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Non-Seminoma Testicular Tumors Clinical Stage I: Management Strategies

Rajendra Nerli*, Adarsh Sanikop, Shoubhik Chandra, Shridhar C. Ghagane, Shashank Patil and Pulkit Gupta

Department of Urology, JN Medical College, KLE Academy of Higher Education & Research, JNMC Campus, Belagavi-590010, India

Abstract

Clinical stage I is the most frequent clinical presentation of non-seminoma testicular cancer. Despite a survival rate of close to 100%, the management of patients with this disease stage is controversial. The recurrence rate is 15% to 50% for those with stage I non-seminoma. A highly sensitive and specific biomarker that can predict or confirm relapse of disease, and help to drive a definitive risk-adapted management is still not available. Lymph Vascular Invasion (LVI) in the orchiectomy specimen has been used as a risk factor in patients with stage I non-seminoma, however, the discriminative power of LVI is modest at best. Presently there is no definitive biomarker that can predict a recurrence following a radical orchiectomy. In situations such as this, active surveillance of these patients helps avoid overtreatment in 50% to 85% of patients, with no risk of long-term side effects in non-relapsing patients and a preserved overall survival of almost 100% after specific treatment for recurrent disease. Although active surveillance has been accepted as the preferred option for stage I low-risk non-seminoma, its role in high-risk stage I non-seminoma remains controversial.

Treating all patients with adjuvant chemotherapy following orchiectomy results in overtreatment of a significant proportion of patients. The challenge is in identifying the patient population that requires adjuvant chemotherapy and in determining how much chemotherapy to give to adequately reduce relapse risk. The role of RPLND in this group of patients too remains controversial. The relapse and complication rates of RPLND are significantly higher outside of expert surgical centres.

Efforts need to be made to focus on maintaining cure rates and at the same time to minimize treatment-related long-term toxicity. Both the patient and the physician need to participate in the decision-making process, and management should be tailored to the individual patient's needs and wishes.

Keywords: Active surveillance • Biomarkers • Retroperitoneal lymph node dissection • Testicular cancer • Chemotherapy • Alpha fetoprotein

Introduction

Testicular tumors constitute a morphologically and clinically diverse group of tumours, of which more than 95% are germ cell tumours (GCTs). GCTs are broadly categorized as seminoma and Non-Seminoma Germ Cell Tumour (NSGCT) because of differences in natural history and treatment. GCT is a relatively rare malignancy, accounting for 1% to 2% of cancers among men. [1]. Cryptorchidism, family history of testicular cancer, a personal history of testicular cancer, and intratubular germ cell neoplastic (ITGCN) are the four well-established risk factors for testicular cancer [2,3]. Testicular cancer is associated with elevation of serum tumour markers, namely lactate dehydrogenase (LDH), Alpha Fetoprotein (AFP), and beta Human Chorionic Gonadotropin (HCG) that are essential in its diagnosis and management. Serum tumour marker levels are obtained at diagnosis, after orchiectomy, so as to monitor for response to chemotherapy, and to monitor for relapse in patients on surveillance and after completion of therapy [4].

Patients having a testicular neoplasm should undergo a radical inguinal orchiectomy with removal of the tumour-bearing testicle and spermatic cord to the level of the internal inguinal ring (Figure 1) [1]. Radical orchiectomy helps in establishing the histological diagnosis and primary T stage, provides important prognostic information from the tumour histology, and is curative in 80% to 85% of Clinical Stage (CS) I seminoma and 70% to 80% of CSI NSGCT [1].

Clinical staging of testicular tumours

The decisions regarding the initial management and the prognosis of the GCT are dictated by CS of the disease, which is based on the histopathologic findings and pathologic stage of the primary tumour, serum tumour marker levels measured after orchiectomy, and the presence and extent of metastatic disease as determined by physical examination and staging imaging studies (Figure 2) [1]. The American Joint Committee on Cancer (AJCC) and Union International Centre le Cancer (UICC) jointly proposed an international consensus classification for GCT in 1997, which is unique, as for the first time a serum tumour marker category (S) based on post-orchiectomy AFP, HCG, and LDH levels was used to supplement the prognostic stages as defined by the anatomic extent of disease [5]. This staging system was updated in 2002, and the new systems considered the presence of lympho-vascular invasion (LVI) in the primary as pT2 in an otherwise organ-confined tumour [5].

