
0-3	25	14
4-6	16	8
>6	13	5
Pre-orchidectomy tumor markers		
Abnormal	21	12
Histology of primary lesion		
Teratoma	18	6
Yolk sac tumor	17	8
Mixed tumors with ECa (%ECa<50%)	12	11
Mixed tumors without ECa	7	2
Follow-up (month)		
Median (range)	66.2 (6-164)	65.9 (8-179)
Follow-up rate		
Overall percentage(%)	90.7	85.2

*RPLND = Retroperitoneal lymph node dissection; %ECa = Percentage of embryonal carcinoma

Table 3. Patients Experiencing Tumor Relapse

Patient		Age(yr)	Pathology	Metastasis site	Time to relapse (M)	Salvage treatment	Result
Surveillance Group	1	25	Seminoma + %ECa<50%	RLN	8	RPLND+BEP	Cured
	2	46	Teratoma	RLN	2	RPLND+BEP	Cured
	3	23	Yolk sac + %ECa<50%	RLN, lung	5	BVP	Cured
	4	22	Teratoma	RLN	5	BEP	Cured
	5	36	Yolk sac + Teratoma	RLN	8	RPLND+BEP	Cured
RPLND Group	1	30	Seminoma + %ECa<50%	RLN	2	BEP	Cured
	2	27	Yolk sac	Lung	11	BEP	Cured
	3	31	Teratoma	RLN	10	BEP	Cured

*RLN = retroperitoneal lymph node; RPLND = retroperitoneal lymph node dissection; BEP = bleomycin+etoposide+cisplatin; BVP = bleomycin+vincristine+cisplatin; %ECa = percentage of embryonal carcinoma

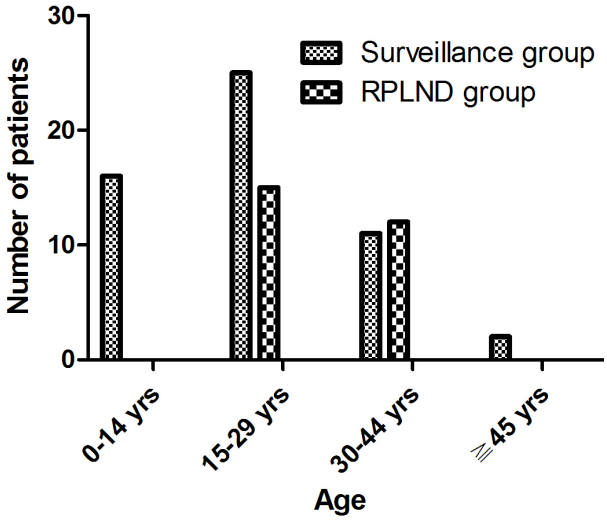

Figure 1. Age Distribution of the Four Cohorts Of Patients (RPLND, Retroperitoneal Lymph Node Dissection)

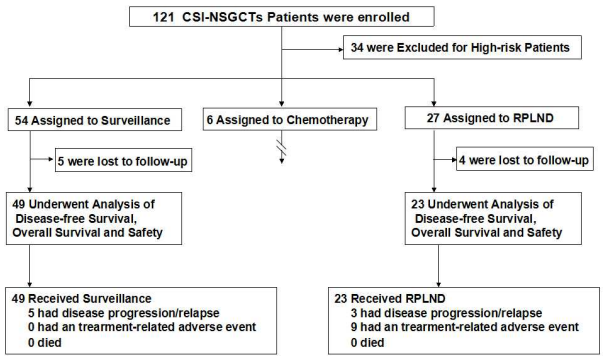

Figure 2. Patient Enrollment and Outcomes (CS I, clinical stage I; NSGCTs, non-seminomatous germ cell testicular tumors; RPLND, retroperitoneal lymph node dissection)

2. As of the data cut-off date of February 2014, 5 of 54 patients in the surveillance group and 4 of 27 patients in the RPLND group were excluded because of missing follow-up information (Figure 2).

Treatment

Among the patients in the four cohorts, 27 received RPLND, including 4 laparoscopic RPLND and 23 open RPLND. None of the laparoscopic RPLND transitioned to open RPLND because of successful operations. The median number of dissected nodes was 6 (range 3-14), and no positive node was confirmed by pathology.

