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Testicular Cancer

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From the Desk of Director Research

Testicular cancer is one of the less common cancers and a relatively rare tumor type, accounting for approximately 1% of all male cancers globally and in India. In recent decades, the incidence of testicular cancer has been increasing a doubled since 1960s in many Western societies. However, testicular cancer has a very distinctive age distribution and usually affects young men with 85% diagnosed between 15 and 44 years of age. There is also secondary peak in incidence after age 60 years. Testicular cancer has one of the highest cure rates of all cancers with an average five-year survival rate of 95%.

The most common type of this cancer is known as 'Testicular germ-cell tumor' (TGCT), which accounts for around 95% of all cases and most of the remaining 5% are sex cord-gonadal stromal tumors derived from Leydig cells or Sertoli cells. There are two main subtypes of TGCT, seminomas, and non-seminomas, both account for around 40-45%. Presentation is usually a painless lump in the groin area and scrotum, testicular pain and/or abdominal pain, gynaecomastia and hydrocele. Generally it is detected at an early stage, and men often find the cancer themselves while performing self-examination. However, some testicular cancers may not cause symptoms and may go undetected until they have spread to other parts of the body.

Testicular cancer could be successfully treated with surgery, chemotherapy, and/or radiation therapy. In the past, metastatic testicular cancer was usually fatal, but recent advances in treatment such as new drugs and new drug combinations, eliminating certain drugs, replacing them with others for reducing side effects, high-dose chemotherapy and stem cell rescue, have considerably improved the prognosis. These cancers are very sensitive to chemotherapy and are curable even when the disease is metastatic. Testicular cancer is a bright spot in the oncological landscape and is now considered the model for the treatment of solid tumors.

Even though significant numbers of patients are being cured of testicular cancer, unfortunately a major side effect of treatment includes temporary or permanent loss of fertility. As more and more young men are surviving testicular cancer, fertility has become an increasingly important issue. However, advances in assisted reproduction methods, such as in vitro fertilization and sperm cells removed from a testicular biopsy specimen, have made fatherhood possible for many patients. For survivors, there is a need for continued research to understand the many factors influencing men's knowledge and awareness of this cancer, particularly with regard to social support and to formulate strategies or interventions that will promote practice of self-examination in young adult males.

The present issue of the Cancer News highlights newer advances in the field of "Testicular Cancer" and features the regular articles, such as Special Feature, Guest Article, Perspective, In Focus, Research and Development, Clinical Trials and Globe Scan. We are grateful to Dr Sameer Khatri, Senior Consultant, Dept of Medical Oncology, HCG Centre, Delhi for contributing the Guest Article, and Dr Rajeev Sood, Professor and Head, Dr Raman Tanwar, Senior Registrar; Department of Urology, PGIMER and Dr RML Hospital, New Delhi, for their jointly written feature "In Focus".

Suggestions/ comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

TESTICULAR CANCER

Early detection of testicular tumors has been touted as beneficial for more than 100 years. In earlier eras, timely detection was virtually the only way to improve outcomes. As per statistics that has been tracked in the literature, the delay from initial symptoms to definitive diagnosis by radical orchiectomy has averaged 4 to 5 months. Patient mediated delay owing to ignorance, embarrassment, fear of cancer, or fear of emasculation, are well known. Physician mediated delay most commonly results from misdiagnoses of testicular tumour as an infection. Painful presentation is not uncommonly responsible for a false diagnosis of epididymitis. In the modern era of effective chemotherapy, the effect of the delayed diagnosis on survival can be overcome but at the cost of a more morbid treatment regimen. Although screening on population basis is not currently recommended, teaching testicular self examination to young men, particularly those who have risk factors, is reasonable.

Intratubular Germ Cell Neoplasia (ITGCN) of the Testis and Contralateral Testicular Biopsy: A noninvasive precursor lesion (ITGCN or Carcinoma in Situ) had been characterized that would progress to invasive testicular tumors. Microscopically, ITGCN cells are larger than normal spermatogonia and usually have a prominent irregular nucleus, distinct nucleoli, coarse clumps of chromatin, and abundant cytoplasm. The malignant transformation to the ITGCN cell is believed to take place in utero during the early development of the germline stem cells. Testicular tumors increase the risk of ITGCN in contralateral testis. Other risk factors include cryptoorchidism, infertility, atrophic testis, familial testicular cancer, and gonadal dysgenesis. Clinical diagnosis is based on surgical biopsy of the testis. Contralateral testicular biopsy in patients with unilateral testis cancer at the time of orchiectomy is still a highly controversial subject due to the procedural adverse effects. Protracted coarse of ITGCN, side effects of therapy, and the realization that second primary germ cell tumors respond well to treatment are other factors which indicate that one should not get carried away by this entity.

Seminoma

Management of Low–Stage Testicular Seminoma: Early-stage seminoma, represents stage I and IIa (minimal retroperitoneal spread). Testicular seminoma represents a modern model of a multidisciplinary approach to a curable neoplasm. Surgeons, radiation oncologists, and medical oncologists play an important role in disease detection, diagnosis, treatment and follow-up). In stage I disease, the major controversies continue to revolve around surveillance versus adjuvant treatment and more recently, adjuvant radiotherapy or carboplatin based chemotherapy. Focus on long-term complications, such as cardiovascular disease, gastrointestinal disease and secondary cancers, has led to the concept of increased surveillance with therapy for those who relapse. Radiation therapy remains the mainstay of therapy for patients who have stage IIa disease.

Nonseminomatous Germ Cell Tumours

Management of Clinical Stage I Nonseminomatous Germ Cell Testicular Cancer: The optimal management of patients who have clinical stage I nonseminomus germ cell tumors remains controversial. Surveillance, retroperitoneal lymph node dissection (RPLND) and chemotherapy with two cycles of bleomycin-etoposide- cisplatin are established treatment options and all are associated with long-term cancer control rates of 97% or greater. Studies have consistently identified the presence of lymphvascular invasion and a predominant component of embroyonal carcinoma in the primary tumor as risk factors for occult metastatic disease in these patients. Patients who do not have these risk factors are optimally managed by active surveillance given the low risk for relapse. For patients at high risk for relapse and who are not candidates for surveillance, the evidence supports RPLND over primary chemotherapy. Staging RPLND is recommended over non-surgical staging as data suggests that 20-25% stage I patients are under staged by available modalities of non surgical staging.

Nerve Sparing Retroperitoneal Lymphadenectomy for Stage IIA and IIb: Surgery for retroperitoneal nodal metastases of testicular germ- cell tumors has evolved considerably since its inception. The most consistent long-term morbidity of a standard bilateral RPLND has been the loss of antegrade ejaculation and consequently,

potential infertility, owing to damage of sympathetic fibres. Minimizing injury to sympathetic nerves has involved their exclusion from resection boundaries and/ or nerve sparing, by identifying and preserving nerves within the resection field. These measures improve long-term procedure- related morbidity with equivalent rates of cancer controls. Nerve sparing techniques are believed to be the standard of care and enforce good principles of surgery by demanding attention to anatomy and exposure. Experience with this procedure knowledge of retroperitoneal anatomy, and thoughtful clinical and surgical decision making are imperative to achieving acceptable results. It enables urologic oncologists to offer patients maximal therapeutic benefit combined with minimal morbidity and that retroperitoneal lymphadenectomy should be nerve sparing by definition.

Laparoscopic/Robotic Retroperitoneal Lymph Node Dissection for Nonseminomatous Germ-Cell Tumors-Current Status: Review of published literature regarding the technical feasibility oncologic outcomes, morbidity and cost- effectiveness of laparoscopic retroperitoneal lymph node dissection (LRPLND) has proved that it is feasible, several centres have become expert in LRPLND and morbidity appears to be less than that of open RPLND. As the technique improves, it is likely that LRPLND will become equally if not more cost-effective than conventional RPLND. However, the oncologic outcomes, while on par with open RPLND series, are difficult to attribute to successful LRPLND alone when nearly all patients with positive lymph nodes received chemotherapy postoperative. Although uncertainties exist, LRPLND holds much future promise. Robotic RPLND has evolved as the latest technique in the armamentarium of Uro-oncologist offering excellent precision with ease of operating in retroperitoneum and the special advantage of robotics over the laparoscopy being the relative ease in isolating and clipping the lumbar vessels and taking of hemostatic sutures in case of any inadvertent vascular injury due to degrees of freedom of robotic arms.