CS I has been defined as disease clinically confined to the testis, CS II indicates the presence of regional (retroperitoneal) lymph node metastasis, and CS III represents nonregional lymph node and/or visceral metastasis. The most common presentation of testicular cancer is Clinical stage I and approximately 75% of all patients are diagnosed at this stage. By definition, stage I is characterized by negative tumour markers and no evidence of metastases after orchiectomy for the primary tumour [6,7].

Management of stage I non-seminoma

The expected relapse rate following radical orchiectomy for stage I non-seminoma is between 10% and 50%. The rate of relapse in the primary tumour is 50% in the presence of lympho-vascular invasion and 15% in LVI-negative patients (Figure 3). LVI positivity has only modest discriminative power because 50% of LVI-positive patients are cured by orchiectomy alone [8]. Patients with stage I non-seminoma have three management options namely, surveillance, chemotherapy, and retroperitoneal lymph node dissection (RPLND). Regardless of the treatment chosen, the Overall Survival (OS) exceeds 98% for patients with stage I non-seminoma. In LVI-positive patients, who are considered to be at high risk, as of now no consensus exists regarding the management, whereas most guidelines recommend active surveillance for LVI-negative patients [9-11].

Several other markers such as proportion of Embryonal Carcinoma (EC), rete testis invasion, and MIB-1 staining have been proposed, so as to identify

***Address for Correspondence:** Rajendra Nerli, Department of Urology, JN Medical College, KLE Academy of Higher Education & Research, JNMC Campus, Belagavi-590010, India, Tel: +91-9008351217; E-mail: rbnerli@gmail.com*

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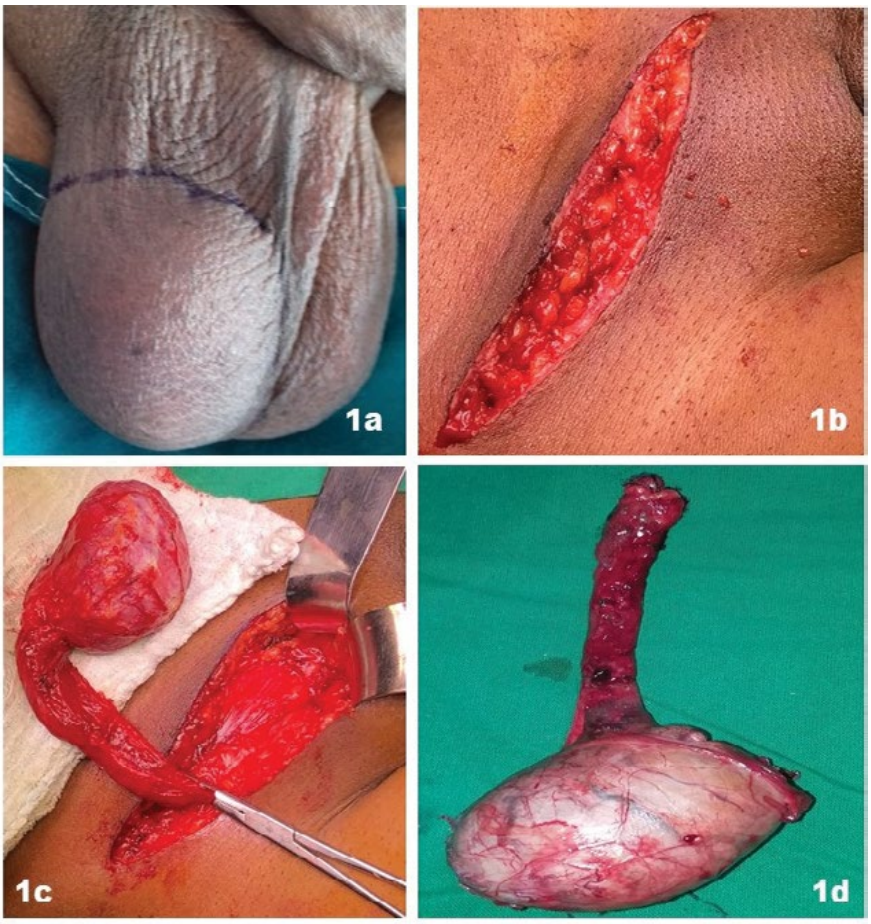

Figure 1. Shows Rt. Sided testicular mass (a), High Inguinal incision (b), Clamping of the cord structures at the level of deep ring (c), High inguinal orchiectomy (d).

