

Review Article

The key application of serum tumor markers in testicular cancer: a review and update

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ABSTRACT

Testicular neoplasm is the most common solid tumor in male. The recent advancement in the medical field has made it possible to become one of the most highly treatable neoplasms. Testicular neoplasm is mainly classified into two main groups: non-seminomatous germ cell tumor and seminomatous germ cell tumor. In this review article, we analyzed the current role of serum biomarkers in diagnosis, prognosis, staging, measurement of response to therapy and early detection of relapse of testicular neoplasm. The commonly used tumor markers are alpha-fetoprotein (AFP), beta-human chorionic gonadotrophins and lactate dehydrogenase. Apart from them, a new set of tumor biomarkers like placental-like alkaline phosphatase, gamma-glutamyltranspeptidase, miRNA, mitochondrial DNA and serum trace elements are also proven to be potentially helpful in the management of testicular neoplasm. Progressive elevation of serum tumor markers often indicates the presence of testicular cancer and aids in histological classifications. According to an additional category, the rate of elevation of respective biomarkers is advantageous to appropriately stage testicular neoplasm (S) in the tumor nodes metastases (TNM) staging classification. Besides, it is found that higher elevation of serum tumor markers is associated with a poorer prognosis. Post-treatment assessment where there is a rate of reduction of serum tumour biomarkers suggests the effectiveness of initial management of testicular neoplasm.

Keywords: Tumor markers, Lactate dehydrogenase, Alpha-fetoprotein, β -human chorionic gonadotropin, Seminoma, Non-seminomatous germ cell tumor

INTRODUCTION

Testicular cancer is a curable form of solid malignancy affecting males globally. Over the past thirty to forty years, the incidence of testicular cancer has been increasing progressively. According to global cancer observatory (GLOBOCAN) by WHO, incidences of testicular cancer worldwide reported are on the rise from over 52,000 cases in 2008 to 55,266 cases in 2012.¹ The sharp increase was observed in 2018 (71,105 cases) according to the latest update by the GLOBOCAN in 2019.

Testicular cancer had been affecting primarily caucasian populations. Young white men in nordic countries (northern Europe) have a ten times higher incident rate

than black and Asian men.¹ GLOBOCAN estimated that about 71,110 new testicular cancer cases and 9510 testicular cancer-related deaths in 2018 as shown in Table 1.

According to the WHO 2016 classification of testicular and para-testicular tissue tumor, germ cell tumors (GCTs) are divided into seminoma and non-seminomatous germ cell tumor (NSGCTs) with the subclass of post-pubertal yolk sac tumor, teratoma, embryonal carcinoma, oriocarcinoma and other trophoblastic tumours. GCTs account for 95% of malignant testicular tumor.²⁻⁴ It may occasionally occur in the extragonadal primary site yet still managed similarly as testicular GCTs. This neoplasm involves patients of the age of 15 until 35 years old.^{5,6}

Cryptorchidism increases the development of testicular neoplasm by up to eightfold if left untreated or surgically corrected in the post-pubertal phase. The risk of developing neoplasm is, however, only twofold if orchiopexy was done before puberty.⁷ The other leading causes are low birth weight, small gestational age, twins, genetics, family history, down syndrome, testicular dysgenesis and testicular microlithiasis.⁸ Within the past 40 years, the incidence of these tumors worldwide marked more than double.⁸ Additionally, hypercholesterolemia can also be a significant risk factor for various cancers and chronic illness.⁹

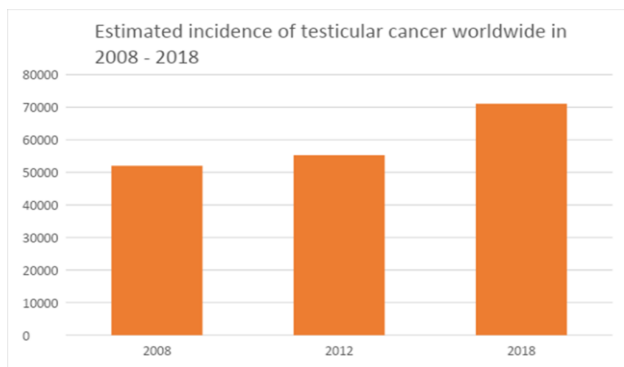


Figure 1: Estimated incidence of testicular cancer worldwide in 2008-2018.