Adjuvant Chemotherapy for Stage II Nonseminomatous Germ-Cell Tumors: Management options for patients who have stage II nonseminomatous germ-cell cancer, completely resected at retroperitoneal lymph node dissection (RPLND) include two cycles of adjuvant cisplatin-based chemotherapy or close surveillance, with chemotherapy reserved for patients who relapse. Both options are associated with cure in an equally high percentage of patients. The choice of options is influenced by the extent of the tumors resected and patient compliance. Surveillance is a strong consideration for patients who have low-volume nodal disease at RPLND because the replase proportion is 30 % or less. In contrast, patients who have high volume nodal involvement at RPLND have a relapse rate of 50% to 90% with surveillance alone, and adjuvant chemotherapy is the preferable option in this group.

Chemotherapy for High stage Good-Risk Germ-Cell Tumors (Stage IIc and StageIII): Through a series of well designed randomized clinical trials, the treatment of patients with cisplatin-based chemotherapy has evolved such that approximately 90 % of patients who have good-risk metastatic germ-cell tumors (GCT) will be cured of their disease. At present, first line chemotherapy for patients who have good risk metastatic GCT, is three cycles of bleomycin/etoposide/ cisplatin. An alternative to this is four cycles of etoposide/ cisplatin.

The Challenge of Poor- Prognosis Germ-Cell Tumors: Patients who have poor prognosis can be identified by various prognostic factors. Poor prognostic factors include mediastinal primary, nonpulmonary visceral metastasis, and AFP>10,000ng/ml, hCG > 50,000 IU/L or LDH > 10 times upper limit of normal. Prognostic groups as defined by the international germ cell consensus classification should be used in the clinic, in clinical trials and when reporting results. High dose chemotherapy and autologous bone marrow transplantation can be used in these groups of patients resulting in complete response in 35-45% patients and long-term survival in about 25%. Although the majority of patients will achieve durable complete remission with standard first line therapy, 20-30% of them either experience relapse or fail to achieve an initial complete response and eventually die. High dose chemotherapy includes four cycles of chemotherapy composed of bleomycin, etoposide and cisplatin, and two additional cycles of etoposide and carboplatin. Surgery to resect residual masses after chemotherapy and in the salvage setting is a vital component of optimal care. The best outcomes occur with treatment at a centre with experience and expertise in their management. Further major improvements are likely to require novel systemic therapies rather than modifications of existing approaches.

Role of Post Chemotherapy Surgery in Germ-Cell Tumors**:** Surgery after systematic chemotherapy for

advanced testicular cancer has maintained its role in staging and therapeutic management. The clinical outcome is strongly influenced by patient selection and extent of extirpative surgery. Although extensive predictive modelling has attempted to define appropriate post-chemotherapy surgical candidates based on various parameters, like histology of primary tumour i.e, seminoma/ nonseminoma, presence and size of residual radiographic masses, and known distributions and natural history of various post-chemotherapy mass histologies, the accuracy of these models remains controversial. Complete removal of all post-chemotherapy residual masses in nonseminomatous germ-cell tumors remains the standard of care and allows for improved prognostication of the long- term oncologic and functional outcome.

Post Chemotherapy RPLND in Patients with Elevated Markers; Current Concepts and Clinical Outcome: Elevated serum tumor markers after cisplatin-based chemotherapy usually contraindicate surgery because of the presence of active germ-cell elements; however, some patients have undergone PCRPLND with curative intent. Role of surgery to resect retroperitoneal only markers positive tumors was evaluated in few studies. Residual germ-cell cancer was identified in 50% of patients with elevated tumor markers with one-third alive at 5 years; 5- year survival with residual teratoma or necrosis was 77.5% and 85.7%, respectively. Predictors of retroperitoneal teratoma or fibrosis included declining tumor markers at surgery, beta HCG less than 100, and first line chemotherapy. Predictors of death included rising preoperative HCG, elevated AFP, redo RPLND, and active germ-cell cancer in the resected specimen. Select patients with elevated tumor markers after chemotherapy are cured with surgery.

Reoperative Retroperitoneal Surgery: Although RPLND is both a diagnostic and therapeutic procedure, it must be performed with therapeutic intent. Adequacy of initial RPLND is a prognostic variable for clinical outcome. Effective cisplatin-based chemotherapy will not reliably compensate for suboptimal initial surgery. Many patients undergoing either primary RPLND or PC-RPLND, will have unresected extratemplate disease if modified templates are used. Anatomic mapping studies which provided the basis for modified templates, have significant limitations. Teratomatous elements are often found in the retroperitoneum of patients requiring reoperative surgery, which can be performed with acceptable morbidity in tertiary centres with experienced surgeons. The integration of chemotherapy and reoperative surgery can result in survival rates of almost 70% in patients with retroperitoneal relapse after initial suboptimal RPLND.

Management of Non-Retroperitoneal Residual Germ Cell Tumor Masses: The appropriate management of residual disease outside of the retroperitoneum after chemotherapy is a critical component of the comprehensive approach to treating advanced testicular germ-cell tumor (GCTs). Although some data suggest that certain variables,eg histology at retropritoneal lymph node dissection) can accuretly predict non-retroperitoneal histology, a multitude of studies demonstrate significant histologic discordance among different sites. In patients who have normalized serum tumor markers, therefore resection of all sites of residual disease outside of the retroperitoneum is recommended. After excision of residual viable GCT, evidence suggests that at least intermediate-risk patients who have received only induction chemotherapy, benefit from further systemic treatment.

Late Relapse of Testis Cancer: Most relapses of germ-cell tumors occur within 2 years of initial treatment. In 2 to 4% of patients, relapse may occur later. The retroperitoneum is the primary site of late relapse, and alpha-fetoprotein is the predominant marker. These tumors are highly resistant to chemotherapy. Surgical resection is the preferred treatment. If the recurrent disease is inoperable, chemotherapy may be instituted, followed by resection of residual masses. Patients successfully managed for testis cancer need lifelong surveillance.

Infertility and Testis Cancer: Testicular cancer is a common solid organ tumor in young men and affects men during their reproductive years. Current therapeutic regimens have significantly improved survival but often adversely impact fertility. Understanding the effects of testicular cancer, the systematic effects of neoplasia, and the effects of treatment protocols, such as radiotherapy, chemotherapy, and retroperitoneal lymph node dissection, is essential to restoring and maintaining fertility in men who have germ-cell neoplasms.

(Dr Amit Goel, Consultant, Dept of Genitourinary Onco Surgery; Dr S K Rawal, Director of Surgical Oncology; RGCI&RC)

GUEST ARTICLE

TREATMENT OF TESTICULAR GERM-CELL TUMOR - A SUCCESS STORY

Introduction

The advances in the treatment of testicular cancer have emerged as one of the greatest success stories in cancer treatment. The results such as cure in 95% of all patients; refined surgical techniques that preserve sexual function; minimization of short-term and long-term toxicities of therapy are astonishing. Even the majority of those with advanced disease are now curable. Equally important, most men who are diagnosed with the disease are able to return to a normal state of health after treatment and maintain their fertility.

Early Challenges

Before the era of platinum based combination chemotherapy, testicular cancer was curable in its' earliest stages with surgery and radiation, but fatal in advanced stages. A patient was evaluated by physical examination and radiographic procedures like chest x-ray, abdominal x-ray, urogram, venocavogram, or lymph angiogram and many patients required surgical staging. The lack of convenient and accurate imaging techniques made effective management challenging.

After World War II, the treatment included orchiectomy with retroperitoneal lymph node dissection (RPLND), radiation, or both, regardless of histology. Seminomas were more radiation-sensitive. If distant metastases were found, radiation was given to the abdomen, mediastinum, and supraclavicular area and even to lung metastases. In nonseminomatous germ cell tumors (NSGCT), no patients with lymph node involvement responded to radiation, and all died within 2 years. RPLND replaced radiation for patients with stage I or II NSGCT, achieving cures in nearly 50% of patients with non-metastatic, lymph node (LN)-positive disease.