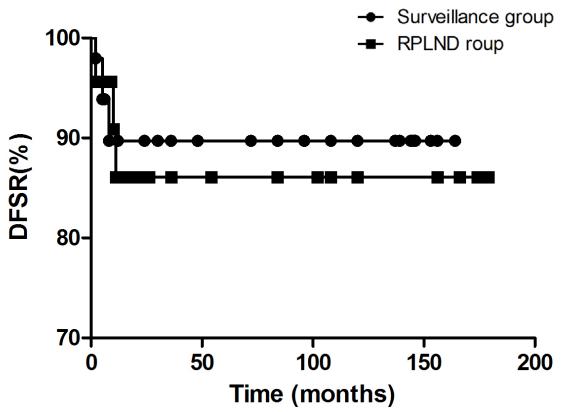

Figure 3. Kaplan-Meier Curves of Disease-free Survival from the Four Cohorts (HR=0.779; 95% CI=0.175-3.464; X_2=0.108; *P*=0.743) (DFSR, disease-free survival rates; RPLND, retroperitoneal lymph node dissection; HR, hazrad ratio)

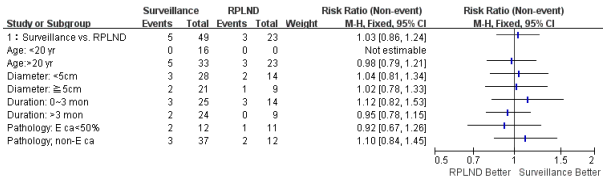

Figure 4. Disease-free Survival for Subgroups (RPLND, retroperitoneal lymph node dissection; ECa, embryonal carcinoma)

Efficacy

Progression-free and overall survival: The median follow-up duration was 66.2 (range 6-164) months in the RPLND group and 65.9 (range 8-179) in the surveillance group. During the follow-up period, five patients in the surveillance group and three patients in the RPLND group experienced tumor relapse (radiology experts assessed the relapse). As expected, no significant difference of cumulative DFSR was observed between the two groups (89.8% *vs* 87.0%, X_2=0.108, *P*=0.743; Figure 3). Among the patients who experienced relapse, three were cured by both RPLND and chemotherapy, and five were cured by chemotherapy (Table 3). At the time of analysis, the overall survival rate was 100% for surveillance and RPLND groups.

Outcome according to risk factors

In this study, the effect of %ECa, age, tumor size, and pre-orchidectomy duration on different treatments was

analyzed. No significant difference was observed between the two treatment regimens (P>0.05; Figure 4).

Serum determination of tumor markers was performed before orchidectomy. Among the 72 patients, 33 (45.8%) had abnormal tumor marker serum levels. After undergoing orchidectomy, 23 patients were included in the normalization dose, and 10 patients satisfied the expected half-life values. RPLND was recommended for the 10 patients and 6 of these patients were classified in the normal level after RPLND. Furthermore, 4 of these patients, who refused further treatment, underwent rigorous surveillance. After 5 and 8 months, 2 of the 4 patients experienced relapse, respectively.

Univariable analysis of %ECa was performed in our study. No significant statistical difference of surveillance was observed versus RPLND in patients with low percentage of embryonal carcinoma (%ECa <50%). The median DFSR of 83.3% in the subgroup of surveillance was similar to the result of RPLND group (90.9%, RR: 0.92; 95% CI: 0.67-1.26). For surveillance, the median DFSR rate of 91.9% observed in patients without embryonal carcinoma was also similar to that of RPLND (83.3%, RR: 1.10; 95% CI: 0.84-1.45). Based on these results, an exploratory analysis was conducted to assess the prognosis of the patients with a low percentage of embryonal carcinoma (%ECa<50%) and without embryonal carcinoma. Overall, no significant difference in DFSR was observed for these two subgroups (DFSR: 87.0% versus 89.8%, X_2=0.154, P=0.695; Figure 5).

To assess the influence of age on the treatment effect, we divided the patients into two groups: <15-year cohort and ≥15-year cohort. Patients aged less than 15 years old were recommended for active surveillance. The DFSR was 100% in the <15-year cohort and 86.2% in the ≥15-year cohort (X_2=2.085; P=0.149; Figure 6).