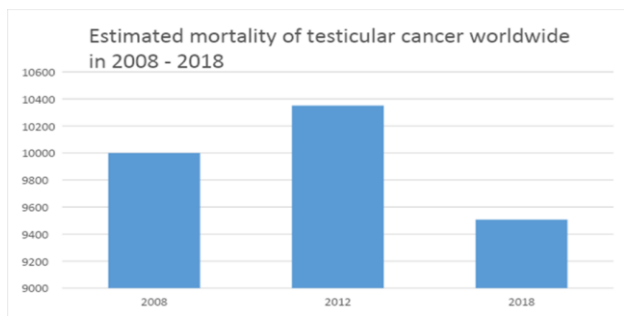


Figure 2: Estimated mortality of testicular cancer worldwide in 2008-2018.

Patients of testicular neoplasm typically present with painless testicular enlargement, a vague sense of scrotal

heaviness or hydrocele.⁷ Classical treatments of testicular cancer are radical inguinal orchiectomy, chemotherapy and radiation therapy which may be done depending on the stage of the neoplasm. The mechanism behind chemotherapy is the activation of autophagy which can cause tumor suppression.¹⁰ Therefore, chemotherapy is the choice treatment in advanced testicular neoplasm.¹⁰ Serum tumor markers like AFP, beta-human chorionic gonadotrophin, lactate dehydrogenase play a pivotal role in the diagnosis and management of testicular neoplasm. However, other potential tumor biomarkers such as microRNAs (miRNAs) and epigenetic markers such as DNMT3A, CALCA and MGMT are usually associated with poor clinical outcome in testicular GCTs.¹¹

AFP is an onco-fetal antigen that is clinically beneficial when using together ultrasonography and cross-sectional imaging with MRI or CT of the chest, abdomen and pelvis for preoperative assessment during initial management, early recurrence, or metastases detection upon following up. AFP is found in 90% of cases of prepubertal tumour such as yolk sac tumours. The level of serum AFP is high in the neonates (up to 50,000 ng/ml), drop to normal value by 12 months of age and further decreases with ageing.¹² The normal value of serum AFP is less than 15 ng/ml after one year old.⁹ The half-life of AFP is from 5 to 7 days.¹³ Any increase in the serum level in an adult may indicate occult NSGCTs, as these tumor marker are produced by NSGCTs but not in pure seminoma. Elevation of serum AFP concentration above 10,000 mg/l in men may also be associated with liver and gall bladder pathology.¹⁴

β - human chorionic gonadotropin (β -hCG) has a half-life of 1-3 days. It is raised in 10%-20% of clinical stage I(CSI) of NSGCTs cases and raised in 40% of advanced cases. β -hCG is also raised in 15%-20% of advanced seminoma patients.⁶ This tumour marker is predominantly raised in choriocarcinoma patients. LDH is an enzyme found in tissues in the body, elevated in 40%-60% of men with testicular GCTs. LDH has less specificity for GCT. Elevated levels are correlated to high tumour burden in seminoma and recurrence in NSGCTs. Assays for LDH does not measure actual quantity but measures enzymatic activity.

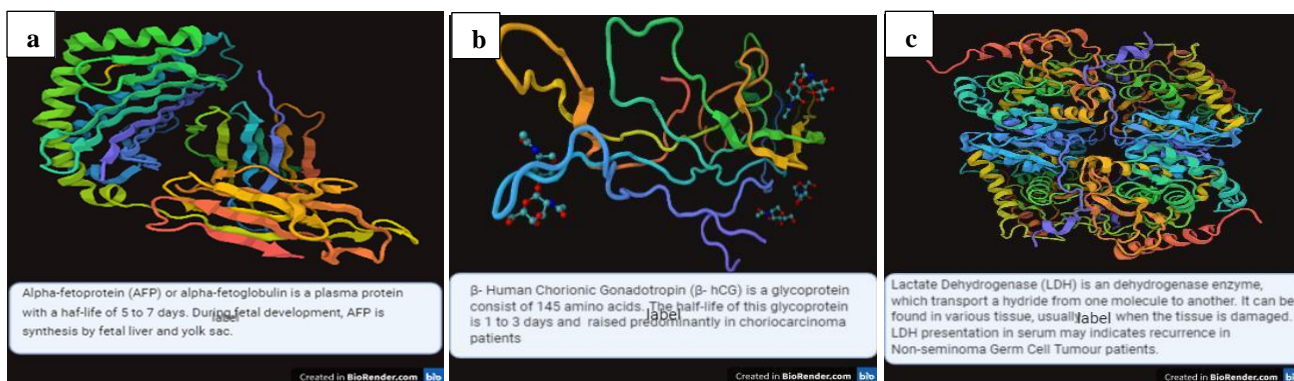


Figure 3: (a) Molecular structure of AFP; (b) Molecular structure of β -HCG; (c) Molecular structure of LDH.

