

Germ Cell Tumors in Undescended Testis-Prognostic Factors and Treatment Outcome

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ABSTRACT

The medical records of 270 patients with germ cell tumors of the testis (147 seminoma and 123 non-seminoma) seen at our institute between 1975-1997 were reviewed. Thirty-five (13%) patients had tumors in undescended testis, seminoma in 28 and 7 patients had non-seminoma. The mean age at diagnosis was 34 years. Orchiopexy was performed in only 4 patients. The involved testis was in the scrotum in the 4 patients who had orchiopexy, in the inguinal canal in 15 and in the lower abdomen in 16. Pain and palpable mass were the most common presenting symptoms. Using the modified Royal Marsden Hospital staging system, the stage at diagnosis was I in 14 patients, II in 18 and IV in 3. Orchiectomy was carried out in 26 patients, open biopsy in 3 and fine needle aspiration in 6. For patients with seminoma, 14 patients received external radiation (XRT) only, 7 chemotherapy, and combined XRT and chemotherapy in 6 patients. One patient had orchiectomy only. Patients with non-seminoma were treated with chemotherapy. Complete response was achieved in 84% of the seminoma cases. At a median follow up of 52 months (range 2 months-19.5 years), the 5-year overall actuarial survival rate for patients with seminoma was 85% compared to 68% in patients with non-seminoma. Univariate and multivariate analyses for survival were done for the 28 patients with seminoma. Early stage and complete response to treatment were associated with significant high survival rate in univariate analysis. None of the above were significant on multivariate analysis.

Conclusion: Patients with undescended testes have a higher risk for developing seminoma than non-seminoma. Treatment results of germ cell tumors in undescended testis are equivalent to those in normally located testis.

Key Words: *Germ cell tumors - Undescended testis - Seminoma.*

INTRODUCTION

Testicular cancer is the most common malignancy in men between 20 and 34 years of age

and the incidence has been increasing [15]. The raised risk of testicular cancer in men with undescended testis has been known for more than a century [16]. The probability of malignancy occurring in an undescended testis is 30-50 times greater than in a normally descended testis [1]. It has been stated that the higher the current position of the testis, the higher the risk of malignancy [8]. Undescended testis is found in 0.3%-0.8% of adult male population and in 25% of these are bilateral [5]. In general, the management of undescended testicular germ cell tumors is basically the same as for tumors arising in descended testis, as the biological behavior is identical in both [9].

The purpose of this retrospective review of patients with germ cell tumor in undescended testis is to study the clinicopathological features and disease outcome for this relatively rare but intriguing problem.

PATIENTS AND METHODS

Over a 22-year period from January 1975 to December 1997, 270 patients with the histologic diagnosis of germ cell tumor of the testis (147 seminoma and 123 non-seminoma) were seen at King Faisal Specialist Hospital and Research Centre (KFSH & RC), which is a national tertiary care cancer centre in Saudi Arabia. Out of the 270 patients, 35 (13%) had germ cell tumor in undescended testis. All histologic materials were reviewed by pathologists at KFSH & RC at the time of initial referral. The pa-

tients' medical records were reviewed for initial history and physical examination. Staging work-up varied depending on methods available at the time of diagnosis. Thirty-four patients had CT of the abdomen and pelvis. Beta human chorionic gonadotrophin (BHCG) serum concentration was measured in 30 patients, alpha-fetoproteins (AFP) in 29 patients and lactic dehydrogenase (LDH) in 22 patients. Four patients had orchiopexy of the undescended testis 2 to 32 years prior to the diagnosis of tumor. Orchiopexy was performed at age 3-35 years. The tumorous testis was located in the scrotum in the 4 patients who had orchiopexy, in the inguinal canal in 15 and in the lower abdomen in 16. One patient had the diagnosis of female hermaphrodite for which he underwent hysterectomy. Staging was performed retrospectively according to a modified Royal Marsden Hospital (RMH) staging system [16]. Twenty-eight patients had pure seminoma, 4 embryonal carcinoma, 2 teratocarcinoma and one patient had yolk sac tumor.