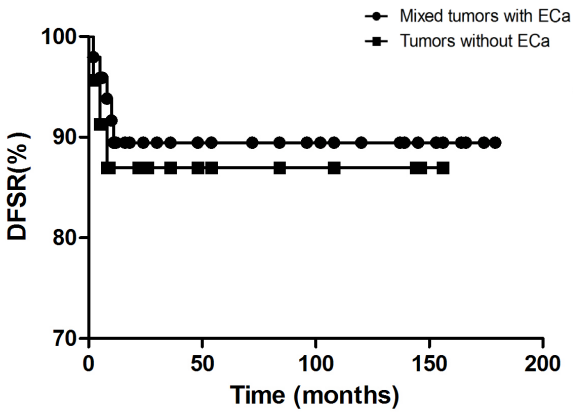

Figure 5. Kaplan-Meier curves of Disease-free Survival for the %ECa Group and Non-%ECa Group (HR=0.7430; 95%CI=0.164-3.334; X_2=0.154; P=0.695). (DFSR, disease-free survival rates; ECa, embryonal carcinoma; HR, hazrad ratio)

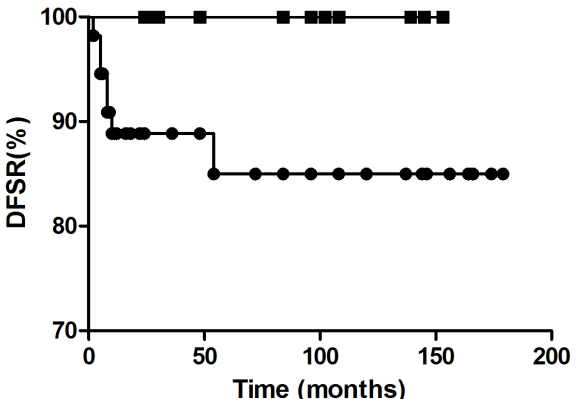

Figure 6. Kaplan-Meier Curves of Disease-free Survival for the ≥15-Year Group and <15-Year Group (HR=3.748; 95% CI=0.6497-21.62; X_2=2.085; P=0.149). (DFSR, disease-free survival rates; HR, hazrad ratio)

Adverse events

The common adverse events associated with RPLND in this study were infection (one case), obstruction (two cases), and ejaculatory dysfunction (six cases) with an overall occurrence in 39.1% (9/23) of the patients. Most of these events were mild or treated easily. The most common adverse event was ejaculatory dysfunction, including one retrograde ejaculation and five diminished ejaculations. No erectile dysfunction was observed in our study.

Discussion

Active surveillance, primary chemotherapy, and RPLND were proposed for NSGCTs. RPLND demonstrated a favorable effect in terms of low relapse rate, especially in the treatment of CSI-NSGCTs, which can lead to a high disease-free survival and overall cure rates of nearly 100% (Tong et al., 2014). RPLND could provide accurate pathology staging for planning follow-up treatment regimens. However, many clinical trials have shown that some patients with CSI-NSGCTs can also benefit from surveillance, thereby avoiding treatment-related complications of RPLND (Duran et al., 2007; Kollmannsberger et al., 2010).

Risk-adapted surveillance is the preferred option in most patients with CSI non-seminoma (Wood et al., 2010; Albers et al., 2011). The risk factors of the recurrence of NSGCTs are high clinical stage, lymphatic vascular invasion (LVI), embryonal predominant disease (%ECa >50%), and abnormal tumor marker levels following orchidectomy (Vidal et al., 2014). Race (Bridges et al., 1998), age (Maule et al., 2012), history of cryptorchidism (Giwercman et al., 2004), marital status (Jaffe et al., 2007), and educational and economic levels (Arai et al., 1996) also demonstrated prognostic factors for patients with NSGCTs. Pathological characteristics exhibit a strong correlation between many of these factors, including LVI and %ECa >50%. As Divrik et al (Divrik et al., 2006). reported, the relapse rate can be calculated up to 35.9% in CSI-NSGCT cases with only 1 risk factor, which was defined as either the presence of LVI or %ECa > 50%. Patients confirmed with LVI or %ECa > 50% factors had significantly worse prognosis, thereby increasing the probability of relapse by factors of 2.7 and 3.5, respectively (Heidenreich et al., 2012).

