Current Update of Management of Clinical Stage I Non Seminomatous Germ Cell Tumors of Testis

T. B. Yuvaraja

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Abstract The management of patients with testicular germ cell tumors (GCT) has evolved significantly over the past 30 years with cure rates approaching nearly 100% for low-stage disease and more than 80% for advanced disease. Controversy surrounds about ideal management of clinical stage I non seminomatous germ cell tumors (CS I NSGCT) of the testis due to multiple treatment options available with more or less equal efficacy. Nerve-sparing retroperitoneal lymph node dissection (RPLND), adjuvant chemotherapy with two cycles of bleomycin, etoposide, and cisplatin, or surveillance have all achieved long-term survival in nearly 100% of patients with clinical stage I NSGCT. Retroperitoneal lymph node dissection is still favoured as the therapy of choice for clinical stage I non-seminomatous germ cell tumors in many centres, but as risk factors for the primary tumor have become better understood, surveillance and risk-adapted therapy, including surveillance for low-risk patients and adjuvant chemotherapy for the high-risk group, is now being considered a therapeutic option. The objective of this study is to review current developments in the management of CS I NSGCT testis with emphasis on risk stratification and treatment recommendations.

Keywords Testis cancer · NSGCT stage I · Surveillance · Chemotherapy · RPLND

Introduction

Testicular germ cell cancer occurs in 5–7/100,000 men and is the most common solid malignancy in the age group 15–35. After introduction of cisplatin-based chemotherapy, testicular cancer has become a model for a curable neoplasm. It is now established that more than 95% of patients with early-stage testicular cancer and up to 70% of patients with advanced disease will survive.

Clinical stage I Non Seminomatous Germ Cell Tumor (CS I NSGCT) refers to tumor involvement that is limited to the testis, with negative radiographic staging studies and normal serum tumor markers after high inguinal orchidectomy. If the tumor markers persist after orchidectomy with negative imaging study the stage is termed as Stage IS and all of these patients should receive chemotherapy BEP 3#. Management of CS I NSGCT remains controversial. Few randomized controlled trials are available to inform clinicians on the management of CS I NSGCT. CS I is associated with a 20–50% incidence of occult retroperitoneal disease creating the controversy regarding “the best” treatment modality [1, 2]. Currently, three approaches are considered for treatment in CS I NSGCT: retroperitoneal lymph node dissection (RPLND), surveillance, and primary chemotherapy. It is generally agreed that all approaches ultimately result in similar cancer cure rates regardless of the management option selected. Overall and disease-free survival rates are over 95% for all management approaches, even though recurrence rates are higher in the patients managed by surveillance.

The primary issue in the management of CS I patients is treatment those who have occult metastatic disease sparing those who don't have. It is therefore essential to identify pathological risk factors which represent high risk of occult metastatic disease.

T. B. Yuvaraja (✉)
Consultant Uro-Oncologist, Centre for Cancer,
Kokilaben Dhirubhai Ambani Hospital, Four Bungalows,
Andheri West,
Mumbai 400053, India
e-mail: uroraj@rediffmail.com

General Principals and Risk Factors for Relapse

Risk factors predictive of recurrence include vascular invasion (VI) of the primary tumor, lymphatic invasion (LVI), the presence of embryonal carcinoma (EC), absence of yolk sac tumor and a positive MIB-1 staining [1, 2]. Vascular invasion is the predominant finding which can help to predict relapse in 48% of patients. Those patients with zero to two risk factors are found to recur on surveillance about 20% of the time. Using these factors, a combination of VI positivity plus >70% MIB-1 staining plus >50% EC predicts relapse in 64% of patients [3]. Though somewhat variable, high-risk groups with the presence of either or both LVI and embryonal dominant primary carry an approximate 50% recurrence rate.

