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Mini Review

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Treatment of Stage I Seminoma

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ABSTRACT

Stage I testicular seminoma is a curable condition. The primary treatment is high inguinal orchiectomy. The treatment options after surgery includes radiotherapy, chemotherapy with single agent carboplatin and active surveillance. Radiotherapy has evolved over the past decades with reduced treatment volume and radiation dose without compromising the outcome. Para aortic strip radiation 20 Gy in 10 fractions is equivalent to single agent carboplatin. Active surveillance is an acceptable approach for patients without adverse factors. There is no data comparing treatment versus active surveillance till date. This article reviews the evidences for each approach.

KEYWORDS: Seminoma stage I surveillance; Radiotherapy; Tumors; Treatment.

INTRODUCTION

Testicular cancer constitutes 1-2% of all cancers in men. The age standardized incidence varies from 0.6 in Asia to 12.2 in Norway per 100,000 men.[1] Testicular Germ Cell Tumors (GCT) are broadly classified into Seminoma and Non-seminoma groups. They represent one among the few curable malignancies. Their exquisite sensitivity to chemotherapy and radiation is the reason behind the success story. Pure seminoma accounts for nearly half of all diagnosed GCT and appear increasing.[2] The median age at presentation is around 40 years, a decade later than non-seminoma. Stage I seminoma refers to disease limited to testis with normal tumor markers. The options available for stage I seminoma after orchiectomy are chemotherapy, radiotherapy or active surveillance. Regardless of the treatment strategy, the disease specific survival is close to 100%.[3-5] Because of long-term survival, treatment related morbidities are a concern. This has given rise to a debate of selecting the optimal treatment strategy.

INITIAL WORK UP AND MANAGEMENT

Most often patients with testicular tumor present with discomfort or swelling in the scrotum. If an intratesticular mass is suspected, an ultrasound of the scrotumaids in confirming the diagnosis as well as evaluate the contralateral testis. Initial investigations required for suspected testicular tumor is given in Table 1. A pre-operative estimation of tumor markers including beta Human Chorionic Gonadotropin (βHCG), Alpha Feto Protein (AFP) and Lactate dehydrogenase (LDH) is mandatory. βHCG can be produced by both seminomatous and non-seminomatous tumors, but AFP is produced by non-seminomatous tumors only. If the pathological diagnosis is pure seminoma with elevated pre-operative AFP, then it must be considered and treated as non-seminoma. Sperm abnormalities can be found in patients with testicular cancer. Furthermore, treatment with either chemotherapy or radiation can impair fertility. Hence, semen analysis and sperm banking should be discussed prior to start of therapy.

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Complete blood count, Renal function test, Liver function test
Chest X-ray, CT Abdomen and Pelvis
Tumor markers- βHCG, AFP and LDH
Semen Analysis

Table 1: Investigations.

SURGERY

Initial treatment of a testicular tumor is high inguinal orchidectomy. The spermatic cord is ligated high in the internal inguinal ring. The surgical removal of testis aids in a definite pathological diagnosis and curative in more than 80% of patients with stage 1 seminoma. There is no role for retroperitoneal lymph node dissection. The essential pathological details to be mentioned in histopathological report are given in Table 2. Post-operative measurement of tumor marker is mandatory. If the tumor markers remain high after surgery, it indicates residual tumor and it does not qualify as stage I despite normal imaging.

Histology of the tumor
Presence or absence of lymphovascular invasion
Involvement of tunica albuginea, tunica vaginalis, rete testis, epididymis or spermatic cord
Presence or absence of Testicular Intraepithelial Neoplasia (TIN)

Table 2: Essential pathologic microscopy details.

RISK FACTORS FOR RELAPSE

Surgery alone cures majority of stage I seminoma patients. About 80-85% of patients may not benefit from adjuvant treatment.[5] Pros and cons of adjuvant treatment are mentioned in Table 3. Many studies have tried to identify risk factors for relapse.[6-8] In a pooled retrospective review of patients followed up with surveillance protocol, tumor size >4 cm and rete testis invasion were independent risk factors for relapse. The 5 year relapse rate was 15.9% and 31.5% if either one or both the factors were present.[6] In yet another pooled retrospective review, a validation of the above mentioned risk factors was attempted. On multivariate analysis only tumor size (more than 3 cm) was found to have significant correlation with relapse rate.[8] In the Danish surveillance, tumor size was significant along with vascular invasion or involvement of epididymis.[9] These risk factors described are not validated in a prospective study till date.

For Adjuvant Treatment	Against Adjuvant treatment
Late relapse Cost of Surveillance No reliable tumor marker Anxiety Compliance	Unnecessary treatment for majority Treatment related morbidity Recurrence can be salvaged

Table 3: Pros and Cons of adjuvant treatment.

Risk adapted approach to patients with stage I seminoma was evaluated by the Spanish Germ Cell Cancer Group (SGCCG) in the consecutive studies.[7,10,11] A pooled analysis of these studies reported that at median follow-up of 80 months, 14.8% patients on surveillance and 3.2% patients treated with adjuvant carboplatin relapsed. Actuarial overall 5-year Disease-Free Survival (DFS) was 92.3% (88.3% for surveillance *vs.* 96.8% for chemotherapy, p=0.0001). On multivariate analysis, tumor size more than 4 cm and rete testis invasion were independent factors affecting DFS.

