·Clinical Research·

Ten-year experience in the treatment of clinical stage I seminoma

Xue-Qi Zhang,[1,2] Zhuo-Wei Liu,[1,2] Fang-Jian Zhou,[1,2] Hui Han,[1,2] Zi-Ke Qin,[1,2] Yun-Lin Ye,[1,2] Yong-Hong Li,[1,2] Guo-Liang Hou[1,2] and Zhi-Ling Zhang[1,2]

[1]State Key Laboratory of Oncology in South China, Guangzhou, Guangdong 510060, P. R. China; [2]Department of Urology, Sun Yat-sen University Cancer Center, Guangzhou, Guangdong 510060, P. R. China

[Abstract] Background and Objective: Clinical stage I seminoma accounts for 70%–80% of seminoma. This study was to analyze the relationship between different therapeutic methods and the prognosis of this disease. **Methods:** Clinical data of all patients with clinical stage I seminoma treated by multi-disciplinary approach between 1999 and 2008 at the Sun Yat-sen University Cancer Center were analyzed. The patients were divided into 3 groups based on the treatment they received after orchiectomy: 30 patients treated with chemotherapy, 8 with radiotherapy, and 20 under surveillance. The prognosis of different treatment groups was evaluated. **Results:** Among the 58 patients with stage I seminoma, 57 were followed up successfully. The median follow-up time was 50 months (range, 8–115 months). No relapse or metastasis was seen in the chemotherapy group. One patient relapsed in the radiotherapy group. Four patients had metastasis of retroperitoneal lymph node in the surveillance group. The disease-free survival was higher in the chemotherapy group than that in the surveillance group ($P = 0.005$). There was no significant difference in the relapse-free survival between the surveillance group and the radiotherapy group ($P = 0.364$). **Conclusions:** In stage I seminoma, the results of chemotherapy or radiotherapy are satisfactory. But for patients under surveillance, the relapse rate is 20%. For those who are well compliant, a close follow-up is recommended.

Key words: Testicular carcinoma, seminoma, stage I, treatment, prognosis

In Western countries, testicular germ cell tumors comprise 1.0%–1.5% of all male malignancies and 5% of genito-urinary tumors, and the annual incidence is about 3–6 per 10 millions.[1,2] In the past 30 years, its incidence has increased markedly.[3,4] Seminoma accounts for more than half of testicular germ cell tumors, of which 75%–80% were clinical stage I seminoma.[5] Although great changes have taken place in management of the clinical stage I seminoma in the past 20 years, few reports about its treatment have been published over the last decade due to its low incidence.

In this study, clinical data of 58 stage I seminoma patients treated at the Sun Yat-sen University Cancer Center were analyzed, different therapeutic methods were compared to find out their correlation with the prognosis of the disease, and the literature was reviewed to explore a rational treatment protocol for this disease.

Data and Methods

Clinical data

Between May 1999 and December 2008, 296 patients with intrascrotal tumor, including 76 patients with seminoma, were treated at Urology Department of Sun Yat-sen University Cancer Center. In this study, clinical data of 58 patients with clinical stage I seminoma were analyzed. All patients had detailed medical records, and the 2004 WHO Histological Classification of Testis Tumors was used as pathologic classification and diagnostic criteria.[6]

The median age of the 58 patients was 36 years (range, 14–64 years). The median tumor size was 4 cm (range, 2–13 cm). Of these patients, according to the AJCC 2002 staging system, 45 were at stage Ia, 7 were at stage Ib, and 6 were at stage IS; 36 had tumors in the right side, 22 in the left side; 20 (35.08%) had a history of cryptorchidism, of which 2 had a family history of cryptorchidism and 2 had a history of asynchronous contralateral testicular seminoma. Fifty-four naive patients underwent radical orchiectomy, and 4 patients with incomplete

Correspondence to: Fang-Jian Zhou; Tel: +86-20-87343312; Fax: +86-20-87343312; Email: zhoufj@mail.sysu.edu.cn

This paper was translated from Chinese into English by *CJC* Medical Translation and edited by Jing-Yun Ma on 2009-09-29.

The Chinese version of this paper is avaiable at: http://www.cjcsysu.cn/cn/article.asp?id=16258.

Grants: Natural Science Foundation of Guangdong Province (No.7301049)

Received: 2008-06-14; Accepted: 2009-09-23

dissection underwent re-operation (inguinal radical operation) at the Urology Department of our hospital. Four stage IS patients had elevated HCG (5.79, 10.24, 14.2 and 131.8 IU/L, respectively), two had elevated LDH (426 and 508 U/L, respectively), and normal AFP (alpha fetoprotein). After radical orchiectomy, tumor markers of all patients decreased to normal, except the patients with stage IS disease. In pathological diagnosis, 31 were typical seminoma, and two were anaplastic type, the other 25 patients were unclassified. According to International Germ Cell Cancer Collaborative Group (IGCCCG)[7] classification of prognostic risk, all patients had favorite prognosis factors.