Seminomas: For the 28 patients with seminoma, inguinal or abdominal orchiectomy was carried out in 23 patients, fine needle aspiration only (FNA) in 3 and open biopsy for non-resectable intra-abdominal tumor in 2.

One patient had orchiectomy and did not receive additional therapy. External radiation therapy (XRT) was delivered to 20 patients. XRT was the only treatment modality post orchiectomy in 14 patients and in 6 patients as consolidation following chemotherapy. The major factors influencing XRT volume and dose selection appeared to be the location and size of the primary tumor and involved nodes. XRT fields included paraaortic and ipsilateral pelvic nodes in 7 patients, paraaortic and bilateral pelvic nodes in 5 and whole abdomen with or without para-aortic nodes boost in 8. Four patients with seminoma had tumor spread to the ipsilateral pelvic and/or inguinal nodes; pelvic nodes in 2 patients, pelvic and inguinal in 1 and inguinal nodes in 1. The two patients with pelvic nodes had stage IIC & IID and received whole abdominal XRT while, the patient with both pelvic and inguinal nodes had stage IIC and received consolidation XRT covering the para-aortic and ipsilateral pelvic nodes.

The patient presenting with inguinal nodes had stage IV tumor and received consolidation

XRT to the whole abdomen. Three patients with stage IID treated in the early eighties received elective mediastinal and supraclavicular irradiation after whole abdominal irradiation. The XRT dose ranged between 25.5-44 Gy (median of 34.5 Gy). Treatment was given in 15-29 fractions using Cobalt-60 or higher energy beams (6-18 MV linear accelerator).

Thirteen patients received chemotherapy. Chemotherapy was given alone in 7 patients and before XRT in 6. Two different combination chemotherapy regimens were utilized; cisplatin, vinblastine and bleomycin (PVB) in 8 patients, while etoposide replaced vinblastine (BEP) in 5.

Univariate and multivariate analyses were done for the 28 patients with seminoma to identify possible prognostic factors affecting the overall survival. Factors analyzed included: age (> 30 years versus < 30 years), lymph nodal status, stage, LDH level, BHCG, treatment modality and response to therapy.

Non-seminomas: Of the 7 patients, 3 had orchiectomy, 3 FNA and one had open biopsy, PEB was given in 3 patients, PVB in 3 and PVB plus dactinomycin and cyclophosphamide in one.

Statistical methods:

Overall survival (OS) was calculated from the day treatment started to the date of death or last follow-up. Relapse-free survival (RFS) was applied only to patients who achieved a complete response. Univariate analysis was used to screen the potential prognostic factors. The multivariate approach was used to examine the joint effect of those variables found to be significant in the univariate analysis. Individuals who were lost to follow-up were treated as censored observations.

RESULTS

The mean age at diagnosis was 34 (range 12-60) years. Table (1) summarizes pertinent clinical features. The majority of patients (69%) presented with a swelling and pain and 20% experienced pain only. A high proportion of patients (51.5%) had stage II disease at presentation. None of the patients presented with stage III tumor. Three patients presented with extral-

lymphatic metastases; 2 in the lung and 1 in the liver. Stage I, II and IV accounted for 36%, 57% and 7%, respectively, in patients with seminoma. In non-seminoma patients, 4 had stage I, 2 stage II and 1 stage IV. The total incidence of ilioinguinal lymph nodes in patients with nodal metastases was 4 of 18 (22%).

In seminoma, the LDH was elevated in nearly half of the patients (8/18) and BHCG in 7 out of 24 patients in whom those markers were measured. For non-seminoma, AFP was high in 4 out of 6 patients and BHCG in 2 of 6 patients.

The primary treatment was XRT alone in 14 patients (40%), chemotherapy in 13 (37%), combined chemotherapy and XRT in 7 and surgery alone in one patient. The distribution of treatment modalities according to stage and pathology is summarized in Table (2).

Two patients died of acute chemotherapy toxicity, one with septicemia and the other with renal failure. Out of the 35 patients, 32 were evaluated for assessment of tumor response. In the whole series, complete response was achieved in 26 patients (81%), partial response in 5 (16%) and disease progression in one patient. A higher complete response rate was achieved in patients with seminoma (84%) compared to those with non-seminoma (67%).

