

## UROLOGY FOR THE PRACTITIONER NONSEMINOMATOUS TESTICULAR CANCER

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**ABSTRACT : Testicular cancer is the most common solid malignancy in young men between the ages of 20 and 40 years. Its incidence is increasing worldwide.**

**The success achieved in its treatment has not been seen in any other cancer.**

**This communication will present some of the controversies in the management of nonseminomatous germ cell tumors, the changes that were introduced over the last two decades to decrease the toxicity from treatment and will discuss the most up-to-date treatment of every clinical stage of the disease.**

### INTRODUCTION

Testicular cancer is a relatively rare disease. In 2002, 7,600 new cases were reported, accounting for 1% of all cancers in men in the United States [1]. However, in the age group in which it has its peak incidence, 20 to 40 years, it is the most common malignancy. That, together with the fact that it affects men during the most productive years of their life and its treatment causes major disability such as infertility, makes it a significant and challenging disease for the patient and the treating physician.

A recent review by Huyghe et al. [2] demonstrates a trend towards an increasing incidence of testicular cancer, worldwide. This is true in the United States also : in 1992, 6300 new cases were reported compared to 7600 in 2002. This represents a 20% increase in one decade. The reasons for the increase are not clear. Except for cryptorchidism, there are no known risk factors for testicular cancer.

Before 1970, the majority of men who developed testicular cancer died of their disease. The introduction of cisplatin combination chemotherapy in the mid 1970's, the multidisciplinary approach to treatment, the more aggressive surgical approach in advanced disease and the fact that chemotherapy can cure patients who relapse, have significantly reduced the mortality from testicular cancer. In this day and age, it is the rare patient

who dies from testicular cancer. Because of this great success, urologists and oncologists have concentrated their efforts during the past decade on finding ways to reduce the toxicity of therapy while maintaining the curability of testicular cancer.

### EVOLUTION OF THERAPY OF TESTICULAR CANCER

#### Chemotherapy

In the 1960's, chemotherapy for metastatic testicular cancer was actinomycin-D, chlorambucil and methotrexate and the complete response rate was in the order of only 10% to 15%. In 1970, vinblastine and bleomycin were introduced and gave a better response rate of 25%. In 1974, cisplatin was added to vinblastine and bleomycin and the complete response rate markedly improved to 85% when combined with surgical resection of residual disease [3]. Because of the success of this combination, the standard chemotherapy became 4 cycles of cisplatin, vinblastine and bleomycin (PVB) and reports of complete response rates of 80% or better were not uncommon. But with success came more toxicity : peripheral neuropathy, decrease in glomerular filtration rate, ototoxicity, pulmonary fibrosis and significant neutropenia, which led oncologists to modify treatment in order to decrease toxicity but hope to maintain the high rate of response. Several modifications of the PEB (platinum, etoposide, bleomycin) protocol in prospective randomized studies followed :

1. To decrease the peripheral neuropathy from vinblastine, etoposide (VP16) was substituted for vinblastine (PEB instead of PVB) and response rates were observed to be as good or better [4].
2. To decrease the nephrotoxicity from cisplatin, carboplatin was used instead of cisplatin but response rates were inferior [5-6].
3. To eliminate pulmonary toxicity, bleomycin was eliminated from PEB but response rates dropped [7].
4. To decrease the overall toxicity, 4 cycles of PEB were compared to 3 cycles of PEB in good risk patients and the overall and disease free survival were identical [8].

Based on all these studies, the standard chemotherapy for advanced testicular cancer in the majority of cases became, and is now, 3 cycles of PEB chemotherapy.

#### Surgical Treatment

Surgical treatment of clinical Stage I, and early Stage II nonseminomatous testis cancer was always, and still is in many cases, orchiectomy followed by bilateral retroperitoneal lymph node dissection (RPLND). The standard, bilateral RPLND interferes with the sympathetic

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nerve supply to the ejaculatory ducts and bladder neck and causes loss of ejaculatory function or retrograde ejaculation, both of which lead to infertility. Modifications in RPLND such as removing the lymph nodes on the side of the tumor only and preserving the opposite side, nerve-sparing lymphadenectomy, prospective identification and sparing of the sympathetic nerves, and more recently, laparoscopic RPLND, have all led to varying degrees of preservation of ejaculatory function.

Because chemotherapy is very effective in curing the great majority of patients with metastatic disease and those who relapse after surgical treatment, urologists were encouraged to place on surveillance those patients with clinical Stage I disease and favorable prognosis, instead of subjecting everyone to RPLND. The argument for surveillance is that the majority of patients (70% to 85%) with clinical Stage I disease are cured by orchiectomy alone and never relapse. Therefore, by subjecting every patient with clinical Stage I disease to RPLND, we will be operating unnecessarily on, at least, 70 % of patients. Furthermore, the great majority of the 15% to 30% of patients who may relapse after orchiectomy will be cured by present day chemotherapy. The arguments against surveillance are the significant relapse rates of up to 30%, the need for very close and intensive follow-up with CT scans. Furthermore, patients on surveillance may be lost to follow-up, and if their disease recurs, it may be too far advanced to be cured with chemotherapy by the time it is discovered.