SURVEILLANCE

Surveillance involves close follow-up of patients with clinical examination, evaluation of tumor markers and imaging at regular intervals. This enables detection of relapses early and prompt curative treatment. The relapse rate of patients on surveillance is 11.1-27%.[7,12-14] A close follow-up and early detection of recurrence is necessary for a successful salvage treatment. This requires frequent imaging and good patient compliance. There are problems for surveillance in the young patient population who move around for employment and may not show up for reviews. Loss of follow-up is reported by US and Japanese teams.[15]

The most common site of relapse for patients on surveillance is retroperitoneum and hence radiological imaging is necessary. The imaging frequency should be more in the first three years when the risk of relapse is high.[16] However, the timing and frequency of imaging is not well defined. The Royal Marsden Hospital (RMH) and the Princess Margaret Hospital (PMH) surveillance protocol is given in table 4. The RMH protocol incorporates Computed Tomography (CT) imaging of abdomen and pelvis imaging is advised if there was a scrotal violation or prior pelvic surgery. After 5 years, imaging is done only if indicated.[17] In the PMH surveillance protocol, CT abdomen and pelvis is done at increased frequency and carried on for 10 years. Serum markers are monitored at every visit in the first three years.[18] Imaging frequency of above two approaches is given in table 4.

	Royal Marsden Hospital protocol[17]	Princess Margaret Hospital Protocol[19]
CT imaging	Biannually in the first two years, annually from third to fifth year	CT abdomen and pelvis every 6 months in the first three years and CT abdomen only done annually thereafter till year 9
Chest X ray	Biannually in the first two years, annually from third to fifth year	Annually in the first three years

Table 4: Imaging frequency of two surveillance protocol.

The value of chest x ray has been questioned recently.[16,20] Similarly, the value of serum markers is also limited.[21,22] Another concern with multiple CT imaging is radiation induced malignancy. Frequency of CT scans is different in many institutions and the Medical Research Council (MRC) sponsored study TRISST will tell us whether 3 scans can replace 7 and whether Magnetic Resonance Imaging (MRI) is better.[23] A universal consensus for surveillance is yet to evolve.

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ADJUVANT RADIOTHERAPY

Radiotherapy in stage I seminoma traditionally involved radiating para aortic lymphatics and ipsilateral iliac lymph node using the "Dog Leg (DL)" field. The primary lymphatic drainage of testes is para aortic lymph nodes. If they are uninvolved, it is unlikely that the iliac lymph nodes will be positive. This was addressed in the Medical Council Research trial, comparing Paraaortic field (PA) and dog leg (DL) field.[24] The relapse free rate at 3 year was 96% and 96.6% in PA and DL group respectively. The pelvic relapse free rate in PA group was 98.2%. All relapses in DL group was supra diaphragmatic. Para aortic radiation has less hematologic, gastro intestinal and gonadal side effects. If there was prior lymphatic violation i.e. inguinal or scrotal surgery, extended field or "dog field" radiation is used. A dose of 30 Gy in 15 fractions was the standard in treatment of stage I seminoma. A reduced dose of 20 Gy in 10 fractions was compared with 30 Gy in 15 fractions in a randomized trial and reported that there was no difference in five year relapse free rates.[25] These trials have resulted in the evolution of standard portals of a PA field using 20 Gy in 10 fractions over two weeks. The most common site of relapse is in the pelvic nodes and the borders of the radiation field. The relapse rate after RT varies from 0.8-6% in various reports.[3,26,27]

RADIATION TOXICITY

The acute toxicity of radiation includes fatigue, nausea, vomiting and mild diarrhea. Usually these are self limiting and subside after treatment.[24] The long-term toxicity which is of concern are second malignancy and cardiac toxicity.[28,29] In a larger series, though the cardiovascular toxicity was not high, second malignancies were reported more.[30]

ADJUVANT CHEMOTHERAPY

GCTs are very sensitive to platinum agents. Various studies have evaluated the use of single agent carboplatin as one or two cycles in stage I seminoma. A non-inferiority trial by MRC compared adjuvant Carboplatin with a dose of Area Under the Curve (AUC) 7 *versus* adjuvant radiotherapy.[3] The relapse free rate at 5 yrs was 94.7% *vs*. 97% and contralateral GCT free rate was 99.8% *vs*. 98.8% in carboplatin and radiotherapy arm respectively. The most common site of relapse was in the retroperitoneum requiring close follow-up with abdominal imaging. Carboplatin dose calculation needs to be considered carefully as GFR by radio isotope is the best method, otherwise underdosing could occur.[31] Some even recommend two courses of the drug.[27] Compared to radiation the treatment duration and acute toxicity is less. Long-term toxicity of chemotherapy cannot be ascertained until long-term follow-up is available. One study reported decreased contralateral testicular tumour in chemotherapy arm.[3] But delayed appearance is possible based on a German study.[32]

The patients who receive adjuvant treatment should be followed with history, physical examination and serum tumor markers every four months in the first two years and annually thereafter up to 10 years. Imaging can be done in the same frequency as followed in surveillance protocol.

CONCLUSIONS

Orchiectomy alone is curative in 80-85% of patients with stage I seminoma. The rest 15-20% could be cured with either radiotherapy or chemotherapy. Regardless of surveillance or adjuvant treatment, excellent long-term results can be accomplished in stage 1 disease. The difference lies in the relapse patterns, follow-up schedule and long-term toxicity. There is no standard treatment approach, but discussing the pros and cons of each strategy with the patient helps in making a decision. It would be preferable to recommend surveillance to most patients and adjuvant radiotherapy or carboplatin to high risk or unreliable patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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