In patients with seminoma, the complete response rates were 100%, 92% and 50% for combined chemotherapy/XRT, XRT alone and chemotherapy alone, respectively.

There was no difference in complete response by the site of tumor. With a median follow up of 52 months (range 2 months-19.5 years), the 5-year OS was 85% in patients with seminoma compared to 68% in non-seminoma with no statistically significant difference ($p = 0.3$) (Fig. 1).

In patients with seminoma, there was no statistically significant difference for age, nodal status, LDH, BHCG and treatment modality.

The 5-year overall survival rates were 100%, 75% and 100% in patients with seminoma stages I, II and IV, respectively ($p = 0.2$). Significant difference was seen between stage I and all other stages collectively and also between both stage I and IIA compared to the other stages ($p = 0.05$) (Fig. 2).

Patients who did not achieve complete response to the primary therapy had an inferior 5-year OS (37%) compared to 100% in those with complete response ($p = 0.0001$). None of the statistically significant factors in univariate analysis were significant on multivariate analysis.

Patients who did not achieve complete response were not included in the analysis for local recurrence and relapse-free survival. Twenty-six patients were evaluated for this analysis. Two patients had tumor relapse, one in the para-aortic nodes and the other one in the lung.

The relapse free survival rates at 5 years for the 22 patients with seminoma who achieved complete response after primary therapy was 86% (Fig. 3).

Table (1): Patient characteristics.

Features	Number	Percentage (%)
<i>Location:</i>		
Inguinal	15	43
Abdominal	16	46
Scrotal	4	11
Right	23	66
Left	12	34
<i>Symptoms:</i>		
Pain and mass	24	69
Pain	7	20
Mass	3	8
Incidental	1	3
<i>Pelvic-inguinal lymph nodes:</i>		
Yes	4	11
No	31	89
<i>Stage:</i>		
I	14	40
IIA	3	8
IIB	3	8
IIC	5	14
IID	7	20
IV	3	8

Table (2): Treatment modalities according to stage and pathology.

Stage	I	IIA	IIB	IIC	IID	IV	Total
<i>Seminoma:</i>							
XRT	8	2	1		3		14
Chemotherapy	1		1	2	2	1	7
Combined chemotherapy + XRT		1	1	3		1	6
Surveillance	1						1
<i>Nonseminoma:</i>							
Chemotherapy	4				1	1	6
Combined chemotherapy + XRT					1		1
Total	14	3	3	5	7	3	35

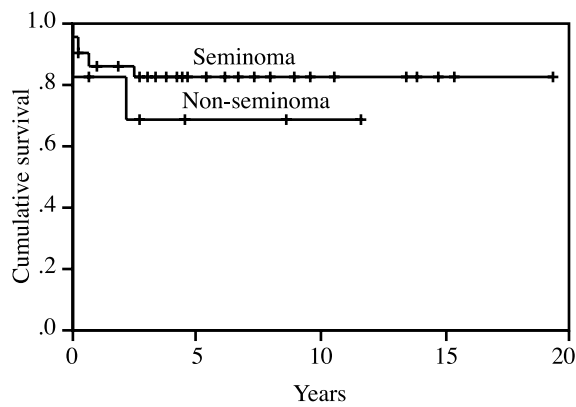


Fig. (1): Overall survival.

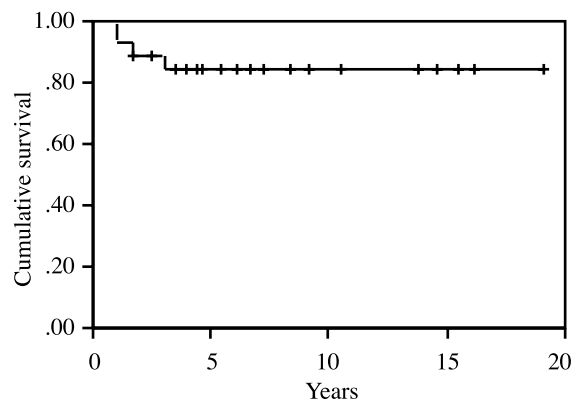


Fig. (3): Relapse free survival for seminoma.