#### SURVEILLANCE VERSUS RPLND

The author is a proponent of surveillance and in 1989 reported on the results of a study comparing the recurrence rate of patients with clinical Stage I nonseminomatous testis cancer on surveillance to the recurrence rate after RPLND in patients with pathologic Stage I disease [9]. The following is an update of that study.

#### The criteria used for placing a patient on surveillance were :

1. Tumor confined to the tunica albuginea of the testis.
2. No microvascular or microlymphatic invasion within the primary tumor.
3. Normal post orchiectomy markers.
4. Normal CT scans of the chest, abdomen and pelvis.
5. Normal bipedal lymphangiogram. In the 1980's and early 1990's, bipedal lymphangiograms were part of the evaluation process but not recently.

Thirty-three patients satisfied all the above criteria and were placed on surveillance and followed every 3 months during the first year, every 4 months during the second year, every 6 months during the third year, and once a year thereafter. With every follow-up, patients had physical examination, tumor markers and CT scans of the chest, abdomen and pelvis. Thirty-one patients who did not satisfy all the criteria for surveillance underwent RPLND and had pathologic Stage I disease and

were followed with the same protocol like those on surveillance.

Table I lists the recurrence rates in both groups. The difference in recurrence rates between this study and others that report recurrences as high as 30% is due to patient selection and to the strict criteria used to place patients on surveillance. All patients who recurred in both groups were cured with chemotherapy.

**TABLE I**  
SURVEILLANCE VERSUS RPLND IN PATIENTS WITH CLINICAL STAGE I NONSEMINOMATOUS TESTIS CANCER

	SURVEILLANCE	RPLND (PATHOLOGIC STAGE I)
<b>No. of Patients</b>	33	31
<b>Recurrences</b>	4 (12%)	3 (10%)
<b>Mortality</b>	0	0

#### Primary Chemotherapy for Clinical Stage I Nonseminomatous Testicular Cancer

Because of the success of chemotherapy in curing metastatic disease, oncologists were encouraged to try it in patients with clinical Stage I disease and a high risk of recurrence. Several studies have appeared in the literature reporting low recurrence rates of 2% to 4%, and excellent survival with two cycles of chemotherapy (Table II). Arguments in favor of primary chemotherapy rather than RPLND for clinical Stage I disease are the discomfort from major surgery and the complications associated with it, such as loss of ejaculatory function and small bowel obstruction, and the significant risk of recurrence even in patients with pathologic Stage I disease. Arguments against primary chemotherapy center around the uncertainty of long-term sequelae of 2 cycles of platinum-based chemotherapy, namely, fertility, secondary malignancy and under treatment or partial treatment of those patients who may have disease in the retroperitoneal lymph nodes undetected by CT scans, a situation which may select for chemoresistant strains and render recurrences unrespon-

**TABLE II**  
REPORTED SERIES OF PRIMARY CHEMOTHERAPY FOR CLINICAL STAGE I NONSEMINOMATOUS TESTIS CANCER

AUTHOR	Year	No.	Relapse	Survival
OLIVER [10]	1991	30	0	100%
CULLEN [11])	1996	114	2	98%
CHEVREAU [12]	1997	38	0	100%
BOHLEN [13])	1999	59	1	100%

sive to platinum-based chemotherapy.

RPLND and surveillance are options that have been tested and have a long track record with cure rates of up to 99% in clinical Stage I nonseminomatous testis tumors. Primary chemotherapy, although its early results are impressive, is a relatively new option, which needs to be tested in more patients followed for longer periods of time. At present, it remains controversial [14].

## TUMOR MARKERS

Alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG) and lactic dehydrogenase (LDH), the serum markers of testicular cancer, play a major role in all aspects of the disease : diagnosis, treatment, and follow-up.

AFP levels are increased only in patients with nonseminomatous testis tumors while HCG can be elevated in both, seminoma and non-seminoma. Both of these markers are specific and increased levels indicate active disease in the great majority of patients. LDH may be elevated in both seminoma and nonseminoma and is most frequently increased in patients with seminoma. It is a measure of tumor growth. It is not as specific as AFP and HCG because it can be elevated in many other disease conditions.

The rate of decline in the level of tumor markers with treatment can be an indirect measure of tumor resistance to chemotherapy. This has been shown to be true for HCG [15]. If the same is true for AFP and LDH, a slow half-life with the first cycle of chemotherapy may be an indication to make changes in therapy early in the course of treatment.

## INTERNATIONAL GERM CELL CONSENSUS CLASSIFICATION BASED ON RISK

Patients can be classified according to their risk of relapse after initial therapy as follows :

**Good Risk Patients** are those with testicular or retroperitoneal primary, no visceral metastasis except lung, and an AFP of less than 1000, HCG less than 5000 and LDH less than 1.5 times the normal value.

**Intermediate Risk Patients** are those with testicular or retroperitoneal primary, no visceral metastasis except lung, AFP between 1000 and 5000, HCG between 5000 and 50,000 and LDH between 1.5 and 10 times the normal value.