Precisplatin Chemotherapy Era

Fifty years ago, a diagnosis of metastatic testicular cancer meant a negligible cure rate with 90% mortality within 1 year. During 1950s and 1960s, the arsenal of chemotherapeutics included alkylating agents, antimetabolites, such as methotrexate, antibiotics including actinomycin-D, and plant products including the vinca alkaloids.

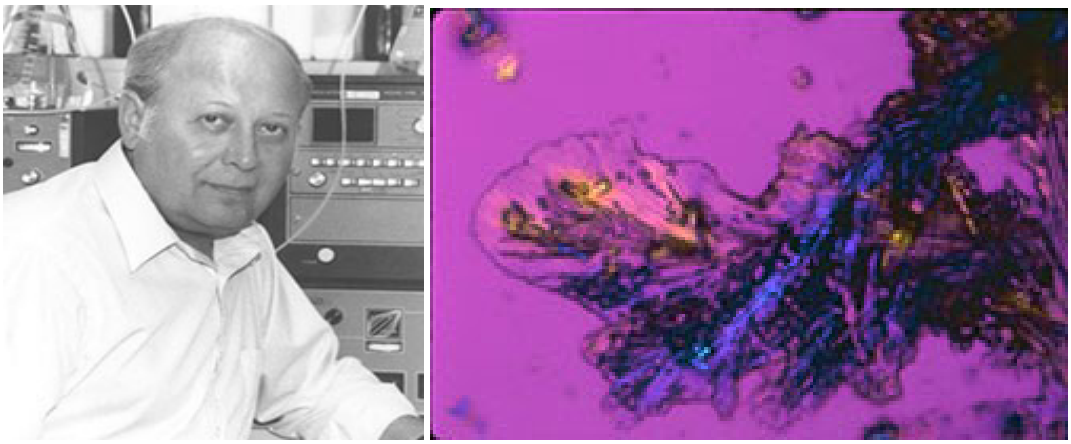
The initial chemo sensitivity of testicular cancer was demonstrated at MSKCC in 1960 by Li et al when actinomycin-D based therapy resulted in durable remissions in 10% to 20% of patients and a cure in approximately 5%. It was combined with an alkylating agent (chorambucil) and antimetabolite (methotrexate) in men with advanced testicular cancer. The best chance of deriving beneût came with the combination of agents from different classes. The concept of combined drug therapy given in a cyclical manner was not new in medicine, as it had been used effectively to treat tuberculosis, but challenged the dogma of the day in cancer treatment.

The plant Vinca rosea Linn (periwinkle) was widely cultivated as an ornamental in gardens throughout the world and enjoyed a popular reputation as a medicinal, including as an effective oral hypoglycemic agent. Hertz et al demonstrated the activity of vinblastine in patients with methotrexate-resistant choriocarcinoma. The activity of vinblastine in testicular cancer was further characterized by Samuels and Howe at MD Anderson in 1970. Based on this and other work demonstrating the activity of bleomycin, authors studied the combination of vinblastine with bleomycin, each with comparable single-agent activity to actinomycing-D, in the first-line treatment of patients with advanced testicular cancer, resulting in a 32% complete response (CR) rate, and remission greater than 2 years in half of patients achieving a CR.

Era of Cisplatin

The discovery of cis-diaminodichloroplatinum (CDDP) by Rosenberg, a biophysicist, in 1965 is a landmark event in the history of oncology and the single most important discovery in the treatment of testicular cancer. Platinum is a component of first-line chemotherapy in many tumor types today.

In 1971, the drug development of cisplatin began following the observation of responses in patients with human malignancies, including testicular cancer. The toxicity was substantial; however, as irreversible renal failure was observed in some patients and nausea/vomiting (sometimes lasting weeks) was universal, it necessitated hospitalization for all patients.



Cisplatin, a platinum-based drug, is used in combination chemotherapy for a wide range of solid tumors. Barnett Rosenberg, Ph.D. who discovered cisplatin, leading to successful treatment for testicular and other cancers.

The addition of cisplatin to the regimen of vinblastine plus bleomycin, known as the PVB regimen, was introduced by Einhorn and Donahue at Indiana University in 1974. Thirty-three of 47 patients achieved a CR with chemotherapy alone resulting in a then astonishing 5-year survival rate of 64%, a 1 log increase in the cure rate compared with contemporaneous actinomycin-D based chemotherapy. Based on these stunning phase II results, the US FDA granted approval for cisplatin as a commercial drug, even in the absence of a randomized trial.

Sequential studies testing PVB were aimed at reducing the neuromuscular and myelosuppressive toxicity of the regimen from vinblastine and challenging the tenet of maintenance therapy and addition of doxorubicin. All the studies concluded that there was no improvement in survival with the addition of doxorubicin to PVB or maintenance therapy. Therefore, PVB four cycles became standard therapy.

The next major advance came with the discovery of etoposide. The dried roots from the American mandrake containing podophyllotoxin were cultivated by native North Americans and natives of Himalaya and used as an emetic agent and to treat worm infections. Etoposide, a synthesized derivative of the podophyllotoxin, entered cancer trials in 1971 and was reported to be active as a single agent in patients with refractory GCT. Based on a leukemia mouse model demonstrating the synergistic effects of etoposide with cisplatin, combination studies were evaluated as second-line therapy in patients not cured with PVB. In a trial from the Southeastern Cancer Study Group (SECSG), 43% of patients achieved a CR, and 23% remained disease-free fora long-term. **This was the first time in oncology that a relapsed solid tumor was cured with second-line chemotherapy.**

Investigators at Indiana University and the SECSG also studied etoposide as an alternative to vinblastine, in the first-line setting. A randomized phase III study compared PVB with BEP from 1981 to 1984. Seventy-eight percent of patients receiving BEP were cured compared with 66% receiving PVB. Based on this improved efûcacy and less toxicity, BEP became a standard of care. Attempts have been made to improve on the efûcacy, toxicity, and convenience of the BEP regimen by testing alternative dose and schedules of BEP.

Each successive cycle of BEP resulted in cumulative chemotherapy- induced nephrotoxicity, neurotoxicity, ototoxicity, and bleomycin- induced pulmonary toxicity. Therefore, from 1984 to 1987, the SECSG randomly assigned patients with good risk disease to receive three versus four cycles of BEP. This was done in an attempt to eliminate the most toxic cycle of therapy, due to cumulative toxicity. 92% cure rates were reported on each arm. For patients with good risk metastatic disease, standard therapy remains BEP 3 or EP 4. Thus from 1974 to 1987 randomized studies substituted etoposide for vinblastine with decreased toxicity and increased efûcacy and shortened duration of therapy from 2 years to 9 weeks for most patients with metastatic disease.

Two achievements in the 1990s laid the groundwork for additional success in the management of patients with testicular cancer, namely, identification of prognostic groups and the discovery of the selective serotonin type 3 (5HT3) receptor antagonists. The first major

achievement came in 1991. Before the advent of effective antiemetics, cisplatin-based chemotherapy was extremely difficult, as frequent and prolonged nausea/ vomiting was universal. As reported in a study, the median number of emetic episodes on day 1 of chemotherapy was 10. This has reduced to nearly zero with modern antiemetic therapy. In 1997, following a multinational analysis, a consensus statement for metastatic GCT was published by the International Germ Cell Cancer Collaborative Group (IGCCCG). The IGCCCG risk stratification system takes into account the primary tumor site, metastatic sites, and amplitude of serum tumor marker levels. Patients with advanced GCT are now subdivided into 3 risk groups: good (90% rate of cure), intermediate (75% rate of cure) and poor (50% rate of cure).

Bleomycin causes severe pulmonary toxicity in a dose-related fashion in some patients. Investigators from the EORTC randomly assigned patients to BEP 4 versus EP 4, and demonstrated inferior results with the deletion of bleomycin (95% v 87% cure rates).These results conûrmed the importance of bleomycin. Therefore, bleomycin remains a valuable contributor to the overall efûcacy of treatment in good-risk patients and can be safely given to most patients when limiting therapy to three cycles.