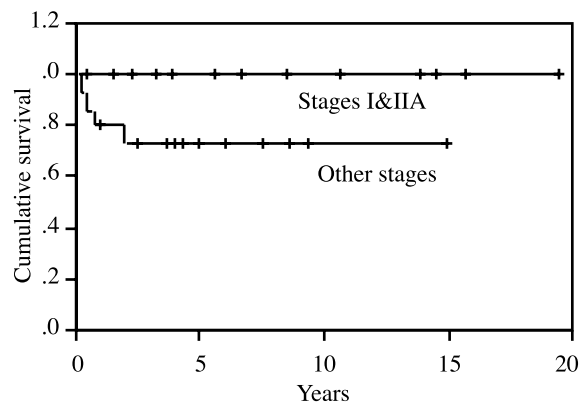


Fig. (2): Overall survival for seminoma according to stage.

DISCUSSION

Testicular cancer accounts for about 1% of all malignant neoplasms in males. However, among young men, it is a relatively common tumor as it represents 23% of all cancers in those aged 20-29 and 12% in those aged 30-39 years [12]. Undescended testis is the most common congenital genitourinary abnormality in males and is associated with infertility and malignancy [14].

In the present series, orchiopexy was performed in 4 patients at ages 3-35 years. Orchiopexy performed at an early age would minimize histopathologic changes in the testis,

improve fertility and facilitate clinical follow-up. There is little evidence that early orchiopexy would prevent cancer development [13]. Prophylactic orchiectomy for unilateral undescended testis especially after puberty has been recommended [11]. Testes that cannot be brought into the scrotum should be excised [6]. Three to 13% of patients with germ cell tumors have a history of undescended testis [10]. In the present series, 13% of germ cell tumors recorded in our tumor registry were in undescended testis.

Histologically, seminomas are more common in undescended testis and reported incidence varies from 50% to 80% [2]. Coupland et al. [7] have found in a large study of testicular tumors that undescended testis was more strongly associated with seminoma than non-seminoma. In our series, the predominance of seminoma (80%) confirms the same findings. In the current study, the primary tumor was located in the abdominal testis in 16 patients and in the inguinal testis in 15. This conforms to some other series [4]. Also, a high proportion of patients presented with advanced stage, with only 40% had stage I tumor. Gauwitz et al. [6] reported 75% stage I tumor in patients with a normally descended testis compared to 38% in patients with undescended testis. In several other studies, patients with undescended testis presented with advanced stage compared to those with normally descended testis [3&10]. In the same study, they reported a higher statistically significant difference in the incidence of pelvic lymph node disease (69%) in patients with undescended seminoma compared to only 14% in patients with seminoma in a normally descended testis. Only 2 patients in the previous study were found to have inguinal node metastases (12.5%). In the present series, 18 patients with seminoma had nodal metastases (64%); 3 had pelvic nodes (17%) and 2 inguinal nodal metastases (11%). Of the 3 patients with pelvic nodal spread; the location of the primary tumor was inguinal in 2 and abdominal in 1 patient. The two patients with inguinal lymph nodes metastases had inguinal undescended testis.

Because of the high incidence of pelvic and inguinal nodal spread, it has been recommended to irradiate the whole pelvis and para-aortic nodes in all patients with pelvic or inguinal nodes as well as in those with primary pelvic testicular seminoma [9].

The high overall tumor response rate in this study (97%) demonstrates that these tumors in undescended testis respond in the same fashion to treatment as in scrotal testis. This was confirmed in other studies [3&9].

Appropriate management results in an extremely good prognosis. In the current study, the 5 and 10-year OS rates for the whole group were 81%. The 5-year OS was better in patients with seminoma (85%) as compared to those with non-seminoma (68%), with no statistically significant difference ($p = 0.3$). The absence of difference may be due to the small number of patients studied.

The OS was significantly better in patients with stage I seminoma compared to higher stages. The OS in the current series was comparable to that reported by Gauwitz et al. [9] who reported a 92% 5-year OS in patients with seminoma in undescended testis. Berkmen et al. [16] reported a 5-year OS of 80% in patients with non-seminoma. Batata et al. [3] concluded that the prognosis of patients with germ cell tumors in undescended testis is primarily determined by the stage and histologic type rather than by historic or current evidence of undescended testis.