**Poor Risk Patients** are those with mediastinal primary germ cell cancer, non-pulmonary visceral metastasis, and AFP more than 10,000, HCG more than 50,000 and LDH more than 10 times the normal value.

This classification rather than clinical stage is used to tailor treatment based on risk assessment [16].

## CLINICAL STAGES AND THEIR TREATMENT

### Stage I

When the tumor is confined to the testis, the post orchietomy AFP, HCG and LDH are normal, and CT scans of the chest, abdomen and pelvis show no evidence of metastasis,

the patient has clinical Stage I disease.

There are three treatment options for the patient with clinical Stage I nonseminomatous testis cancer : surveillance, RPLND and 2 cycles of platinum-based chemotherapy. The author recommends surveillance and close follow-up for those who fit the criteria listed above, otherwise a nerve sparing RPLND is recommended. In recent years and with growing experience with and knowledge of the long-term effects of two cycles of platinum-based chemotherapy, more urologists and oncologists are recommending chemotherapy as primary treatment for patients with clinical Stage I disease.

Between 1983 and 1998, the author treated 103 patients with clinical Stage I nonseminomatous testis cancer. Thirty-three patients were placed on surveillance and 70 underwent RPLND. Of those who underwent RPLND, 31 had pathologic Stage I disease and 39 had retroperitoneal lymph node metastasis (Stage IIA), 26 of whom received adjuvant chemotherapy with two or three cycles of PVB or PEB. Recurrences occurred in 13 of the 103 patients for an overall recurrence rate of 13%. The long-term disease free survival or cure rate is 100%.

### Stage II

Patients with clinical Stage II disease have retroperitoneal lymph node metastasis. Those with lymph nodes that are less than 3 cm in greatest diameter are classified as having clinical Stage IIB disease and those with bulky retroperitoneal lymphadenopathy have clinical Stage IIC disease. There are two treatment options for patients with Stage IIB disease : RPLND and surveillance or RPLND followed by 2 cycles of PEB adjuvant chemotherapy. According to the Multi-institutional Intergroup Testicular Cancer Trial, adjuvant chemotherapy significantly reduces the recurrence rate but has no impact on survival because the majority of patient on surveillance who relapse are cured with PEB chemotherapy but do require more than just 2 cycles of chemotherapy [17].

Between 1983 and 1998, the author treated 82 patients with clinical Stage II nonseminomatous testis tumors : 47 had clinical Stage IIB and 35 clinical Stage IIC. Treatment of patients with clinical Stage IIB disease consisted of RPLND and observation for those with unilateral lymphadenopathy below the renal hilum, and RPLND followed by adjuvant 3 cycles of PVB or PEB for those with bilateral lymphadenopathy and with disease above the renal hilum. Long-term disease free survival in this group of patients is 91%. Treatment of patients with clinical Stage IIC disease consisted of 3 or more cycles of chemotherapy followed by resection of residual disease, if any. The long-term disease free survival in this group of patients is 85%.

### Stage III

The standard therapy for patients with Stage III nonseminomatous testis cancer is 4 cycles of PEB chemotherapy followed by resection of residual disease, if any. About 40% to 50% of these patients, especially those

with poor risk factors, may relapse after initial chemotherapy. About half of those who relapse can still be cured with salvage chemotherapy, making the overall long-term disease free survival of patients with Stage III disease about 75%.

Between 1983 and 1998, the author treated 98 patients with Stage III nonseminomatous testis cancer. Treatment consisted of at least 4 cycles of PVB or PEB followed by resection of residual disease, if any. Those who relapsed were treated with salvage chemotherapy, which is discussed below. The long-term disease free survival of these patients is 78%.

#### *Treatment of Relapsed Testicular Cancer*

Ifosfamide is one of few cytotoxic agents active in germ cell tumors that recur after initial PVB or PEB chemotherapy. When combined with cisplatin and either vinblastine or etoposide (VIP), is associated with response rates of 30% to 35% and long-term survival. Paclitaxel is another agent active in relapsed testicular cancer. In one study, it was combined with ifosfamide and cisplatin (TIP) and given to 30 patients with favorable factors who relapsed after achieving complete response to initial chemotherapy. The complete response rate was 77% [18].

High dose chemotherapy with autologous stem cell rescue is being used more often in relapsed and early in the treatment of poor risk patients based on earlier studies achieving complete response rates of 57% [19].

#### SUMMARY

The successes achieved during the last 3 decades in the treatment of men with testicular cancer has not been duplicated in any other solid tumor. The sensitivity of germ cell tumors to chemotherapy, the aggressive surgical management and the multidisciplinary approach to treatment, have all contributed to make this cancer a curable one. Furthermore, the changes that were introduced in the management of these young men have significantly reduced toxicity of both chemotherapy and surgery.

There is still a relatively small number of men who die of testicular cancer and efforts are being made to eliminate that altogether by identifying those at poor risk early in the course of therapy and treating them aggressively.

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