Additional attempts to reduce toxicity and preserve efûcacy in good risk patients included substitution of carboplatin for cisplatin. Unfortunately, carboplatin substitution (a platinum agent with less nephrotoxicity and emetogenic potential) for cisplatin also results in inferior outcomes.

While greater than 90% of patients with good risk metastatic disease are cured with chemotherapy, patients with intermediate or poor-risk disease have a much less certain future. The worldwide standard for poor-risk disease is four cycles of triple-drug therapy, but nearly half of these patients are not cured. Therefore, intensification of therapy beyond BEP 4 has been investigated. The SECSG evaluated BEP and compared double dose (40 mg/m2 day 1 through 5) cisplatin versus standard dose (20 mg/m2 day 1 through 5) cisplatin for four cycles. Two-thirds of patients in each arm were cured. A EORTC study randomly assigned patients to BEP with or without paclitaxel (T) in patients with intermediate risk disease demonstrating no survival difference in both arms. Investigators from ECOG randomly assigned 304 men with advanced disseminated GCT to BEP 4 or cisplatin, ifosfamide, and etoposide (VIP) 4 cycles. Overall complete remission rate and 2-year overall survival (VIP, 74%; BEP, 71%) were not significantly different among the two treatments, despite more toxicity in the VIP arm.

Two randomized clinical trials compared BEP 4 with BEP 2, followed by high-dose chemotherapy as first-line treatment in patients with poor-risk GCT. Another trial compared BEP 4 with VIP 1, followed by high-dose VIP 3. All of these studies failed to demonstrate any advantage over BEP 4 with durable CR's seen in approximately 50% of patients, and toxicity more severe with the investigational regimens. Furthermore, some have advocated intensification of therapy based on the rate of tumor marker decline, an independent prognostic variable in patients with poor risk disease, following the ûrst or second cycle of BEP. This strategy may result in fewer relapses requiring salvage therapy, but has failed to prove a survival advantage to date.

Salvage Therapy for Relapsed GCT

Patients who relapse after initial chemotherapy can still be cured with second-line and even third-line regimens. VIP, vinblastine (VeIP), or paclitaxel (TIP) are commonly used. Bone marrow transplantation (BMT) entered patient care in the 1950s and was increasingly successful by the end of the 1960s with the use of platelet transfusion support, improved antibiotics, growth factor support, and more effective cancer drugs. In 1986, investigators at Indiana University began work with high-dose chemotherapy (HDCT) in patients with relapsed testicular cancer. Significant escalation of cisplatin dose is limited by extramedullary toxicities; therefore, high-dose carboplatin and etoposide were evaluated since myelosuppression, which can be managed with bone marrow rescue, is their dose-limiting toxicity. In a phase I/II trial, 33 patients with recurrent disease were treated from 1986 to 1988. Enough bone marrow for two courses of therapy was harvested a few days before chemotherapy. The median time to hematopoietic recovery was about 25 days and 25% achieved CR. Cures were observed even in the third- and fourth-line setting, which was unprecedented at the time.

In 1995, it was reported that peripheral blood stem cells (PBSC) resulted in sustained trilineage reconstitution after HDCT more rapidly than bone marrow. Therefore, in 1996, PBSC transplantation could replace BMT for

Table 1. Standard Treatment of Seminoma

Stage	Treatment Options	5-Year OS (%)
I	Surveillance or 20 Gy radiation or carboplatin x1,2	>99
II	30-36 Gy radiation preferred for non bulky disease (<3 cm) ,BEP x 3 or EP x 4 preferred for bulky disease (>3 cm)	>95
III	EP x 4 or BEP x 3	>90

Abbreviations: BEP-bleomycin, etoposide, and cisplatin; EP-etoposide and cisplatin; OS-overall survival

the treatment of recurrent GCT at Indiana University. Einhorn et al of Indiana University reported the experience with HDCT (using carboplatin and etoposide), followed by PBSC rescue in 184 patients with metastatic GCT that had progressed after first-line chemotherapy. Of the 184 patients, 63% achieved a CR without relapse during a median follow-up of 48 months; 70% of patients who received the treatment as second-line therapy were cured, as were 45% treated in greater than or equal to the third-line setting.

Refinements in the use of HDCT continue today. Patients with recurrent disease have been classified into very low, low, intermediate, high, and very high risk categories. In a large 1,500-patient multi-institutional retrospective study, HDCT cured 27% of patients with very high risk disease compared with only 3% with standard-dose salvage therapy. In addition, two other report that patients with recurrent disease and unfavorable prognostic features are curable with HDCT, a result rarely seen with standard-dose therapy. Based on this data, some have argued using HDCT for most patients in the second-line setting, while others have proposed HDCT only in high- or very high–risk groups unlikely to be cured with standard- dose salvage therapy.

Long-Term Issues in Survivors

Given the high cure rates in patients with testicular cancer, this young population has been evaluated for the long-term toxicity of diagnostic studies, therapy, and other issues affecting survivors. There has been an emerging concern about the risks of second cancers due to the frequent exposure to diagnostic radiation to the abdomen and pelvis in young patients undergoing active surveillance. Similarly, the risk of treatment-related second cancers from surgery, chemotherapy, and therapeutic radiation has been reported. Testicular cancer survivors are also at risk for metabolic syndrome, cardiovascular disease, infertility, neurotoxicity, nephrotoxicity, pulmonary toxicity, hypogonadism, psychosocial disorders, and behavioral issues including problem drinking. A multinstitutional effort is underway to understand the genetic underpinnings of long-term cisplatin toxicities, identify single nucleotide polymorphisms associated with these toxicities, and to systematically collect data regarding various cardiovascular risk factors in testicular cancer survivors.

Remaining Issues and Future Perspective

The last 50 years of testicular cancer research have produced stunning results, but multiple challenges remain. Ninety-ûve percent of patients with testicular cancer, including 80% with metastatic disease, can be assured they will be cured.

The primary focus today is to develop more effective treatments for those with poor- risk disease, especially those with multiple poor-risk features at diagnosis, and those whose disease has relapsed following first-line chemotherapy.

Table 2. Standard Treatment of Nonseminomatous Germ-Cell Tumors

Stage	Treatment Options	5 - Year OS (0%)
I	Surveillance or RPLND or BEP x 1	>99
II	RPLND preferred for non bulky disease (<3 cm) BEP 3 EP 4 preferred for bulky disease (>3 cm)	
III (Good risk)	BEP 3 or EP 4	>90
III (Intermediate / poor risk)	Four cycles of 3-drug therapy	50-90

Abbreviations: BEP- bleomycin, etoposide, and cisplatin; EP-etoposide and cisplatin; OS-overall survival; PFS, progression-free survival; RPLND-retro- peritoneal lymph-node dissection

Table 3. Landmark Achievements in Testicular Cancer

Year	Event	Significance
1937	hCG first reported in the urine of patients with testicular cancer	Improved ability to diagnose, stage, assess response, detect relapse, estimate prognosis
1940s	Seminomas are radiation-sensitive	95% cure rate for stages I or II seminoma prior to era of cisplatin-based chemotherapy
1960	Actinomycin-Dbased chemotherapy tested in advanced testicular cancer	Durable complete responses and some cures reported for the first time in patients with metastatic testicular cancer
1965	Discovery of cisplatin	Revolutionized the treatment of testicular cancer, achieving cures in 80% of patients with metastatic disease
1974	PVB regimen first tested	Increased cure rate by 1 log compared with contemporaneous chemotherapy
1980s	Nerve-sparing RPLND	Preserves ejaculatory function in 90% of patients undergoing this procedure
1981	PVB with or without maintenance vinblastine	Eliminated need for maintenance therapy
1985	EP regimen	Cures possible in the second-linesetting
1987	PVB versus BEP	BEP supplants PVB as standard therapy
1989	BEP 3 versus 4 cycles in good risk	Eliminates fourth cycle of BEP in good risk patients
1997	IGCCC prognostic groups	Allows for more accurate study of treatment outcomes by risk groups
2007	Largest series to date reported on HDCT in relapsed disease	Cures achieved in third- line, poor-risk groups, including platinum-refractory patients

Abbreviations: BEP, bleomycin, etoposide, and cisplatin; EP, etoposide and cisplatin; hCG, human chorionic gonadotropin; HDCT, high-dose chemotherapy; IGCCC, International Germ Cell Cancer Collaborative Group; PVB, cisplatin, vinblastine, and bleomycin; RPLND-retroperitoneal lymph-node dissection.