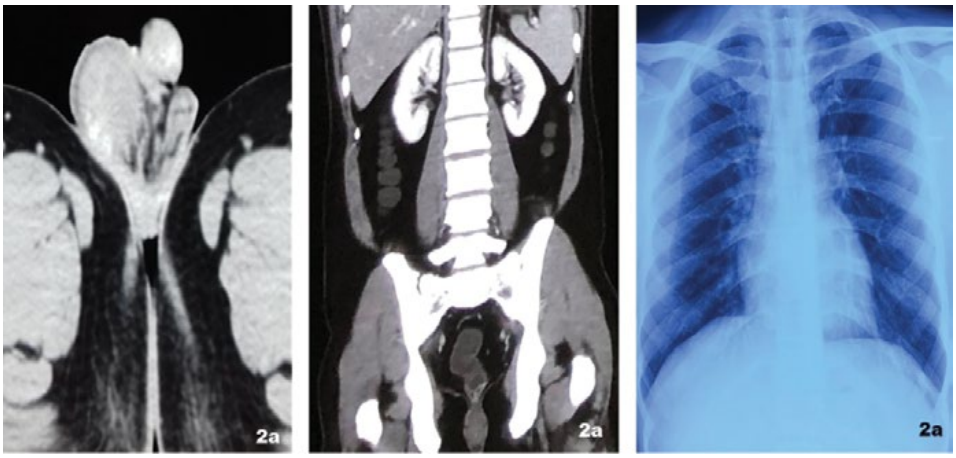

Figure 2. CT scan of scrotum showing Rt. Testicular mass (a), CT of the retroperitoneal shows no evidence of secondary's, c. Chest radiography shows no evidence of metastasis (b).

patients who are likely to develop relapse, however the results have not been fully validated. Tumours showing no components of embryonal carcinoma are generally believed to have a low rate of recurrence [12]. Recently, CXCL12 expression has been proposed as a prognostic marker and validated in two data sets [13-15]. On the basis of this marker and vascular invasion, three risk groups have been proposed including low (10% risk), intermediate (30%-40% risk), and high (70%) risk groups though this remains to be validated [12].

Active Surveillance

Active surveillance is recommended by most guidelines for the management of LVI-negative stage I non-seminoma. With active surveillance, the patient can be watched carefully with the aim of detecting early relapse and treatment of recurrence by bleomycin, etoposide and cis-platinum (BEP) based chemotherapy [16]. This is approach has the virtue of avoiding treatment (and its attendant toxicities) except when necessary. The use of surveillance has grown over the years but it has its own share of troubles. Patients who relapse need to undergo full-dose chemotherapy. Active surveillance alone may cause psychological stress and can make it difficult for some patients to return to a normal lifestyle for fear of recurrence. Compliance is also a matter of concern in these patients. It is feared that patients that are non-complaint usually relapse with more advanced disease and a poorer prognosis [17].

Based on the data of patients on surveillance, the median time to relapse is 4 months for LVI-positive patients and slightly longer (8 months) for LVI-