Risk stratification into high risk and low risk would enable directed therapy: RPLND or primary chemotherapy for the high-risk group and observation for the low-risk group. Even with this stratification, 50% of high-risk patients will be over-treated when otherwise cured with orchiectomy. Likewise, 20% of the low-risk group will be destined to relapse on surveillance and subjected to systemic chemotherapy and possible post-chemotherapy (PC) RPLND. (Fig. 1)

Primary Chemotherapy

The aim of primary chemotherapy is to minimize the risk of relapse and to allow men to avoid RPLND and induction

Fig 1 Treatment Algorithm for CS I NSGCT

chemotherapy. Clinicians expect primary chemotherapy to provide at least 95% efficacy in the eradication of micrometastatic disease. The administration of chemotherapy after orchiectomy in CS I NSGCT nearly eliminates the risk of relapse. A pooled analysis of 13 studies involving 1043 patients revealed a relapse rate of 1.6% with six patients (0.6%) dying of disease [4]. Given the two cycles of BEP, only 3% of patients relapse; therefore, the risk reduction for relapse is 90%. The risk-adapted 5-yr survival with adjuvant chemotherapy is without doubt excellent, at 99% [5] (Table 1)

A recent randomized trial and a population-based study by Albers et al have investigated the use of BEP×1 as primary chemotherapy for CS I NSGCT. Over a median follow-up of less than 5 years, the risk of relapse after BEP×1 ranged from 1% to 3% and the cancer-specific survival approached 100%. Relapse rate were higher in surgery group but was explained by surgery performed by in-experienced surgeons. The hazard ratio to experience a tumor recurrence with surgery as opposed to chemotherapy was 7.937 (95% CI, 1.808 to 34.48). BEP×1 needs to be compared with BEP×2 in a randomized trial to verify its safety and efficacy [6].

The main disadvantages of primary chemotherapy are that it does not treat retroperitoneal teratoma, necessity of long term surveillance CT of the retroperitoneum, exposure to potential risk of late toxicity (cardiovascular disease and secondary malignant neoplasms among others) of chemotherapy and relatively chemo resistant relapse in the retroperitoneum. The toxicity of BEP chemotherapy has been well documented, mostly with reference to the usual salvage treatment dose of three cycles. Toxic effects includes hair loss and neutropaenia in most cases; transient infertility is likely, and cryopreservation is necessary; a 2–7 times increased risk of cardiovascular effects, including hypertension, Reynaud's phenomenon, myocardial ischaemia or infarction, and cerebrovascular accident up to 15 yr later [7]; renal impairment in 20–30% of patients, mostly sub-clinical [8]; anxiety, depression, and weight gain [9]; too-toxicity in 23–30% of patients [10]; neuropathy in 30% of patients [10]; and finally, an estimated 1.5 times risk of second primary cancer development [11].

Surveillance

Surveillance is the process of monitoring the disease in order to minimize over treatment while detecting and treating early relapse. The rationale for surveillance includes 1) the low rate of progression (30% for all comers and 50% for the “high-risk group”) and 2) patients that do relapse remain curable. Irrespective of risk classification, RPLND or immediate chemotherapy, will subject 100% of patients to therapy while arguing benefiting only 30% and up to 50%

Table 1 Primary chemotherapy in stage I nonseminomatous germ cell tumor

Author	Year	No.	Patient Characteristics	Chemo/ Surveillance	Relapses (%)	Median Follow-Up, Mo	Overall Survival
Madej and Pawinski	1991	30	Vascular/lymphatic invasion pT $\geq$ 2 ($\geq$ 1 of 3)	PVB surveillance	0	31 (12–60)	100
		42	Low risk		1 (2)	31 (12–60)	100
Oliver et al	1992	22	MRC intermediate/high risk	EBCi3 surveillance	1 (5)	43	95
		19	MRC low risk		3 (16)	44	100
Kratzik et al	1996	87	Vascular invasion	PEB surveillance	4 (5)	62	98
		114	No vascular invasion		16 (14)	62	97
Cullen et al	1996	114	MRC ($\geq$ 3 of 4)	BEP	2 (2)	48 (7–48)	98
Böhlen et al	1997	59	Embryonal carcinoma	BEP/PVB	1 (2)	65	100
			Vascular invasion pT $\geq$ 2				
Chevreau et al	1997	38	Embryonal carcinoma	BEP/PVB	0	36 (2–114)	100

Sternberg CN: The management of stage I testis cancer. *Urol Clin North Am* 1998;25:435–449.