Secondly, patients with late relapse (2 years from diagnosis) and those with malignant transformation of teratoma are less chemotherapy-sensitive. They are managed primarily with surgery and less than half will remain continuously free of disease following treatment.

Thirdly, common clinical scenarios can still be vexing for clinicians less experienced in managing patients with testicular cancer.

Conclusion

The success in the treatment of testicular cancer is not the result of a single individual or institution, but rather the collective work of an international community of cancer researchers (Tables 1 and 2). Each major discovery is dependent on the discoveries that precede them (Table 3). Refinements in surgical mapping of disease, discovery of radiation and its application to cancer care, isolation of tumor markers initially in the urine and subsequently in the serum, development of preclinical tumor models to test the potential of cancer drugs, development of chemotherapy principles, and the discovery of cisplatin each predated the landmark trial of PVB in 1974. The refinement of chemotherapy at each institution added to the experiences reported from other institutions. This collaborative spirit continues today as an international group of researchers work with a common spirit to ensure no person will die of testicular cancer in the future.

(Dr Sameer Khatri, Senior Consultant, Dept of Medical Oncology, HCG Centre Delhi)

PERSPECTIVE

ROBOTIC RPLND IN MANAGEMENT OF TESTICULAR TUMORS

Testicular cancer is relatively a rare tumor type, accounting for approximately 1% of all male cancers globally. Testicular cancer has a very distinctive age distribution and in many developed countries it is the most commonly diagnosed malignancy among men aged between 15–40 years. Western and Northern Europe have high age-standardized incidence rates of 7.8 and 6.7 per 100,000 men, respectively, compared to rates of 0.6 per 100,000 men in the black population of Northern Africa and 0.5 per 100,000 men in India. In recent decades, the incidence of testicular cancer has been increased, and doubled since 1960s in many Western societies.

The natural history of testicular cancer provides the basis for its evaluation and management, and, in turn, is favorably influenced by effective treatment. Predictable and systematic pattern of metastatic spread from the primary site to the retroperitoneal lymph nodes and subsequently to the lung and posterior mediastinum and lymphatic spread is common to all forms of germ-cell tumors. Right-sided testicular drainage includes the interaortocaval lymph nodes, followed by the precaval and paracaval nodes, whereas left-sided drainage includes the left para-aortic and preaortic lymph nodes.

The retroperitoneal lymph node dissection(RPLND) forms an important part of management of testicular cancer because retroperitoneal lymph node spread is usually the first and often the only site of metastatic disease and the fact that best of the imaging studies under-stage the disease in 15-40 % of the patients. The RPLND is indicated in patients with stage I and selected stage II disease patients. Open RPLND stays the gold standard procedure of choice when RPLND is indicated. Modified templates have been designed to preserve the antegrade ejaculation but long-term data are disappointing. With the advent of minimally invasive surgery into all surgical aspects, laparoscopic RPLND (L–RPLND) was initiated. L-RPLND is a technically demanding procedure with a steep learning curve. The results of L-RPLND, as demonstrated in various series, have shown the non-inferiority of the method over the open approach in relation to oncological outcomes in the form of yield of lymph nodes and recurrence free survival rates. Even though laparoscopic- RPLND method has been shown to be associated with lesser morbidity, the technical difficulty associated with the procedure has limited its wide spread usage, and is mostly done by an experienced laparoscopic surgeon in high volume centers. With the introduction of robotics which gave the surgeon the extra degree of rotation, the advantage of 3-D vision, there was a new zeal into the minimally invasive surgery. The first case reported by Patrick Davol et al in 2006 demonstrated the technical feasibility, safety, and accuracy of robotic-assisted retroperitoneal lymph node dissection. Stephen B Williams et al published the first case series of the robot-assisted laparoscopic approach to retroperitoneal nodes in 2011 which included 3 patients with a mean age of 31 years. There were no perioperative complications and all 3 underwent modified template nerve sparing RPLND.

The procedure includes dissection of the lymph node basins in an area bounded by renal vessels superiorly, bilateral ureters laterally and common iliac artery bifurcation inferiorly in the classical bilateral RPLND. The robotic procedure involves port placement. Fig 1&2 After thorough visualization of the abdomen kocherisation of the duodenum is done and inferior vena cava is exposed. All lymph nodal tissue in the above said regions is removed. The advantage of robotic over the laparoscopy is the relative ease in isolating and clipping the lumbar vessels and taking of hemostatic sutures in case of any inadvertent vascular injury. With the extra degree of motion the robotics provide the surgeon relatively easy handling the great vessels which probably help reducing the vascular injuries.

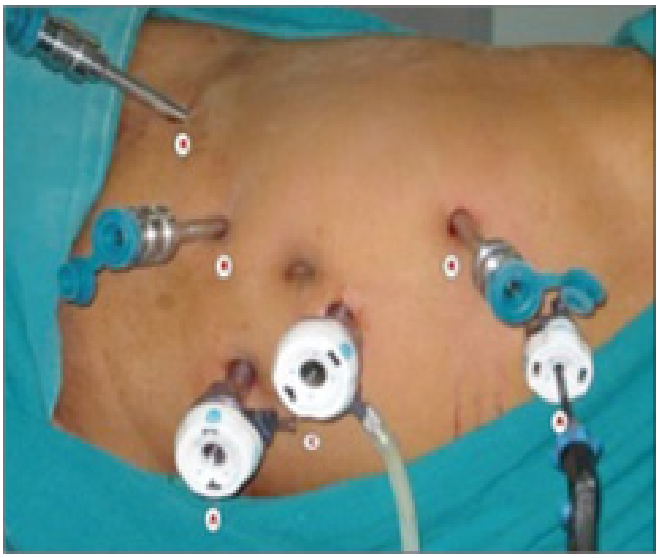


Fig 1: Port placement for robotic RPLND

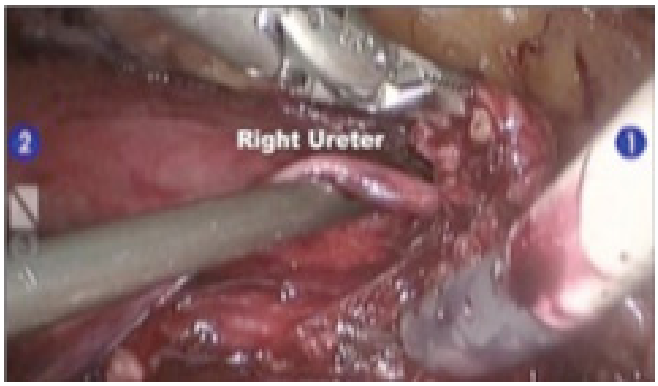


Fig 2: Para caval dissection during robotic RPLND

There have been a few published case series demonstrating the safety, feasibility and short-term oncological outcomes of robotic RPLND. Scott M. Cheney et al report that 18 consecutive patients who underwent robotic RPLND had a mean follow-up of 22 months (1-58 months),the mean LN yield of 22 LNs, and no retroperitoneal recurrences, and two of 17 (12%) patients with NSGCT had pulmonary recurrences. Antegrade ejaculation was maintained in 91% of patients with a nerve-sparing approach. Patients receiving primary RA-RPLND had shorter operative times compared to those with post-chemotherapy (311 vs 369 min, P = 0.03). There was no significant difference in LN yield (22 vs 18 LNs, P = 0.34), estimated blood loss (100 vs. 313 mL, P = 0.13), or length of hospital stay (2.75 vs. 2.2 days, P = 0.36).