Objective and methodology

The key objective of this review article was to determine the role of tumor markers in the diagnosis, staging, prognosis, and management of testicular neoplasm in the current era. We have extensively reviewed the published

articles in reputed indexed journals from the year 1970 until 2020 about the various role of tumor markers in managing testicular neoplasm. The popular online databases (such as ScienceDirect, Pubmed, UpToDate, Research Gate, Google Scholar, Nature Review and others) were used to search relevant articles comprehensively.

Table 1: Incidence and mortality of testicular cancer in 2018 by continents*.

Testicular germ cell carcinoma incidence				Testicular germ cell carcinoma mortality	
Continents	Male population (thousands)	n	ASR	n	ASR
Eastern Africa	209,604	477	0.30	226	0.17
Middle Africa	84,370	168	0.26	79	0.15
Northern Africa	119,218	625	0.53	142	0.14
Southern Africa	32,363	236	0.74	79	0.30
Western Africa	191,785	291	0.23	154	0.16
Caribbean	21,322	257	1.00	49	0.19
Central America	85,982	5,281	5.50	690	0.71
South America	208,646	9,801	4.20	1 243	0.52
North America	180,301	9,459	5.10	466	0.23
Eastern Asia	850,003	7,115	0.78	1 022	0.09
South-eastern Asia	327,352	2,601	0.78	538	0.17
South-central Asia	1,013,759	6,842	0.67	2 737	0.29
Western Asia	141,767	2,794	1.80	397	0.28
Central and eastern Europe	138,180	5,505	3.50	868	0.50
Western Europe	95,584	9,616	9.70	380	0.30
Southern Europe	74,512	4,904	6.70	277	0.29
Northern Europe	51,925	3,962	7.40	121	0.19
Australia and New Zealand	14,731	1,097	7.20	27	0.15
Melanesia	5,461	70	1.40	12	0.28
Polynesia	342	4	1.10	0	0
Micronesia	272	0	0	0	0
World	3,847,487	71,105	1.7	9 507	0.23

*ASR=age-standardized rate per 100,000 individuals; population size data were retrieved from the department of economic and social affairs, population division, United Nations; (<http://esa.un.org/unpd/wpp/Download/Standard/Population>).

Table 2: WHO 2016 classification of tumor of the Testis and para-testicular tissue.

WHO 2016 classification of tumor of the Testis and para-testicular tissue	
Non-invasive germ cell neoplasia	
Germ cell neoplasia in situ (GCNIS); previous synonyms: carcinoma in situ testis, intratubular germ cell neoplasia unclassified	
Gonadoblastoma (in patients with disorders of sex development, also contains sex-stromal elements)	
Germ cell tumors derived from GCNIS	
Seminoma	
Non-seminomatous germ cell tumors	Embryonal carcinoma
	Teratoma (post-pubertal type)
	Yolk sac tumor (post-pubertal type)
	Choriocarcinoma and other trophoblastic tumors
Germ cell tumours unrelated to GCNIS	
Childhood tumors	Teratoma (pre-pubertal type)
	Yolk sac tumor (pre-pubertal type)
Spermatocytic tumor (median age of diagnosis around 50 years)	

Table 3: Staging of testicular neoplasm corresponding to a level of tumor.

SX	No serum tumor markers detected
S0	Serum tumor markers are within normal value
SI	LDH <1.5x upper limit of normal
	AFP <1000 ng/ml
	β-hCG <5,000 mIU/ml
SII	LDH 1.5-10x upper limit of normal
	AFP 1,000-10,000 ng/ml
	β-hCG 5,000-50,000 mIU/ml
SIII	LDH >10x upper limit of normal
	AFP >10,000 ng/ml
	β-hCG >50,000 mIU/mL

Table 4: Prognosis of testicular neoplasm.