EBCi, etoposide, bleomycin, cisplatin (3 days);MRC, Medical Research Council;PEB/BEP, bleomycin, etoposide, cisplatin;PVB, cisplatin, vinblastine, bleomycin.

based on risk classification. That is, even in the high-risk group, 50% of patients are unnecessarily treated with RPLND or chemotherapy. (Table 2)

Two groups have recently reported excellent results. In Toronto, 371 patients were managed by surveillance between 1981 and 2005. Overall, as expected, 28% of these patients relapsed, which included 52% of the high-risk VI-positive patients and 16% of the low-risk VI-negative patients. Five-year disease-specific survival (DSS; following salvage BEP with or without RPLND) was almost 100%, with just three (<1%) deaths [12].

The British Columbia group described surveillance of 223 patients, with a median follow-up of 52 months. Of note, only 27% of patients exhibited VI. Overall, 26% of patients relapsed, including 51% VI-positive patients and—surprisingly—at least 37% of VI-negative patients. The authors reported that 74% of patients were spared any further treatment, while DSS was 100% [13].

Surveillance therapy should be considered an active form of treatment, with careful follow-up being mandatory. Various regimes of serial clinical examinations, serological tumour markers, and CT imaging (chest, abdomen, and pelvis) have

Table 2 Recent surveillance trials in clinical stage I nonseminomatous germ cell tumor

Author	Year	No.	Relapses (%)	RPLN Relapses (%)	Months to Relapse	Median Follow-Up in Months (Range)	Overall Survival (%)
Gels et al ^[†]	1995	154	42 (27)	38 (25)	4 (2–24)	84 (24–144)	98
Sogani et al	1998	105	27 (26)	17 (63)	5 (2–24)	136 (49–202)	99
Sharir et al	1999	170	48 (28)	—	7 (2–21)	76 (1–173)	99
Colls et al	1999	248	70 (28)	—	—	5 (31–85)	98
Hendry et al	2000	357	89 (25)	45 (18)	—	103 (12–244)	99
Napier and Rustin	2000	185	26 (14)	13 (7)	4 (1–4)	98 (2–180)	100
Francis et al	2000	183	52 (23)	24 (46)	6 (1–22)	70 (1–260)	99
Alexandre et al	2001	88	24 (27)	14 (16)	—	—	96
Spermon et al	2002	90	23 (26)	18 (20)	12 (3–44)	92 (12–179)	99
Germa-Lluch et al	2002	262	58 (22)	—	—	33	—
Daugaard et al	2003	301	86 (29)	—	5 (1–171)	60 (1–226)	99
Atsu et al	2003	132	32 (24)	18 (14)	5 (2–23)	38 (6–265)	99
Amato et al	2004	23	2 (9)	—	—	38 (9–69)	100
Oliver et al	2004	234	71 (30)	—	—	84 (2–219)	97
Total		4009	1073 (27)	348 (9)			99

Sternberg CN: The management of stage I testis cancer. *Urol Clin North Am* 1998;25:435–449

been described. The most of common site of relapse is retroperitoneum. Because 88% of relapses occur during years 1 and 2 postorchietomy, while relapses are rarely reported after >5 yr follow-up, surveillance tends to be more intensive during the first 2 yr and decreases beyond 5 yr. The surveillance program which is generally practiced is shown in Table 3. A randomized trial evaluated CT scans at three and 12 months versus three, six, nine, 12, and 24 months and found no benefit in more frequent CT scans [14].