Caveats in Robotic RPLND

1. There are no randomized control studies comparing the robotic approach with either open or laparoscopic approach.
2. Not much data is available regarding long-term oncological outcomes.
3. The true benefit of robotic approach will be seen in post-chemotherapy patients in whom the other two methods have shown significantly higher morbidity compared to naïve patients. Here the theoretical advantages of robotics will be tested to see if these get transformed into significant results. The publications in the next few years are probably going to answer this question.
4. The magnification, the high definition vision and 3-D approach do help the surgeon in better visualization but do it help in doing a better nerve preserving surgery needs to be answered.
5. The other important issue that needs to be addressed to is the cost-effectiveness of robotics. Currently, all robotic procedures bear a significantly higher initial cost to the patient but studies are underway to see the total cost effectiveness of the robotic approach taking into factor the early discharge and faster recovery time.

Hence, robotic approach to retroperitoneal lymph node dissection is safe, feasible approach to open method with a shorter learning curve when compared to laparoscopic approach. Current literature has enough evidence to show the feasibility and short term oncological outcomes of the robotic approach. However, further studies are required to compare the three approaches and the long-term oncological outcomes.

Rajiv Gandhi Cancer Institute and Research Centre data: From March 2012 to August,2014 RGCI&RC performed 8 cases of postchemotherapy Robot Assisted Laparoscopic Retroperitoneal Lymph Node Dissection. All patients had Testicular Non Seminomatous Germ-Cell tumors. BEP chemotherapy was administered and patients were reassessed with repeat CT scans. All patients had residual masses in retroperitoneum. Patients were positioned in true lateral position and port introduced. After mobilization of ascending colon, duodenum was kocherized. Inferior vena cava and aorta were visualized. Paracaval space was entered and ureter and gonadal vessels identified. The extent of lymph node dissection included the infrahilar lymph nodes in the paracaval, para aortic and interaortocaval region upto bifurcation of common iliac on both sides. The gonadal vessels on the side of testicular tumour was dissected in entirety and sacrificed. Attempt was made to identify and preserve the para-aortic sympathetic chains. Bilateral renal arteries and veins were identified and preserved.

Robot-assisted laparoscopic RPLND was technically successful in all 8 post-chemotherapy patients. Patients median age, body mass index were 27 years (22-33years) and 23(22-24), respectively. Average operative time was 177 min (155-200min), and blood loss was 115 ml (90-150ml). The average lymph node yield was 28. All 8 patients had tumor necrosis in histopathology. The patients were ambulated from day 1 of the procedure and were allowed orally from day 2. Mean hospital stay was 2 days. Drain was removed on day 3. Patient had no vascular or bowel complications due to robot-assisted laparoscopic RPLND. One patient had chyle leak which resolved with treatment. Ejaculatory function was preserved in 3 of the 8 patients.

(Dr Suhas KR, DNB Trainee, Dept of Surgical Oncology, Dr Amit Goel, Consultant, Dept of Genitourinary Onco Surgery; Dr S K Rawal, Director of Surgical Oncology, RGCI & RC)

RESEARCH & DEVELOPMENT

Death Receptors in Testicular Cancer Cells

The most common solid tumor is testicular cancer among young men. Bleomycin is an antitumor antibiotic used for the therapy of testicular cancer. TRAIL is a proapoptotic cytokine that qualified as an apoptosis inducer in cancer cells. A new study from Turkey investigated the apoptotic effects of bleomycin, TRAIL, and their combined application in NTera-2 and NCCIT testicular cancer cell lines. Caspase 3 levels as an apoptosis indicator, and TRAIL receptor expressions using flow cytometry were measured. Both NTera-2 and NCCIT cells were fairly resistant to TRAIL's apoptotic effect. Incubation of bleomycin alone caused a significant increase in caspase 3 activity in NCCIT. Combined incubation with bleomycin and TRAIL led to elevated caspase 3 activity in NTera-2. It can be concluded that TRAIL death receptor expressions in particular are increased in testicular cancer cells via bleomycin treatment, and TRAIL-induced apoptosis is initiated.

(Anticancer Agents Med Chem, Aug 29, 2014)

Relapse in Clinical Stage I Testicular Cancer

A recent study evaluated the performance of active surveillance as a management strategy in broad populations and included data from 2,483 clinical stage I (CSI) patients, 1,139 CSI nonseminoma and 1,344 CSI seminoma managed with active surveillance, with the majority treated between 1998 and 2010. Relapse occurred in 221 (19%) CSI-nonseminoma and 173 (13%) CSI-seminoma patients. Median time to relapse was 4 months (range, 2-61 months), 8 months (range, 2-77 months) and 14 months (range, 2-84 months) for lymphovascular invasion-positive CSI nonseminoma, lymphovascular invasion-negative CSI nonseminoma, and CSI seminoma. Five-year disease-specific survival was 99.7% (95% CI, 99.24% to 99.93%). The study concluded that active surveillance for CSI testis cancer leads to excellent outcomes. The vast majority of relapses occur within 2 years of orchiectomy for CSI nonseminoma and within 3 years for CSI seminoma. These data may inform further refinement of rationally designed surveillance schedules.

(J Clin Oncol, Aug 18, 2014)

CLINICAL TRIALS

Antiemetic Combination Therapy

An open-label, single-arm, multicenter study performed in patients with testicular germ-cell tumor (TGCT), combination of palonosetron, aprepitant, and dexamethasone found it to be highly effective as antiemetic therapy and well-tolerated in patients with TGCT receiving 5-day cisplatin-based combination chemotherapy. Researchers recruited thirty patients. The antiemetic therapy consisted of palonosetron 0.75 mg on day 1, aprepitant 125 mg on day 1 and 80 mg on days 2 to 5, and dexamethasone 9.9 mg on day 1 and 6.6 mg on days 2 to 8. The primary endpoint was defined as no vomiting and no rescue medication in the overall period of (0 to 216 h) in the first chemotherapy course. Results showed that 90.0% of the patients had no vomiting during first chemotherapy, and the response rates were 82.1 and 78.3% respectively in further second and third cycles of chemotherapy. The adverse drug reactions were hiccups (13.3%), anorexia (3.3%), and stomach pain (3.3%).

(Support Cancer Care, Aug 2014)

Combination of Gemcitabine, Cisplatin, and Ifosfamide

A prospective, multicenter phase II trial was conducted at Institut Gustave Roussy, University Paris Sud in patients with relapsed metastatic germ-cell tumors (GCT) to observe the activity of gemcitabine in patients with GCT relapsing after first-line chemotherapy. The standard treatment of these patients is cisplatin and ifosfamide-containing three-drug regimen, which usually yields a complete response (CR) rate <50%. Total thirty-seven patients were accrued in the trial and given four cycles of the GIP regimen plus G-CSF support once every 3 weeks. The primary endpoint was the complete response (CR) rate. Of total recruited patients, 29 (78%) achieved a favorable response, including a CR in 20 (54%) and a partial response with normalization of tumor markers (PRm) in 9 (24%). The 2-year overall survival rate was 73% and the continuous progression-free survival rate 51%. Myelosuppression was the main toxicity, no grade 3 and 4 peripheral neurotoxicity or renal toxicity occurred. Overall results showed that the GIP regimen yielded a high survival rate and avoided severe neurotoxicity.

(Ann Oncol, May 2014)

GLOBE SCAN

Organ-Sparing Therapy

Due to a number of medical achievements, the cure rate of testicular cancer has notably increased through the last decades. In the meanwhile the main focus is on reducing therapy load, scrutinizing radical orchiectomy as the only adequate therapy for the primary tumor. A selective literature search was performed in PubMed. A set of data suggests that endocrine and exocrine function of the testis can be preserved using an organ-sparing approach and many patients could benefit regarding their quality of life. Different from kidney tumors, precancerous lesions (testicular intraepithelia neoplasia, TIN) can almost inevitably be found in the surrounding tissues of testicular tumors. This has to be considered when making a decision in favor of an organ-sparing approach, because radiation therapy on the affected testis has to be performed after tumor resection. After careful selection of patients, particularly young men can profit from an organ-sparing therapy regimen. Therefore, organ preservation should always be considered in the surgical treatment of testicular masses.