Risk status	Seminoma	Non-seminoma
Good	Stage IIC and III (5 years OS; overall survival rate: 86%)	Stage IIC and IIIA (92% of 5 years OS)
	Any primary sites	Retroperitoneal or Testicular primary tumor
	Without metastasized to non-pulmonary visceral	No metastasized to visceral and non-pulmonary
	Normal AFP	LDH <1.5-10x upper limit of normal+
	Any LDH	AFP <1000ng/ml
Intermediate	Any β-hCG	β-hCG <5000 IU/l
	Stage IIC and III (5 years OS; overall survival rate: 86%)	Stage IIIB (80% of 5 years OS)
	Any primary sites	Retroperitoneal or testicular primary tumor
	Metastasized to non-pulmonary and other visceral	No metastasized to non-pulmonary and visceral
	Normal AFP	LDH 1.5-10x upper limit of normal OR
Poor	Any LDH	AFP 1000-10,000 ng/ml OR
	Any β-hCG	β-hCG: 5000-50,000 IU/l
	-	Stage IIIC (48% of 5 years OS)
	-	Mediastinal primary tumor OR
	-	Metastasized to non-pulmonary visceral OR
-	LDH >10x upper limit of normal OR	
-	AFP >10,000 ng/ml OR	
-	β-hCG >50,000 IU/l	

Table 5: Tumor eradication response corresponding to effective chemotherapy.

Type	Tumour marker	Radio-imaging	Results
Type 1	-	-	No Tumor
Type 2	-	+	Tumor present
Type 3	+	+	Tumor present
Type 4	++	++	Disease progression

DISCUSSION

Application of tumor marker in diagnosis perspective

At least one of the three tumor markers rise in 85% of cases of NSGCT and some seminoma cases. Occasionally, even before the clinical or radiographic manifestation of the disease, there is evidence of an increase in serum tumor

markers.¹⁵ Tumor markers are highly crucial in diagnosing testicular cancers and especially, the elevation of serum AFP and β-hCG is very significant to it.¹⁶ Conversely, serum LDH is rarely recommended for diagnostic purpose as it is commonly present in the human body and the rise of it can be associated with other illnesses. It has been proven that patients with an elevated level of LDH have been often classified as false positive for testicular cancer.¹⁷

Although, as discussed earlier, the rise of AFP and β -hCG indicates testicular cancer, the differential diagnosis for them are pretty vast.¹⁸ Elevation of AFP during early stages of life in children indicates genetic disorder such as ataxia-telangiectasia and hereditary tyrosinemia. In adults, a malignant condition such as hepatocellular carcinoma is commonly associated with an increased level of AFP.¹⁹ However, AFP level can also rise in non-neoplastic liver disorders such as alcoholic liver diseases and hepatitis.^{6,14} In the context of testicular cancers, AFP serum level can be elevated in yolk sac tumors and embryonal carcinoma but not in choriocarcinoma or pure seminoma. Thus, a patient who presents with an evident testicular mass with the rise of AFP is categorized under NSGCT and treated accordingly.²⁰

β -hCG serum level increases by 10 to 20 percent in pure seminoma, all choriocarcinoma and forty to sixty percent in embryonal carcinoma.¹⁷ Extensive research has been conducted to study the rise of β -hCG. In this research, it is classified into two categories knowingly, if there is a slight elevation of β -hCG, it does not exclusively suggest testicular cancer. Contrarily, if there is high elevation β -hCG in the patient's serum, this strongly suggests testicular cancer.²¹

The elevated level of serum tumor markers should always be correlated with physical examination findings and imaging studies for accurate diagnosis of testicular cancers. However, in conditions where the patient requires urgent treatment or the histological findings are non-specific, the levels of tumor markers can also be helpful for further management.²⁰

Recent studies have been proven that few other markers can also be used for diagnosing testicular cancer. Gamma-glutamyltranspeptidase (GGT), an enzyme primarily used in associated liver diseases, has shown mild elevation in pure seminoma. Placental-like alkaline phosphatase (PLAP) has also shown elevation in pure seminoma, but unfortunately, it can give rise due to other malignancies and smokers.¹⁵ Thus, this PLAP might be only valuable for non-smokers.²² However, a combination of these tumor markers along with AFP, β -hCG and LDH can aid in the diagnosis of pure seminoma and its management.²³

Besides, trace elements in a patient's serum such as cobalt, copper, magnesium, lead, zinc, iron and manganese are known to be involved in testicular cancers. Nonetheless, they do involve in other malignancies which could give a vast differential diagnosis.²⁴