The largest reports of the surveillance strategy indicate a cumulative relapse rate of about 30%, with 80% of the relapses occurring during the first 12 months of follow-up, 12% during the second year and 6% during the third year, decreasing to 1% during the fourth and fifth years, and occasionally even later [15, 16]. About 35% of relapsing patients have normal levels of serum tumor markers at relapse. About 60% of the relapses are in the retroperitoneum. Despite very close follow-up, 11% of relapsing patients presented with large-volume recurrent disease.

The disadvantages of surveillance program include highest risk of relapse, the need of long term follow up, potential for second malignancies due to repeated CT scans [17] and more intensive therapy required in case of relapse. A potential pitfall with surveillance is poor patient compliance, which could result in late presentation of advanced disease less amenable to curative salvage treatment although this lacks evidence. All CS I NSGCT patients be offered surveillance, provided they are considered appropriate for this approach and do not prefer immediate adjuvant treatment. There is evidence from a randomized trial conducted in patients with metastatic disease showing better survival rates among patients treated in multidisciplinary centers of excellence compared to patients treated in community centers.

RPLND

An adequately performed Nerve Sparing-RPLND remains the preferred treatment option in patients with T1 tumors who are noncompliant with surveillance or prefer surgery

and those with T2–4 stage I NSGCT. A bilateral NS-RPLND is both a diagnostic and therapeutic procedure when performed in tertiary centers by experienced surgeons, obviating the need for templates that could compromise oncologic outcome [18]. There is clinical evidence that the retroperitoneal nodes are usually the first, and often the only, site of metastatic disease in NSGCT [19]. Despite effective cisplatin-based chemotherapy, unresected retroperitoneal metastasis can potentially result in repeat surgery, late relapse, and decreased survival [20]. Chemoresistant teratoma is present in approximately 20% to 30% of patients with pathologic stage II disease [21]. RPLND is a curative procedure in approximately 90% of pN1 eliminating the need for adjuvant chemotherapy and 50% of pN2 patients for whom 87two cycles of etoposide plus cisplatin with or without bleomycin is often recommended [22]. Nerve-sparing techniques also preserve antegrade ejaculation in more than 95% of patients.

In patients with low-volume (N1) retroperitoneal disease, surgical cure is possible with surgery only and without adjuvant chemotherapy [23–25]. The outcomes of 464 patients with CS I NSGCT were reviewed by Donohue et al with a mean follow-up of 96.2 months [26]. In this analysis, 323 (70%) patients had pathologic Stage I disease with 37 (11%) relapsing, with an overall survival of 99.4%. Pathologic Stage II disease was identified in the remaining 112 (30%) patients. Of these, 64 did not receive adjuvant chemotherapy, of whom 22 (34%) relapsed with one death. None of the 48 patients receiving adjuvant chemotherapy relapsed.

Sweeny et al [27] published the results of RPLND in patients with high-risk CS- I disease defined by the two criteria of embryonal predominance and vascular invasion in the orchietomy specimen. The presence of each risk factor predicted pathologic Stage II disease at the 46.5% level. Of patients with pathologic Stage II disease who elected not to receive adjuvant chemotherapy only a third had recurrence after RPLND, indicating that two-thirds of these high-risk patients were cured with RPLND only. Therefore, even in so-called high-risk patients, RPLND retains its therapeutic capability.

Table 3 Protocol for surveillance in stage I seminoma and nonseminomatous germ cell tumor

	Years 1 and 2			Years 3 and 4		Year 5	
	Baseline	2 monthly	4 monthly	4 monthly	6 monthly	6 monthly	Yearly
History and physical examination	√	√		√		√	
Serum tumor markers	√	√		√		√	
Liver function tests and complete blood cell count	√	√		√		√	
Chest radiography	√	√					
Computed tomography	√		√		√		√

Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS (eds): Genitourinary Oncology. Philadelphia, Lippincott, Williams & Wilkins, 1999