(Germany: Urolog A, Sep 2014)

Sperm DNA Damage

The aim of this study was to investigate sperm DNA damage induced by chemo- and radiotherapy in patients with testicular cancer. The authors evaluated pre- and post-antineoplastic treatment sperm DNA integrity, expressed as DNA Fragmentation Index (DFI), in a large caseload of testicular cancer patients by sperm chromatin structure assay. The mean total DFI for all patients at T0 was 18.0 ± 12.5%. Sperm chromatin profile was markedly impaired at T3 (27.7 ± 17.4%) and T6 (23.2 ± 15.3%), improving considerably at T12 and T24 (14.0 ± 8.9% and 14.4 ± 10.3%). After chemotherapy, there was a marked increase in DFI at T3 and T6 and a significant reduction at T12 and T24 in comparison with the baseline. In contrast, DFI increased at T3 and T6 after radiotherapy but the subsequent reduction was far less marked, reaching baseline values at T12 and T24. In this study, the authors show that the chromatin profile may be affected in the months immediately following the end of the treatment, improving after 12-24 months.

(Italy: Andrology, Sep 2014)

Testicular Prosthesis

The objective of the study was to compare the complication rate associated with synchronous prosthesis insertion at the time of radical orchidectomy with orchidectomy alone. Data on post-operative complications, length of stay (LOS), re-admission rate and return to theatre rate was collected. Men 904 in numbers (median age of 35 years, range 14 - 88), underwent a radical orchidectomy during the study period. Of these, 413 (46.7%) were offered a prosthesis, of whom 55.2% chose to receive one. There was no significant difference between the 2 groups in LOS (p=0.387), hospital re-admission rates (p=0.539) or return to theatre rate (p=>0.999). To conclude, concurrent insertion of a testicular prosthesis does not increase the complication rate of radical orchidectomy.

(UK: BJU Int, Aug 2014)

Best Practices Recommendations

The judicious use of immunostains can be of significant diagnostic assistance in the interpretation of testicular neoplasms when the light microscopic features are ambiguous. A limited differential diagnosis by traditional morphology is required for the effective use of immunohistochemistry (IHC). The diagnosis of tumors in the germ-cell lineage has been considerably facilitated over the past decade by IHC directed at developmentally important nuclear transcription factors, including OCT4, SALL4, SOX2, and SOX17. In conjunction with other markers, a specific diagnosis can be achieved in most instances through a panel of 3 or 4 immunostains and often fewer. IHC among tumors in the sex cord-stromal group may produce a significant proportion of false-negative cases until more sensitive and equally specific markers are validated. The negativity of these tumors for the IHC stains used for germ-cell tumors is key in the important distinction of neoplasms in these two general categories. The International Society of Urological Pathologists (ISUP) provides diagnostic guidelines in the form of algorithms to assist practicing pathologists confronting a differential diagnostic question concerning a testicular neoplasm. The goal of ISUP is to anticipate commonly encountered differential diagnoses and recommend an efficient and limited pattern of IHC stains to resolve the question.

(USA: Am J Surg Path, Aug 2014)

IN FOCUS

FERTILITY ISSUES IN TESTICULAR CANCER

Introduction

Fertility issues in testicular cancer need special mention because fertility is almost uniformly affected in all patients with testicular tumors. Infertility is not only one of the presenting complaints of patients with testicular cancer but is also severely affected after all forms of therapy for testicular tumors including chemotherapy, radiotherapy and surgery. Incidentally, this disease presents at an age when men are on the peak of their fertility and planning parenthood. Hence, to the patient, diagnosis of testicular cancer raises concern not just about his chances of survival but also about the chances of fatherhood. Patients of testicular face difficulties in fathering children, increased fertility related distress undergo increased fertility testing and hear high rates of investigations and therapy. Paternity rates among those who have tried to father children following treatment have been reported to vary from 49–82%[1]. Patients with nonseminomatous tumors expressed greater fertility distress than those with seminomas[2].

Not only does testicular cancer complicate infertility, it also raises questions on management of infertility with regards to germ line mutations or unhealthy sperms that may lead to a diseased offspring. These issues and many others need further understanding of pathophysiology, treatment related complications and patient perceptions.

Abnormal Testicular Development

The importance of fertility in testicular cancer does not arise simply because of coexistence in a particular bracket of age or direct causation. Abnormalities in testicular maturation, such as gonadal dysgenesis, exposure to gonadotoxins or carcinoma in situ[3], cause both infertility and testicular cancer. These common risk factors lead to infertile men often being diagnosed with testicular tumors and patients with testicular tumors facing difficulty in conception. Testicular germ-cell cancer may be aetiologically linked to other male reproductive abnormalities as part of the so-called 'testicular dysgenesis syndrome'[4]. Several epidemiological studies have shown that conditions like cryptorchidism, impaired spermatogenesis, hypospadias and testicular cancer act as risk factors for each other[5]. Dysgenesis has been demonstrated in biopsies of the contralateral testis of men with testis cancer and in infertile men. Both environmental and genetic factors play a role in testicular dysgenesis which leads to a disturbed Sertoli and Leydig cell function. This leads to androgen insufficiency and impaired germ-cell differentiation leading to carcinoma in situ, hypospadias, cryptorchidism, androgen deficiency and other manifestations like reduced testicular volume.

Effect of Tumor on Sperm Production (Local and Systemic)

Tumor has been postulated to have a direct effect on fertility by its effect on the internal testicular environment, local architecture and the pituitary gonadal hormonal milieu. Many systemic effects of cancer have also been realized and increase in acute phase reactants as a result of tumor have been shown to be correlated with risk of infertility[6]. Semen quality tends to be poorer at higher cancer stages. In a study by Agarwal et al, semen quality was better among patients with pure seminomas than with pure embryonal tumors; quality was worst among patients with mixed germ cell tumors[7]. The presence of anti-sperm antibodies is a direct evidence that tumor also disrupts the blood testis barrier[8]. During a microscopic analysis, Ho et al found that malignant tumors demonstrated a gradient effect, with greatest impairment of spermatogenesis occurring adjacent to tumor[9]. Germ-cells also produce human chorionic gonadotrophin (hCG) and alpha fetoprotein (AFP). hCG may stimulate intratesticularestradiol production and impair spermatogenesis in a paracrine-endocrine fashion[10]. Similarly, elevated AFP levels have also been found to correlate with poor sperm production[11].

Surveillance

Surveillance is an important treatment option for the management of infertility[12]. The major advantage of surveillance protocols is that adjuvant therapy will be administered only to those patients who require therapy. This advantage has to be balanced against a constant psychological threat and a relapse rate of 20-25% necessitating extensive chemotherapy[13].Even though the theoretical risk of infertility is low,rates and nature of sexual dysfunction of surveillance patients have been found to be similar to other treatment groups, except for ejaculatory function[14]. In men who remain stable on surveillance, semen parameters have been shown to improve after orchiectomy[15].

Effect of Surgical Therapy on Fertility

Retroperitoneal lymph node dissection (RPLND) may be followed by "dry ejaculation", in which surgical injury to sympathetic nerves and ganglia may cause loss of seminal emission into the posterior urethra or true retrograde ejaculation[16]. Non-nerve sparing RPLND is the most important treatment modality that influences fertility that should be avoided whenever possible.Most men who undergo modern primary retroperitoneal lymph node dissection maintain antegrade emission and ejaculation. In a series of 176 patients who underwent primary RPLND, 97% reported preserved antegrade emission. Of all patients who tried to father children 73.4% were successful[17]. In another large series where RPLND was done after chemotherapy, up to 90% patients had preserved ejaculation and 50% of them could father children even though the semen volume was reduced in most patients[18]. Semen analyses and DNA histograms suggested fertility in > 70% patients who were managed by primary RPLND and 80% were able to father children[19]. Foster et al suggested that approximately 75% of patients who present with clinical stage I nonseminoma are potentially fertile and nerve sparing could be the best way forward in these patients[20].

Effect of Chemotherapy on Fertility

Sperm genomic integrity and its implication for the patient's fertility after chemotherapy have been poorly understood. Cisplatin is an essential ingredient of chemotherapy for testicular tumors and gonadotoxicity is one of its most common side effects[21]. Serum FSH levels seem to rise immediately after initiation of chemotherapy followed by LH[22]. This may represent a compensatory mechanism to maintain normal testosterone levels and support sperm production but it is a definite sign of testicular dysfunction[23]. Exocrine testicular function is also severely affected, most vulnerable being the differentiating spermatogonia. Partial recovery of spermatogenesis, observed by means of standard semen analysis, has been seen in testicular cancer patients within 2 years after chemotherapy with cisplatin. Duration and severity of the spermatogenic depression depends upon the dose and duration of chemotherapy and baseline testis function prior to therapy. It was realized relatively later that 50–70% of the testicular cancer patients were sub-fertile or had impaired spermatogenesis before the start of chemotherapy[24] and thus direct comparison of semen parameters with healthy men was not justified.