In this retrospective study, two common treatment regimens, active surveillance and RPLND, were directly compared in patients with low-risk CSI-NSGCTs following orchidectomy. Low-risk CSI-NSGCTs are

defined by non-LVI, %ECa <50%, and negative or declining tumor markers to half-life after orchidectomy. RPLND was chosen as a control arm because of its efficacy and widespread use in NSGCTs (Albqami et al., 2005).

As expected, active surveillance could result in a similar DFSR and OSR compared with RPLND (DFSR: 89.8% versus 87.0%, X_2=0.108, *P*=0.743; OSR: 100% versus 100%). These results support the hypothesis that risk-adapted surveillance with similar potent prevention of recurrence, as achieved with RPLND, produces a favorable clinical effect.

A previous study (Divrik et al., 2006) showed that the risk of lymph node metastases is 40.9% if %ECa >50% is present. By contrast, the risk of lymph node metastases decreased to 20.8% in patients with %ECa <50%, which is similar to the patients without embryonal carcinoma. In our study, %ECa indicating mixed tumors (with %ECa <50%) versus non-%ECa tumors had an HR of 0.740 (95% CI: 0.164-3.33; *P*=0.154; Figure 5). No prognostic superiority was demonstrated in RPLND versus surveillance for patients with low-risk CSI-NSGCTs. This finding suggested that %ECa <50% as a prognostic index is feasible and provides clinical advantages for patients with CSI-NSGCTs.

In this study, patients were more likely diagnosed with NSGCT in two age stages: 15-29 years and 30-44 years, with the percentage of those patients at 49.4% and 28.4%, respectively (Figure 1). Patients aged less than 15 years were recommended for active surveillance. In previous studies (Fosså et al., 2011), older age was introduced to assess the prognosis and is considered an important risk factor for disease progression during surveillance. However, in our study, the relapse rate did not increase with age, and no statistically significant difference was observed for those age ≥15 years compared with younger men (X_2=2.085; *P*=0.149; Figure 6). This finding may be explained by the result of low-risk patients with good prognosis. We also found that patients aged less than 30 years, particularly those who are unmarried, usually paid more attention to the long-term benefits of the follow-up process than older men. By contrast, the follow-up awareness of older patients was relatively weak. Therefore, we suggested that conservative treatment following orchidectomy could serve as the preferred treatment strategy for young patients with low risk to avoid the treatment-related complications associated with RPLND. The importance of follow-up should also be emphasized to patients 30+ years of age, especially for the patients with birthed.

This study has some limitations. *i)* As a retrospective study, the data from the four centers may be associated with some bias that could affect the analysis outcomes. For this reason, some measures were considered to reduce potential bias. First, data were polled and analyzed by a masked independent statistics review. Second, two pathologists identified the pathological types and percentage of embryonal carcinoma independently and discussed the disagreements with a third pathologist to obtain consistency. *ii)* Considering their good prognosis, we found that most of these patients were advised to keep their follow-up appointments at the local hospital; basic follow-up information from these patients was obtained by telephone or letter. We did not proceed to assess further the post-treatment life quality of the patients because of the convenient and simplified follow-up method. In the follow-up process, some patients in the active surveillance group were anxious about their prognosis to some extent. A similar phenomenon was observed in patients who experienced ejaculatory dysfunction in the RPLND group, and most of them were young, unmarried, and non-parents. The patients in the RPLND group had a lighter psychological burden following treatment compared with the patients treated under active surveillance. However, we firmly believe that post-treatment psychological problems will be addressed eventually through health education and related research.

The results of this retrospective study of active surveillance showed similar DFSR and OSR compared with RPLND in patients with low-risk CSI-NSGCTs. The safety profile of active surveillance was better than that of RPLND. No treatment-related adverse events were observed. These results indicated that active surveillance could be an optimal therapy for patients with CSI-NSGCTs, non-LVI, %ECa < 50%, and normal tumor marker serum level following orchidectomy.

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