Recent Trends in Management of Testicular Cancer

Essay

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By

Mohamed Elsaeed Yousef

M.B.B.Ch.

Under supervision of

Prof. Dr. Ahmed Salah Eldin Hegazy

Professor of Urology
Faculty of Medicine
Ain Shams University

Dr. Mohamed Ibrahim Ahmed

lectuer of Urology
Faculty of Medicine
Ain Shams University

Faculty of Medicine
Ain Shams University

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List of Abbreviations

AFP	alpha fetoprotein
AJCC	American Joint Committee on Cancer
AUC	area under plasma concentration-time curve
Beta-hCG	beta-human chorionic gonadotropin
cave	cumulative doses of bleomycin
CCND2	cyclin D2 gene
CDDP	Cisplatin
Cg A	chromogranine A
CS1	clinical stage I
CT	Computed tomography
DES	diethylstilbestrol
EGCCCG	European Germ Cell Cancer Consensus Group
EP	Etoposide
FDG-PET	Fluoro deoxyglucose-positron-emission tomography
G-CSF	granulocyte colony-stimulating factor
GCT	germ cell tumors
GFR	glomerular filtration rate.
GWAS	Genome Wide Association Study
HIFU	high-intensity focused ultrasound
ICSI	intra-cytoplasmic sperm injection
IGCCCG	International Germ Cell Cancer Collaborative Group
IVF	In vitro fertilization
KITLG	Implicated genome
LDH	lactate dehydrogenase
MRC trial	Medical Research Council
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NGCT	Non seminomatous germ cell tumors.
PA	para-aortic
PEB	cisplatin, etoposide and bleomycin
PEI/VIP	cisplatin, etposide, ifosfamide.
PET	Positron emission tomography
PFS	progression-free survival
PGC	primordial germ cell
PLAP	placental alkaline phosphatase
RPLND	Retroperitoneal lymph node dissection
SNPs	single-nucleotide polymorphisms
TESE	testicular sperm extraction
TGCT	Testicular germ cell tumors

Tin	testicular intraepithelial neoplasia
TIP	paclitaxel, ifosfamide, cisplatin
TSS	Testis sparing surgery
UICC	International Union Against Cancer
US	ultrasonography
VeIP	vinblastin, ifosfamide, cisplatin
W H O	World Health Organization

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Introduction

Testicular cancer is relatively rare cancer that accounts for about 1-1.5% of male cancers and mainly affects younger men in the third or fourth decade of life .It can be classified into three categories :germ cell tumors (90-95%), cord stromal tumors and miscellaneous **(Albers et al, 2012).**

The total crude incidence of testicular and paratesticular cancers was 31.5/1,000,000 person / years, 55% of which were seminomatous and 38% were non-seminomatous. Seminomatous testicular cancer was the most common entity with a total crude incidence of 17/1,000,000, followed by non-seminomatous testicular cancer (12/1,000,000) (**Trama et al, 2012).**

Germ cell tumor (GCT) is a unique neoplasm where biochemical markers play a critical role. Serum tumor markers in patients with testicular cancer are integral in patient management, contributing to diagnosis, staging and risk assessment, evaluation of response to therapy, and detection of relapse **(Ehrlich et al, 2010).**

Radical orchidectomy is currently considered the standard treatment for testis tumors of malignant or unknown origin. In the last 2 decades, however, due to the improvement in oncologic outcome and growing attention devoted to functional issues of cancer survivorship, the management of testis tumors has started to evolve in favour of conservative surgery, mirroring the current trend of organ preservation in the treatment of several other cancers **(Giannarini et al, 2010).**

Conservative treatment allows maintaining fertility, avoids the risk of future hypogonadism, and as a result improves the quality of life by preserving the body image. Nonetheless, most urologists still believe that

when the tumor is located in one testis in the presence of a contralateral normal organ or when the tumour mass is 75% of the testicular volume and frozen section examination reports a suspicious malignant lesion, radical surgery should be preferred over sparing surgery **(Stefani et al, 2012).**

The prognosis for testicular cancer is excellent, with surgery management a 5-year survival rate greater than 95%. Patients affected can therefore expect to be cured after treatment. Successful treatment requires good assessment of the condition and strict follow up **(Brunereau et al, 2012).**

Aim of the Essay

The aim of the essay is to spot light on recent trends in management of testicular cancer, according to the guidelines and recent studies.

Pathology and staging of testicular cancer

Testicular cancer can be classified into three categories: germ cell tumors, cord stromal tumors and miscellaneous. Primary germ cell tumors (GCT) are, by far, the most common histological type.Germ cell tumors are classified as seminoma or nonseminoma. Nonseminomatous tumors include multiple cell types including embroynal cell carcinoma, yolk sac tumor, choriocarcinoma and teratoma. Teratomas are considered to be either mature or immature **(Motzer et al, 2012).**

Testicular cancer appears as painless, unilateral mass in the scrotum or the casual finding of an intrascrotal mass . In approximately 20% of cases, the first symptom is scrotal pain, and up to 27% of patients with testicular cancer may have local pain. Occasionally, trauma to the scrotum may reveal the presence of a testicular mass. Back and flank pain are present in about 11% of cases **(Alber et al, 2012).**

Risk factors for the development of testicular cancer :

- History of cryptorchidism.
- Undescended testis.
- Klinefelter's syndrome.
- Familial history of testicular tumors among first-grade relatives (father/brothers).
- The presence of a contralateral tumor or Tin (testicular intraepithelial neoplasia).
- Infertility.