Elevated rates of DNA damage have been found in semen after chemotherapy. Sperm DNA strand breaks induced during spermiogenesis or incompletely matured sperm with abnormally condensed chromatin may contribute to high rates of damaged sperm in the ejaculate. Damaged cells that should have been eliminated during spermatogenesis can be found in the ejaculates and such damage may not be detectable with standard semen analysis[25]. In circumstances where sperms are required after chemotherapy for assisted reproduction, adequate time should be given for spermatogenesis recovery. Increase in the number of autosomal and sex chromosome aneuploidies have been reported in such patients[26]. Since the long-term data from follow-up of children of men with testicular cancer treated with chemotherapy is scarce, we need to be concerned with risk to the progeny arising from poor sperm quality.

Effect of Radiotherapy on Fertility

The long-term effects of therapy on semen remain unclear[27] and many studies[28] have reported an ill effect of treatment on fertility[29]. In patients who undergo radiotherapy testicular biopsy specimens have shown that spermatogonia are the most susceptible to radiation at doses as low as 10cGy[30].The effects are dose dependent and application of greater than 6 Gy to the testis leads to irreversible azoospermia. At lower doses (<3.5 Gy) azoospermia is reversible and takes about 18-24 months[31]. The probability of spermatogenesis recovery has increased from 48% by 2 years to 80% by 5 years[32] after therapy for cancer. Hahn et al have showed that despite strict adherence to protocol testis receives, some incidental radiation and recovery is dose dependent[33]. Fossa et al have concluded that severe disturbances in spermatogenesis, observed 2 to 3 years after radiotherapy for early seminoma, are likely to be the expression of a highly impaired pre-treatment sperm cell production and only to a lesser degree dependent on the irradiation of the remaining testicle[34]. In a large recent study involving 1814 men[35] radiotherapy had no long-term effects on the assessed markers of spermatogenesis when compared to chemotherapy. Overall, patients treated with adjuvant low-dose RT to the para aortic and pelvic fields for treatment of early-stage seminoma enjoy an excellent long-term cure rate with minimal risk of late RT complications[36].

Fertility Preservation in Bilateral Testicular Tumors

Partial orchiectomy of germ-cell tumors (GCT) provides potential benefits over radical surgery by reducing the need for androgen substitution, lessening

psychological stress, and preserving fertility, with a durable cure rate. Furthermore, many testicular lesions detected clinically or by ultrasonography will be benign, in which case radical orchiectomy represents overtreatment[37].In selected cases with bilateral tumour (metachronous/synchronous), or in the case of tumor in monorchid patients, partial orchiectomy (enucleation of the tumor) can preserve both functions with a low risk of relapse in residual testicular parenchyma, in the absence of intraepithelial neoplasia (TIN). In cases of TIN and normal testosterone levels (80%), the fertility is maintained in 50% of patients[38]. In synchronous bilateral testicular tumors, metachronous contralateral tumors or in a tumor in a solitary testis with normal pre-operative testosterone levels, organ preserving surgery can be performed if tumor volume is less than 30% of testicular volume.

Future Perspective/ Conclusion

Low dose chemotherapy[39] , low radiation doses[40] and limiting radiation to para aortic areas are some of the effective strategies to preserve fertility at the cost of poor tumor control. Sperm cryopreservation still remains the best treatment option for management as infertility cannot be predicted on a case to case basis. Sperm cryopreservation is underutilized in patients with cancer. There is a high rate of success of sperm cryopreservation and clinical policies should be directed to increase utilization[41]. Storage time of cryopreserved semen has no deleterious effect on semen quality[42] and the option of sperm cryopreservation should be given to all patients with testicular tumor[43]. If masturbation fails, electro ejaculation can be considered as a useful option for semen retrieval[44]. Testicular sperm extraction is another useful treatment option for sperm preservation in patients with an ejaculation[45]. Cryopreserved semen may be used for intrauterine insemination when sperm quality is fair or for intracytoplasmic injection when parameters are deranged. A 4% rate of congenital anomalies in patients of testicular cancer after treatment has been demonstrated. Based on such findings, it is imperative that patients be counselled and advised to wait for 12-24 months before planning parenthood[46].

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(Dr Rajeev Sood, Professor and Head, Dr Raman Tanwar, Senior Registrar, Dept of Urology, PGIMER and Dr RML Hospital, New Delhi)

ACTIVITIES OF RGCI & RC

CME on Communication Skills

Department of Counseling, RGCI & RC organized a Continuing Medical Education (CME) Programme on Communication Skills on 23rd August, 2014, at Ashray. This CME was first of its kind conducted by the department since its inception. The programme stressed the importance of communication in the healthcare scenario, particularly in oncology care and aimed at improving the participants' skills for effective communication with patients. The CME was conducted for all the employees of RGCI & RC involved in patient communication directly or indirectly. Although the program highlighted the importance of clinician patient communication and nurse-patient communication, it also emphasized on multidisciplinary approach of patient centered communication and communication of clinical and non clinical teams with the care givers. The programme saw enthusiastic participation from RGCI team members, as well as members from Cancer Sahyog.

Dr. A.K. Dewan, MD RGCI & RC introduced the concept of Communication Skills and its importance in oncology and the role of counseling services as being aspects in oncology care. It was followed by a speech on good communication by Ms Meera Khetrapal and a thought provoking presentation by Dr Swarupa Mitra (Senior Consultant Radiation Oncology) on "New Challenges in Communication with Cancer Patients" with special reference to Indian setting.

One of the interesting attraction of CME was a skit presented RGCI & RC by team, the theme of which was myths and misconceptions in cancer diagnosis and how these myths impact the psychological well-being and QOL of patient and the family. The skit also portrayed how effective communication can help deflate panic situations in patients.

The interactive session with audience was another unique feature of the CME, which aimed at creating a platform for audience, including oncologists, nurses, cancer survivors, and other non-clinical staff to share and express their experiences and difficulties faced in day to day practice. The interactive session was diligently coordinated by Dr Indu Aggarwal and the response interactive session was overwhelming.

A brainstorming panel discussion between some renowned members of RGCI&RC included

Dr. Swarupa Mitra addressing the audience

Dr Swarupa Mitra (Senior Consultant Radiation Oncology), Dr Sandeep Jain (Consultant Pediatric Hematology), Kathleen Glenda (Nursing Superintendent) Mrs Meera Khetrapal (Psychologist), Dr Santosh Gupta (Cancer Survivor). Some of the very important topics were discussed in the panel discussion, were as follow;

- Communicating with patients of different socio-economic status
- Inter-personal communication (Communication among oncology clinicians)
- Impact of communication on treatment decisions
- Impact of communication on treatment compliance
- Communication with difficult patients and caregivers

The panel discussion was moderated by Dr Rayaz Ahmad (Consultant Hematology).

Finally, an encouraging speech delivered by Mr DS Negi, CEO, RGCI&RC, which underscored the importance of communication in health care in general and oncology in particular. In addition to psycho-social issues, specifically financial burden of cancer on patients and caregivers and communicating these issues to clinical team was emphasized.

The CME was concluded with a refreshing high tea which was yet another opportunity for team RGCI&RC to interact and share their intellectual view points and feed back about the CME in order to continue such programmes in future and to make their outcomes better, more interesting and fruitful.

The response for CME was overwhelming and the post-programme comments were very encouraging. Counseling Team consisting of Ms Shailja, Mr Irfan and Ms Pankaj was lauded by all for the interesting content of the programme. The team was also appreciated for its generous and humble effort for putting its hearts in conducting this CME, which has set standards for upcoming programmes.

(Dr Irfan Majid, Clinical Physilogist, Dept of Counseling, RGCI&RC)

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