A contemporary series was recently published by Beck et al [28] evaluating the efficacy of primary RPLND in 118 patients with pathologic Stage IIA NSGCT who have not received adjuvant chemotherapy. At a minimum follow-up of two years, and median follow-up of 43 months, the five-year disease-free survival was 68%. The median follow-up in patients without recurrence was 67.4 months and the median time to recurrence was 5.0 months. Pathologic features including number and histologic subtype of the metastatic lymph nodes failed to predict recurrence. Despite the inability to predict risk factors of recurrence in this population, RPLND cures patients with metastatic disease, alone and without adjuvant chemotherapy.

Williams et al randomized 195 patients with PS II NSGCT to observation or two cycles of adjuvant BEP. The relapse rate in observation patients was 49% compared to 6% in patients treated with adjuvant chemotherapy [29]. Five of the six recurrences in the adjuvant chemotherapy arm occurred before adjuvant chemotherapy was given. Evaluating only patients who received adjuvant chemotherapy, the recurrence rate was 1.1% (95% confidence interval [CI], 0.15% to 7.31%). Based on these additional data, it was the consensus of the Genitourinary Disease Site Group (GU DSG) that two cycles of BEP (with etoposide 500 mg/m²/cycle) represented adequate adjuvant chemotherapy in CS I NSGCT patients.

Primary RPLND cures 70% of patients with pathologic Stage II disease and the 30% that do relapse remain curable with three courses of chemotherapy. Two courses of adjuvant chemotherapy administered to patients with pathologic Stage II disease after primary RPLND does eliminate the risk of recurrence for those 30% destined to relapse but adds to patient morbidity and unnecessarily exposes chemotherapy to the 70% otherwise cured with surgery [30, 31].

Historically, bilateral infrahilar RPLND templates were associated with high rates of ejaculatory morbidity (>90%). Modified templates, all limiting contralateral dissection below the inferior mesenteric artery, have been recommended to preserve antegrade ejaculation. Due to high incidence of the disease outside the template modifies template is not practiced routinely. (Eggner et al, J Urol, 2007). With nerve sparing primary RPLND there is a lowest risk of recurrence and ejaculatory issues are eliminated and only morbidity is due to the incision and <1% long term morbidity of small bowel obstruction due to post operative adhesions [32–34].

Few centers report Laparoscopic primary RPLND as a potential treatment modality in CS I disease. Advantages include decrease in morbidity over open RPLND with similar oncologic efficacy. The group from Austria, has reported the only series of L-RPLND [35] which included 114 CS I patients. The mean operative time was 256 min, the mean blood loss was 159 cc (range: 10 to 3000), and the mean hospital stay was 4.1 days. There was one colon and one renal artery injury.

Conclusion

Treatment recommendations for CS-I NSGCT are frequently governed by patient- and tumor-specific histopathologic risk factors. The philosophy underpinning these recommendations is to avoid the over treatment of men cured by orchidectomy while maintaining the highest possible cancer cure rate in those destined to experience a recurrence. Some patients prefer adjuvant treatment, as they may find it difficult to adhere to the strict follow-up regime required by surveillance, or feel like they are waiting for a recurrence (“sword of Damocles” syndrome). Research into better identification of risk factors including molecular markers in future may help in differentiating low and high risk patients.

Major Recommendations for CS-I NSGCT

- Patients should be made aware of all treatment options and the risks and benefits surrounding each of these options.
- When a primary surveillance approach is adopted, patients should be informed of their estimated risk of recurrence and the need for frequent ongoing investigations, including blood tumour markers and computerised tomography (CT) scans of the abdomen and pelvis, to monitor for recurrence.
- For high risk primary tumors an option of Primary RPLND or Primary chemotherapy should be given to the patient
- Patients with CS I NSGCT should be assessed and have management plans developed at multidisciplinary centres with experience in the treatment of testicular cancer.
- Laparoscopic RPLND is still experimental and long term results with more number patients is required

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