Serum molecular biomarkers such as miRNA and circulating mtDNA can be utilized in diagnosing testicular cancers as they are elevated in this solid tumor.²⁵ miRNA serves for the sensitivity and specificity rate of 84.7% and 99.0%, whereas mtDNA has the sensitivity of 60% and specificity of 94%, respectively in diagnosing GCTs. miRNA serves as tumor suppresser gene, p53 in testicular

cancers and reduce to normal level posts-orchietomy. However, it also elevated in other genitourinary malignancy and thyroid cancers. Furthermore, mtDNA has the potential to distinguish between healthy individuals and cancer patients due to the increasing amount of serum level.¹⁸ Also, SOX2, a transcription factor, is not present in seminomas and yolk sac tumors but is seen in embryonal carcinomas.²⁶ However, further studies needed to verify the support of these tumor biomarkers in handling testicular cancers.

Staging of testicular neoplasm using serum tumor markers

Tumor staging can be said as the vital principle for monitoring prognosis and treatment in testicular cancer.²⁷ Thus, serum tumor markers are utilized in the staging of testicular neoplasm. The staging of testicular neoplasm is mainly divided into three stages; stage I (SI) to stage III (SIII). SIII is the advanced stage of the neoplasm where the tumor spreads to distant lymph nodes such as to the lungs, where it may present with or without increase value in serum tumor markers.

American joint committee on cancer (AJCC) has included serum tumor markers as an additional category in tumor nodes metastases staging, (S). This category is only applied pre-orchietomy. In the 8th edition of AJCC, they included the updated values for each staging (S) of testicular neoplasm, as shown in Table 3.

Clinical staging of NSGCTs is related to the elevated rates of all three serum tumor markers: LDH, AFP and β -hCG in all GCT patients. In the patients with SI disease, if the level of tumour marker fails to return to its normal level, it is considered as clinical-stage Is.²⁸ Besides, if the time for serum tumor marker to return to its normal value is rapid after orchietomy, this also suggestive of SI disease.²⁹ While, in men with NSGCTs, post orchietomy, if there is persistent raise of serum markers, these patients must be treated as SIII patients despite having no abnormal findings radiologically.³⁰ In a new study, in the group of 442 patients studied, it is discovered that there is an association between measured serum levels of the three markers with clinical stages where the lowest level indicates SI and the highest level indicates SIII.²⁸

LDH rises more in the advanced stage. Therefore, LDH useful in monitoring CSII and CSIII.³ Apart from that, serum tumor markers help foretell chances of micro-metastatic disease. A Swedish-Norwegian testicular cancer group discovered that the normal AFP level pre-orchietomy corresponds to a higher risk of retroperitoneal metastasis at retroperitoneal lymph node dissection (RPLND).¹³ Besides, chances of staging error can be reduced with the use of serum tumor markers. This is demonstrated in a study, by using all three serum markers, the staging error is reduced in stage II, from five to ten percent while stage I patients, from fifty-three to around

nine to fourteen percent in embryonal carcinoma of testicular neoplasm.³¹

Application of tumor marker in prognosis of testicular neoplasm

A prognostic factor-based staging system that was published by the international germ cell cancer collaborative group has classified patients into poor, intermediate and reasonable risks.⁶ The practical purpose of prognosis is to assess the efficacy of primary chemotherapy regimen, additional therapy, surveillances post-surgery, RPLND, salvage therapy and post-chemotherapy in recurrent cases that influence the outcome of the patient.

Initial therapy responses and duration of initial remission are another crucial prognostic factor. Patients with progressive disease during or within four weeks after completing cisplatin-based chemotherapy are considered a poor diagnosis. Surgical resection following chemotherapy or as primary treatment is highly recommended.²⁹

Application of tumor marker in evaluate response of therapy

The primary management of testicular cancer involves surgery, chemotherapy and radiotherapy. The common surgeries performed are radical orchiectomy and RPLND (if metastasis occurs to retroperitoneal lymph node). In the context of chemotherapy, it is indicated in post-orchiectomy (high-risk patients) or for clinical stage II and III patients.²⁵ As of current treatment, serum tumor markers are obtained on a day before administering each chemotherapy cycle to indicate the effectiveness of previous therapy.