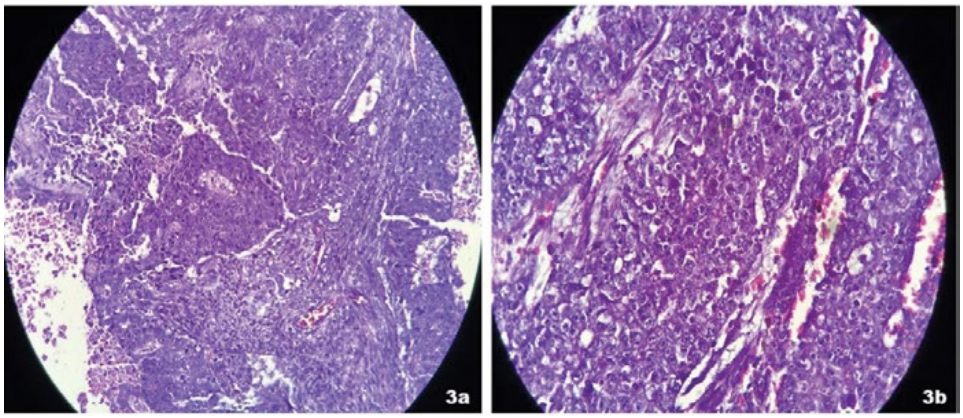

Figure 3. Photomicrograph of mixed germ cell tumour (H & E stain; 200x & 400x) (a and b).

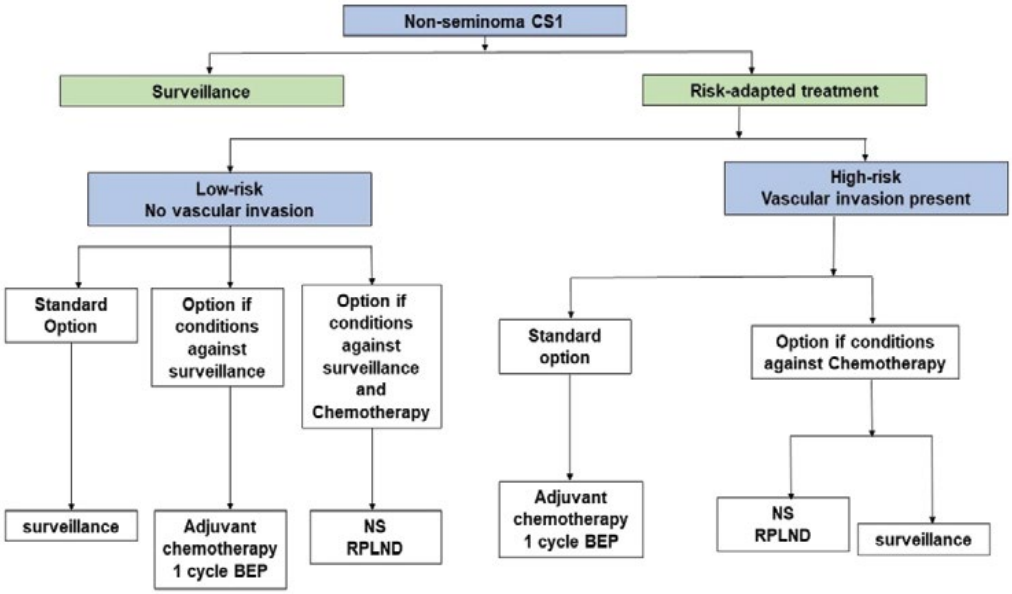

Figure 4. Guidelines suggesting risk adapted treatment.

negative patients. Most patient relapses occur within the first 2 years of active surveillance, and only 1% of patients relapse after 3 years. Overall survival for patients with stage I non-seminoma is very high (98%) regardless of the management strategy because these patients are cured with either chemotherapy or RPLND. Tumour markers are used to detect relapse [16]. Elevation of tumour marker levels represents the first sign of relapsed disease in 61% of LVI-positive patients and 41% of LVI-negative patients. Patients with stage I seminoma, should have a computed tomography (CT) examination done especially during the first year of follow-up, followed by more intense follow-up during the first 2 years, when the risk of relapse is highest. However, the timing and frequency of CT scans remains controversial in stage I non-seminoma [18].

Non-compliance is frequently used as an argument against active surveillance; however the survival rates with active surveillance have been consistently greater than 97%, regardless of the degree of adherence in these studies. As the pattern of metastases from testicular cancer is extremely conservative and predictably limited to the retroperitoneal lymph nodes, CT or magnetic resonance imaging of the abdomen alone is sufficient to detect the vast majority of relapses [17,18].