(Alber et al, 2012) .

- ***Cryptorchidism:***

In patients with cryptorchidism, the risk of developing germ cell tumor is increased fourfold to eight fold; the risk of developing GCT when a cryptorchid testis is intra-abdominal is about 5%. The risk is 1% if the testis is retained in the inguinal canal. Orchiopexy if done when the patient below 6 years of age will lower the risk further **(Pettersson et al, 2007).**

- ***Family history:***

1st degree relative has a higher risk of developing testicular cancer than the general population, although the incidence is low. About 2% of testicular cancer patients report having an affected relative. Brothers are particulary at a higher risk, with a relative risk of 8-10 folds among sons of affected men**(Nathanson et al, 2005).**

- ***Infertility:***

Men with male factor infertility are nearly 3 times more likely to develop subsequent testicular cancer; Intratubular germ cell tumor (carcinoma in situ) has been found in 0.4-1.1 of men undergoing testicular biopsy because of infertility **(Walsh et al, 2009).**

- ***Genetic Basis:***

Genetic changes have been described in patients with testicular cancer**. A** specific genetic marker (an iso-chromosome of the short arm of chromosome 12, i (12p), has been described in all histological types of germ cell tumors **(Bosl & Motzer, 1997).**

Intra-tubular germ cell neoplasia (testicular intraepithelial neoplasia, Tin) shows the same chromosomal changes, and alterations in the p53 locus have been found in 66% of cases of testicular Tin **(Kuczyk et al, 1996).** A deregulation in the pluripotent programme of fetal germ

cells (identified by specific markers like M2A, C-KIT and OCT4/NANOG) is probably responsible for the development of Tin and germ cell neoplasia. There is overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma **(Reuter et al, 2005).**

The characteristic genetic change found is an iso-chromosome of the short arm of chromosome 12 [i (12p)], which is often seen in sporadic cancers. This suggests that genes in this region are important in the development of germ cell tumors. A number of other genes that have a relatively weak effect are also involved in the development of testicular cancer **(Walsh et al, 2009).**

These genetic factors that have a role in the development of testicular cancer is shown by the fact that the risk for the disease is higher in first degree relatives of cancer patients than in the general populations. About 2% of testicular cancer patients report having an affected relative. Brothers are particularly at a higher risk, with a relative risk of 8-10 folds among sons of affected men **(Nathenson et al, 2005).**

- Two models of testicular carcinoma in situ have been proposed:

The first posits that fetal gonocytes whose development into spermatogonia is blocked, may undergo abnormal cell division and then invasive growth mediated by postnatal and pubertal gonadotropin stimulation **(Reuter et al, 2005).**

The second model postulates that the most likely target cell for transformation is zygotene-pachytene spermatocyte. During this stage of germ cell development, aberrant chromatid exchange events associated

with crossing over can occur **(Reuter et al, 2005)**. Normally, these cells are eliminated by apoptosis. On occasion, this crossing over may lead to increased 12p copy number and over expression of the cyclin D2 gene (CCND2). The cell carrying this abnormality is relatively protected against apoptosis because of the oncogenic effect of CCND2, leading to re initiation of the cell cycle and genomic instability **(Reuter et al, 2005)**.

Malignant transformation of germ cells is the result of multistep process of genetic changes. One of the earliest events is the increased copy number of **12p**, or as tandem duplications of chromosome arm **12p**,this abnormality is found in occult carcinoma in situ lesions as well as more advanced disease **(Looijenga et al, 2007).** Further studies indicate that **CCND2** is present at chromosome band **12p13** and that **CCND2** is overexpressed in most germ cell tumors, including carcinoma in situ. Amplification of **CCND2** activates **cdk4/6,** allowing the cell to progress through the **G1-S** checkpoint **(Reutera et al, 2005).**

The most recent Genome Wide Association Study in table 1below stated that identified single-nucleotide polymorphisms (**SNPs**), at **12q22** locus, associated with a 2.55- to 3-fold increased risk of **TGCT**. **(Kanetsky et al, 2009 & Rapley et. al , 2009)**. The **12q22** region contains **KITLG** (implicated genome) which encodes the ligand for the receptor tyrosine kinase (**c-KIT**) the **KITLG-KIT** signaling pathway has a role in gametogenesis with **Kitl** being necessary for primordial germ cell (**PGC**) development **(Mahakali et al, 2005).** Studies have suggested that **TGCTs** arise from **PGCs** and delayed differentiation of **PGCs** have been linked to **TGCT** in situ in individuals with chromosomal abnormalities **(Oosterhuis& Looijenga, 2005).**