Treatment

According to the therapeutic methods used after radical orchiectomy, patients with clinical stage I testicular seminoma were divided into 3 groups: chemotherapy, radiotherapy and surveillance groups. Chemotherapy group was treated with EP regimen (VP-16 100 mg/m^2, d1–5; DDP 20 mg/m^2, d1–5) or BEP regimen (BLM 30 mg/m^2, d1, d5; VP-16 100 mg/m^2, d1–5; DDP 20 mg/m^2, d1–5). Radiation field for radiotherapy group included the primary tumor area and the lymphatic drainage area next to ipsilateral aortic and iliac vessels ("dogleg-shaped field"), and the average dose was 28 Gy (range, 15–40 Gy). Surveillance group was closely followed up without treatment.

Follow-up

For all patients, measurement of tumor markers (AFP, HCG, and LDH) and abdominal B-ultrasound should be performed every 3 months, and chest X-ray and abdominal/pelvic CT was performed every 6 months for the first two years; and follow-up was made every 6 months, and then annually. Follow-up was stopped if the patient died or metastasis occurred, and all the patients were followed up till December 31, 2008.

Statistical analysis

SPSS16.0 statistical package was used for statistical analysis, and Kaplan-Meier method was applied to calculating the 5-year overall survival rate and disease-free survival (DFS) rate, and the comparative analysis of the relationship between the three therapeutic methods and prognosis. The survival rate was compared by log-rank test, and $P < 0.05$ was considered significant.

Results

Group division and recurrence

There were 30 patients in the chemotherapy group (including 4 patients with stage IS disease), 8 in the radiotherapy group (including one patient with stage IS disease without recurrence in the follow-up), and 20 in the surveillance group (including one patient with stage IS disease whose HCG was 5.79 IU/L and no recurrence was found by imaging examinations). In the chemotherapy group, BEP and EP regimens were administered in 24 and 6 patients, respectively, and > 2 and ⩽ 2 courses of chemotherapy were administered in 14 and 16 patients. No obvious adverse reaction was found.

The median follow-up time was 50 months (range, 8–115 months). Fifty-seven of 58 patients were followed up and survived, and 1 was lost to follow-up. No recurrence was found in the chemotherapy group; contralateral recurrence was found in one case (12.5%) of the radiotherapy group; and retroperitoneal lymph node metastases occurred in four cases (20%) of the surveillance group.

Survival analysis

For all patients, 5-year disease-specific survival rate was 100%, and 5-year DFS rate was 93.6% (Figure 1). In chemotherapy and radiotherapy groups, the 5-year DFS rate was 100%, and 80.4% in the surveillance group. Statistical analysis showed that the effects of chemotherapy group was better than surveillance group ($P = 0.005$), while no significant difference was observed between radiotherapy and surveillance groups ($P = 0.364$) (Figure 2).

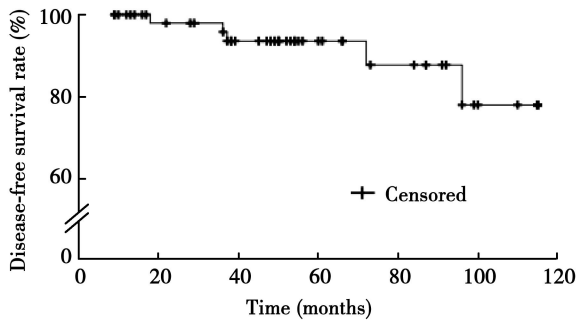

Figure 1 The overall disease-free survival curve of stage I seminoma

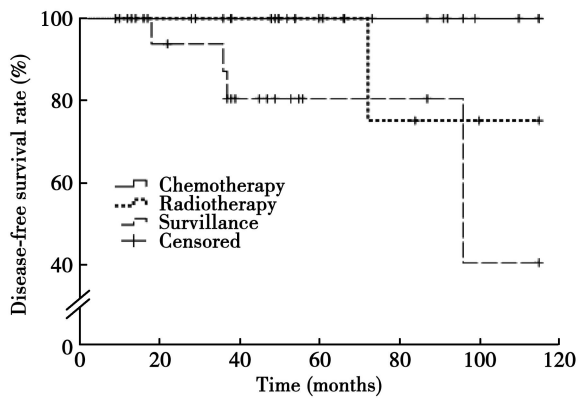

Figure 2 The disease-free survival curves of patients in surveillance group, chemotherapy group, and radiotherapy group