Importantly, stage II testicular tumor, which is only limited to the testis is usually indicated to treat by surgical method. Besides, those with the risks of relapsing can be treated with chemotherapy (RPLND) or surveillance. Outweighing the adverse effects of treatment compared to the curability rate, surveillance is essential. However, patients with a risk of relapsing or relapsed during the surveillance and chemotherapy administration are indicated. Therefore, continuous measurement of serum tumor markers in the period for five years post-orchiectomy is required.³²

Serum tumor markers of the patients are evaluated throughout treatment at different occasions, during the first presentation, before/after radical orchiectomy, before initiating each cycle of chemotherapy and during the surveillance period. The tumor eradication response is classified into four types after effective chemotherapy is administered, as shown in the Table 5.¹⁷

Concurrently, the reduction level of serum tumor marker post-chemotherapy is highly useful in predicting the tumor

status. A quick decline after administration of chemotherapy usually produces a cancer-free patient compared to those who decline slowly. On the other hand, a decline of one tumor marker and a consistent rise of the other predicts a mixed type of tumor.²⁰ To be noted that cancer patients in this current era widely use complementary and alternative medicines. As these medicines interact with chemotherapy, therapeutic failure resulting in alteration of serum tumor marker levels may occur. Thus, an efficient divulgence is needed between healthcare professionals and patients for better outcomes due to the serum tumor marker levels.³³

Application of tumor markers in testicular neoplasm relapse detection

For the early detection of relapse of testicular neoplasm, serum tumor markers can be one of the indicators. Various studies have found evidence of relations between the recurrence rates of testicular neoplasm and the increase of serum tumor marker value, particularly β -hCG and AFP. Any tumor markers that were escalated at the beginning of diagnosis will also be the same marker elevated when the testicular neoplasm relapse.³ A survey shows that it was specified of relapse of testicular cancer when there is an increase in serum tumor markers after a certain amount of time the serum tumor markers regain their standard value subsequent to the primary therapy of testicular neoplasm.¹⁶ Regardless, this is only probable if there is confirmation of evidence of a primary tumor of the testis.²

A Danish study also investigated a cohort of 33 patients with CS-I NSGCTs to assess the rise in LDH-1 pre-orchiectomy. It was concluded as anyone who had a normal LDH-1 level is prone to relapse than those with a rise in LDH-1 level pre-orchiectomy by 80% to 40%, respectively. LDH level has a role in detecting 40% of all relapses.³⁴ Besides, it was also found that AFP and β -hCG level played a crucial role in detecting relapse of testicular cancer. The study on a cohort of 32 patients, whereby three patients without β -hCG elevation at beginning of the disease returned with β -hCG elevation when the disease relapse. In late relapse cases, where relapse occurs after two years of disease-free, most of it was recognized by the increase in AFP serum level.³⁵ Only 10% of patients with NSGCTs have a rise in β -hCG serum level whereby 76 to 52 per cent others dominate in elevation of AFP level. These values can be explained by the discovery of which the most frequent germ cell tumors in patients with relapse are yolk sac tumour.¹³ Nevertheless, in the case of testicular teratoma, it is hard to determine whether a patient is disease-free or is relapsing because the serum tumor markers, β -hCG and AFP are both normal at diagnosis and relapse.³⁶

Apart from the well-known serum tumor markers discussed above, miRNA has also been found to have a great capability as the latest serum biomarker for detecting relapse of testicular neoplasm. A cluster of miRNAs which is miR-371a-3p is found to be beneficial in detecting

testicular neoplasm. A group of patients with testicular neoplasm is studied and through this, they noted higher serum levels of miR-371-3p than individuals who are well.³⁷ This is further proved that patient with seminoma who relapse have raised the level of miR-371a-3p whereas patients who are not relapsing do not have raised serum level of miR-371a-3p. However, miR-371a-3p cannot be detected in patients with teratoma.³⁸

CONCLUSION

The ever-growing role of tumor markers in diagnosis, prognosis, staging, response assessment of treatment and relapse of testicular cancer have shown a significant improvement in managing patients with testicular cancers.

Serum AFP, β -hCG and LDH are the known serum tumor markers commonly used in current clinical practice. However, their differential diagnosis is quite vast with limited sensitivity and specificity in pure seminoma. Concerning it, PLAP and GGT, serum trace elements, micro RNA and mitochondrial DNA are yet to be proven biomarkers to be incorporated in germ cell tumours. Nonetheless, research in bigger scales with a greater number of patients need to be done to ensure optimal usage of these biomarkers in diagnosis and management of testicular cancer in future usage in clinical practice.

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