Adjuvant BEP Chemotherapy

Use of adjuvant chemotherapy is an option following radical orchiectomy in patients with stage I non-seminoma. This was first explored in the early 1990s following the success of BEP chemotherapy in metastatic disease. Using limited chemotherapy in patients with high risk would restrict exposure to chemotherapy and also prevent relapse. The MRC TE05 study, included 114 patients with a predicted recurrence risk based on MRC risk factors of >50%. Relapse was noted in one patient and the 95% CI excluded a risk of relapse of 5%. Similar data has been replicated in a number of reported studies totalling almost 1000 patients and a combined risk of relapse of <2%. Adjuvant treatment of patients with high-risk stage I non-seminoma with 2 cycles of BEP has significantly reduced the risk of relapse, from 50% to 2% [19].

Adjuvant BEP has become an option for high-risk stage 1 NSGCT. Its use has been the subject of much debate and is cantered on the issue of late toxicity from BEP. Acute toxicities of BEP have been recognised for many years and over the last decade, the risk of long-term effects have also been appreciated especially neuropathy, cardiovascular disease, and second malignancy. Proponents of adjuvant chemotherapy point out at the lower doses that can be used, which meant less risk of toxicity.

Several studies recently have demonstrated a similar reduction in relapse risk with only 1 cycle of BEP. Bandstand and colleagues found no difference between 1 and 2 cycles of BEP for high-risk patients. Moreover, they also have compared surveillance with 1 cycle of BEP in LVI-negative patients, confirming that either strategy could be used in these patients with the same results [20].

Retroperitoneal Lymph Node Dissection (RPLND)

Prior to the introduction of cisplatin-based chemotherapy in 1977, the only treatment that was available for patients with stage I non-seminoma was RPLND. As of today, primary RPLND is indicated only in patients who refuse and are not suitable candidates for either chemotherapy or active surveillance. Pathological metastatic retroperitoneal lymph nodes are seen in 15% to 35% of patients with stage I disease [21]. The cure rate with primary RPLND is 84.1% for patients with pathologically confirmed stage I disease, whereas it is only 68.3% for patients with pathologically confirmed metastatic disease. Chest represents the first site of relapse in 70% of cases following RPLND [22].

The role of RPLND based on risk adapted model, in the management of patients with stage I disease has diminished. An European study, has clearly demonstrated the superiority of adjuvant chemotherapy over primary RPLND. The relapse and complication rates increased significantly outside of expert surgical centres. Moreover, an Italian study by Nicolai and colleagues showed that 16% of patients needed chemotherapy after RPLND to eradicate the disease [23,24]. The expertise of the treating center determines the outcomes of primary RPLND. For these reasons, primary RPLND usually is recommended only in referral centres with a high level of expertise, and for patients who do not want and/or are not suitable for chemotherapy or active surveillance [22,25].

Risk-Adapted Treatment (EAU Guidelines)

The European association of Urology (EAU) guidelines have suggested that risk-adapted treatment is an alternative to surveillance for all patients with CS1 NSGCT (Figure 4). Risk-adapted treatment is based on the risk factor of vascular invasion. EAU guidelines further state that, patients with vascular invasion are recommended to undergo adjuvant chemotherapy and patients with absent vascular invasion are recommended a surveillance strategy [26]. In the past, two cycles of BEP were recommended for adjuvant treatment. In view of the low rates of recurrence (2%-3%) and equivalent cure rates, including salvage strategies in large prospective trials with sufficient follow-up, one cycle of BEP is now recommended as adjuvant chemotherapy in patients with vascular invasion [26,27].

In cases of relapse after BEP x 1 in marker negative patients, RPLND should be considered as the relapse may be teratoma. If markers are positive three courses of BEP are recommended. However, only limited evidence exists, which does not support a specific salvage regimen [26].

Conclusion

Nearly 30% of patients with clinical stage I non-seminomatous germ cell tumours (NSGCTs) have occult metastatic disease, and will have a recurrence following a high inguinal radical orchiectomy. Three management options exist for patients with stage I non-seminoma: surveillance, chemotherapy, and retroperitoneal lymph node dissection (RPLND). Judicious use of risk adapted treatment is essential to treat the patients.

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