Discussion

Seminoma cells are highly sensitive to radiotherapy, and its recurrence rate is very low after radiotherapy, which was considered as standard treatment after radical orchiectomy for stage I testicular seminoma over the past few decades. Furthermore,

2009 NCCN guidelines still recommends it as standard treatment for this tumor. In this study, no recurrence was found in the radiation field in the 8 patients treated with classical radiotherapy. As it was reported in literature, radiation therapy with the classical radiation field ("dogleg-shaped field") had many side effects including short-term gastrointestinal reactions (39.2%) and hematological system reaction (3.7%).[8] Compared with the normal population, a higher mortality rates from cardiovascular disease[9,10] and a two-fold higher incidence of secondary cancer[11,12] as well as infertility were found after radiotherapy in the long-term follow-up. In this study, one of the 8 patients with radiotherapy suffered from contralateral testicular relapse six years later, and the possibility of secondary tumor could not be excluded yet. In recent years, researches have focused on how to reduce toxic side effects while making efforts to accomplish a long-term cure. Based on a large randomized trialby Fossa *et al.*,[13] radiotherapy in abdominal para-aortic area achieved significantly lower rates of relapse and toxic side effects than the classical radiation. A multi-center randomized study found no significant difference between 20 Gy and 30 Gy radiations, but less side effects at a low-dose radiation. Therefore, both European and U.S. clinical practice guidelines recommended a low-dose (20–30 Gy) radiation to abdominal para-aortic lymph nodes with or without ipsilateral pelvic lymph nodes.

Although the relapse rate after radiotherapy was as low as 1% –3%,[13-15] a small part of patients who received radical orchiectomy benefited from radiation therapy, meanwhile 80% patients with stage I seminoma was cured by radical orchiectomy, so NCCN recommends the surveillance as one of the options after radical orchiectomy. Follow-up resulted in avoiding the sufferings of side effects of chemotherapy and radiotherapy in some patients, while 15%–20% patients with sub-clinical metastasis still need continuous treatment. According to the report of Princess Margaret Hospital, the rate of retroperitoneal lymph node metastasis was 16.8% in stage I seminoma treated with radical orchiectomy. Four (20%) of 20 patients in the surveillance group had recurrence in this study. Most of the recurrence and metastasis occurred within five years according to the previous reports, but now more and more cases with disease progression were found five years later. Chung *et al.*[16] proposed that follow-up should also be done for more than five years, as the 5-year metastasis rate of retroperitoneal lymph node was about 15%, while the 10-year metastasis rate was 18%.

For stage I patients who chose surveillance and follow-up, the following points should be taken into consideration: first, compliance, which is a prerequisite for patients under surveillance, because the patients can not tolerate long-term and intermittent examinations; second, economic situation, continuous examinations and recurrence resulted in a heavy economic burden for the patients; third, psychological capability, compared with chemotherapy and radiotherapy groups, patients in the surveillance group suffered from a greater psychological pressure; fourth, risk factors of recurrence and metastasis. A multi-center retrospective study showed that tumor size > 4 cm, and invasion of rete testis were significant predictors of retroperitoneal metastasis.[17] For the reasons of compliance and economic situation, follow-up studies were different from the United States and European programs, which were performed every 3 months in the first two years, every 6 months in the third year, and then annually in the fourth and fifth years.

Systemic chemotherapy was one of primary treatments for clinical stage I seminoma. In recent years, single or two courses of carboplatin tended to take the place of cisplatin-based multi-drug chemotherapy. After a 4-year median follow-up, survival, recurrence rate and time of the single dose carboplatin chemotherapy were found similar to the radiation therapy, so single dose of carboplatin may replace radiation therapy or surveillance.[18] Other studies have shown that recurrence rates of single and two courses of carboplatin chemotherapy were 4.5% and 1.8% , respectively, so two courses of chemotherapy achieved better efficacy.[19-23]

In this study, no recurrence or metastasis occurred in the 30 patients of chemotherapy group, who tolerated the therapy well without significant side effects, so we suggested systemic chemotherapy as a safe and effective treatment for stage I seminoma patients with radical orchiectomy. Compared with surveillance and radiation groups, chemotherapy has the advantages of short treatment time and less economic and psychological burden. Follow-up time of most chemotherapy studies was less than 10 years. More investigations should be conducted, including: whether long-term effect of chemotherapy was similar to radiationand how chemotherapy side effects influenced the life quality of patients. Even though this retrospective study covers a small number of patients and follow-up is short, chemotherapy was found markedly better than radiotherapy or surveillance for its recurrence-free survival, which is worth further clinical researches.