It can be concluded that treatment for germ cell tumors in undescended testis should follow same the guidelines as for germ cell tumors in general. Tailoring the radiation field to cover the pelvis is necessary in seminoma patients with pelvic tumors and those with pelvic and inguinal node metastases. Treatment results of germ cell tumor in undescended testis are equivalent to those in normally located testis.

REFERENCES

- 1- Batata M.A., Whitmore W.F., Hilaris B.S., Tokita N. and Grabstald H.: Cancer of the undescended or maldescended testis. *Am. J. Roentgenol.*, 126 (2): 302-312, 1976.
- 2- Batata M.A. and Whitmore W.F.: Cryptorchism and testicular cancer. *J. Urol.*, 124: 382-385, 1980.
- 3- Batata M.A., Chu F.C.H., Hilaris B.S., Whitmore W.F. and Goble R.B.: Testicular cancer in cryptorchids. *Cancer*, 49: 1023-1030, 1982.
- 4- Berkmen F. and Alagol H.: Germinal cell tumors of the testis in cryptorchids. *J. Exp. Clin. Cancer Res.*, 17 (4): 409-412, 1998.
- 5- Cotran R.S., Kumar V. and Robbins S.L.: In Robbins

- (ed.) Pathologic Basis of Disease. 4th Ed. Philadelphia, WB Saunders, 1989, 1103-1104.
- 6- Chilvers C., Dudley N.E., Gough M.H., Jackson M.B. and Pike M.C.: Undescended testis: The effect of treatment on subsequent risk of subfertility and malignancy. *J. Ped. Surg.*, 21 (8): 691-696, 1986.
 - 7- Coupland C.A.C., Chilvers C.E.D., Davey G., Oliver R.T.D. and Forman D.: Risk factors for testicular germ cell tumors by histological tumor type. *Br. J. Cancer*, 80 (11): 1859-1863, 1999.
 - 8- Fordham M., Mason M., Blackmore C., Hendry W.F. and Horwich A.: Management of the contralateral testis in patients with testicular germ cell cancer. *Br. J. Urol.*, 65: 290-297, 1990.
 - 9- Gauwitz M.D. and Zagars G.K.: Treatment of seminoma arising in cryptorchid testes. *Int. J. Radiat. Oncol. Biol. Phys.*, 24: 153-159, 1992.
 - 10- Kulkarni J.N. and Kamat M.R.: Tumors in undescended testis. *J. Surg. Oncol.*, 46: 257-260, 1991.
 - 11- Martin D.C.: Malignancy and the undescended testis. Yearbook Medical Publishers, 1981, 144-156.
 - 12- Pottern L.M., Brown L.M., Hoover R.N., Javadpour N., O'Connell K.J., Stutzman R.E., et al.: Testicular cancer risk among young men: role of cryptorchidism and inguinal hernia. *JNCI*, 74 (2): 337-381, 1985.
 - 13- Pike M., Chilvers C. and Peckham M.: Effect of age at orchidopexy on risk of testicular cancer. *Lancet*, 1: 1246-1248, 1986.
 - 14- Swerdlow A.J., Higgins C.D. and Pike M.C.: Risk of testicular cancer in a cohort of boys with cryptorchidism. *BMJ*, 314 (7093): 1507-1511, 1997.
 - 15- Schultz H.P., Arends J., Barlebo H., Brincker H., Stroyer C.I. and Engelholm S.A.: Testicular carcinoma in Denmark, 1976-1980: Stage and selected clinical parameters at presentation. *Acta Radiol. Oncol.*, 23: 249-253, 1984.
 - 16- Thomas G.M. and Williams S.D.: Testis. In Perez CA, Brady LW (eds): Principles and practice of radiation Oncology. Philadelphia, Lippincott - Raven, 1998, p. 1698.
 - 17- Johnson D.E., Woodhead D.M., Pohl D.R. and Robison J.R.: Cryptorchism and testicular tumorigenesis. *Surgery*, 63: 919-922, 1968.