References

[1] Richie JP. Neoplasms of the testis [M]. Walsh PC et al., eds. Campbell´s Urology. 7th edition. Philadelphia: WB Saunders, 1997:2411–2452.

[2] Schottenfeld D, Warshauer ME, Sherlock S, et al. The epidemiology of testicular cancer in young adults [J]. Am J Epidemiol, 1980,112(2):232–246.

[3] Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review [J]. J Urol, 2003,170(1):5–11.

[4] Klotz LH. Why is the rate of testicular cancer increasing? [J]. CMAJ, 1999,160(2):213–214.

[5] Zagars GK. Management of stage I seminoma: radiotherapy [M]. Horwich A, ed. Testicular Cancer: Investigation and Management. London: Chapman & Hall Medical, 1999:99.

[6] Eble JN, Sauter G, Epstein JI, et al. WHO histological classification of testis tumours [M]. Eble JN, Sauter G, Epstein JI, et al., eds. Pathology & Genetics. Tumours of the urinary system and male genital organs. Lyons: IARC Press, 2004:218,250–262.

[7] International Germ Cell Cancer Collaborative Group. International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers [J]. J Clin Oncol, 1997,15(2):594–603.

[8] Santoni R, Barbera F, Bertoni F. Stage I seminoma of the testis: a bi-institutional retrospective analysis of patients treated with radiation therapy only [J]. BJU Int, 2003,92(1):47–52.

[9] Zagars GK, Ballo MT, Lee AK, et al. Mortality after cure of testicular seminoma [J]. J Clin Oncol, 2004,22(4):640–647.

[10] Huddart RA, Norman A, Shahidi M, et al. Cardiovascular disease as a long-term complication of treatment for testicular cancer [J]. J Clin Oncol, 2003,21(8):1513–1523.

[11] Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40 576

testicular cancer patients: focus on long-term survivors [J]. J Natl Cancer Inst, 2005,97(18):1354–1365.
[12] Wanderas EH, Fossa SD, Tretli S. Risk of subsequent non-germ cell cancer after treatment of germ cell cancer in 2006 Norwegian male patients [J]. Eur J Cancer, 1997,33(22):253–262.
[13] Fossa SD, Horwich A, Russell JM, et al. Optimal planning target volume for stage I testicular seminoma: a Medical Research Council randomized trial [J]. J Clin Oncol, 1999,17(4):1146.
[14] Melchior D, Hammer P, Fimmers R, et al. Long term results and morbidity of paraaortic compared with paraaortic and iliac adjuvant radiation in clinical stage I seminoma [J]. Anticancer Res, 2001,21(4B):2989–2993.
[15] Livsey JE, Taylor B, Mobarek N, et al. Patterns of relapse following radiotherapy for stage I seminoma of the testis: implications for follow-up [J]. Clin Oncol (R Coll Radiol), 2001,13(4):296–300.
[16] Chung P, Parker C, Panzarella T, et al. Surveillance in stage I testicular seminoma-risk of late relapse [J]. Can J Urol, 2002,9(5):1637–1640.
[17] Warde P, Specht L, Horwich A, et al. Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis [J]. J Clin Oncol, 2002,20(22):4448–4452.
[18] Oliver RT, Mason MD, Mead GM, et al. MRC TE19 collaborators and the EORTC 30982 collaborators. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial [J]. Lancet, 2005,366(9482):293–300.
[19] Dieckmann KP, Bruggeboes B, Pichlmeier U, et al. Adjuvant treatment of clinical stage I seminoma: is a single course of carboplatin sufficient ? [J]. Urology, 2000,55(1):102–106.
[20] Krege S, Kalund G, Otto T, et al. Phase II study: adjuvant single agent carboplatin therapy for clinical stage I seminoma [J]. Eur Urol, 1997,31 (4):4057.
[21] Germa-LLuch JR. Adjuvant treatment for stage I germ-cell testicular tumours: preliminary experience of the Spanish Germ-Cell Cancer Group [M]. Jones WG, Appleyard I, Harnden P, et al., eds. Germ cell tumors, vol. IV. London: John Libbey, 1998:139–142.
[22] Nöst G, LipskyH, Wurnschimmel E. Carboplatin monotherapy in clinical stage I of seminoma: an acceptable alternative? [J]. Urology A, 1998,37 (6):629–634.
[23] Aparicio J, Germà JR, García del Muro X, et al. The Second Spanish Germ Cell Cancer Cooperative Group. Risk-adapted management for patients with clinical stage I seminoma: the Second Spanish Germ Cell Cancer Cooperative Group study [J]. J Clin Oncol, 2005,23 (34):8717–8723.