Current Clinical Applications of Testicular Cancer Biomarkers

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KEYWORDS

• Testicular germ cell tumors • Tumor markers • microRNAs • Serum • Markers • Mitochondrial DNA

KEY POINTS

- Aside from classic serum tumor markers for testicular cancer (human chorionic gonadotropin, alpha fetoprotein, lactate dehydrogenase), limited data on additional molecular biomarkers have been published or validated.
- Larger series with consistent results from independent groups are required to validate new testicular cancer biomarkers.
- microRNA-371-3 has potential utility as a molecular biomarker for germ cell tumor detection and prognosis.

INTRODUCTION

Most germ cell tumors (GCTs) originate in the testes and account for approximately 95% of testicular cancers. Occasionally, GCTs originate in extragonadal sites, such as the mediastinum or retroperitoneum. Clinical and pathologic heterogeneity is an important feature of GCTs. Benign forms demonstrate extensive somatic differentiation (teratoma), whereas malignant GCTs are divided into seminoma and nonseminomatous GCTs (NSGCT).

Serum tumor markers (STMs) are prognostic factors and are important for diagnosis and staging. STM should be determined before and following orchiectomy. The 3 classic STMs for testicular cancer diagnosis and staging are alpha fetoprotein (AFP), which is produced by yolk sac cells; human chorionic gonadotropin (HCG), which is expressed by trophoblasts; and lactate dehydrogenase (LDH).

STMs are increased in approximately 60% of testicular cancer cases. AFP and HCG are increased in 50% to 70% and in 40% to 60% of patients with NSGCTs, respectively. Approximately 90% of NSGCTs present with an increase in one or 2 of these markers. Up to 30% of seminomas can present with or develop an elevated HCG level during the course of the disease.

LDH is a less specific marker with its concentration being proportional to tumor volume. Its level may be elevated in up to 80% of patients with advanced testicular cancer. Negative marker levels do not exclude the diagnosis of a GCT. Placental alkaline phosphatase (PLAP) is an optional marker for monitoring patients with pure seminoma but may have limited value in smokers.

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Traditional STMs are not only specific for testicular cancer. Elevations in HCG are commonly seen in a wide variety of carcinomas (gastric, pancreatic, neuroendocrine, lung, head and neck, lymphoma, leukemia). Similarly, elevations of AFP can be observed in hepatocellular carcinoma and benign liver disease.

A biomarker has been defined as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" by the World Health Organization. An ideal biomarker for testicular cancer would be an easily detectable molecule that would be unique for GCTs.

Limited contemporary data have been published regarding the use of biomarkers for testicular cancer diagnosis and prognosis in addition to traditional STMs (AFP, HCG, LDH). Cytogenetic and molecular markers based on microRNA (miRNA), cell-circulating mitochondrial DNA, or DNA methylation are available at limited centers but at present are not commonly used in clinical practice (Table 1).

CLINICAL UTILITY OF TRADITIONAL SERUM TUMOR MARKERS

Screening Utility of Serum Tumor Markers

In the context of screening for GCTs, no role of STM has been demonstrated because of the low incidence and mortality of testicular cancer.[1] It is very unlikely that STM as a screening tool would decrease mortality because of the natural history of the disease.

Diagnostic Utility of Serum Tumor Markers

STMs have been shown to assist in determining the origin of GCTs and in some clinical scenarios will dictate treatment. For example, if only seminoma is observed in an orchiectomy specimen, but increased AFP is detected, patients will be treated according to NSGCT protocols. Few conditions other than GCTs cause extreme elevation of STM, but moderate elevations are not as uncommon. See Table 2 for conditions that may cause elevation of STMs.

Ataxia-telangiectasia is a hereditary from of ataxia associated with various skin conditions. More than 95% of affected patients have elevated AFP.[2] Hereditary tyrosinemia is caused by various enzyme deficiencies in the tyrosine degradation pathway. This condition progresses to liver and kidney failure. Because of liver dysfunction, extreme elevations of AFP are present in affected individuals.[3] Similarly, in patients with cirrhotic liver disease and hepatocellular carcinoma, AFP can be elevated but is not always diagnostic of disease (40% of cirrhotic patients have elevation of AFP due to hepatomas).

In primary hypogonadism, a decline in testosterone may cause increased levels of LH.[4] LH is known to have cross reactivity with HCG in some immunoassays. Marijuana use may also result in elevation of HCG.

Table 1
Current clinical testicular cancer biomarkers

Molecular Marker	Target	Characteristics	Able to Differentiate GCT from Healthy Controls	Correlation with GCT Stage
miRNA	miRNA367-3p, 371a-3p, 372-3p, 373-3p	Noncoding RNA; very stable; interfere in the translation of mRNA to protein	Y	Y
mtDNA	mtDNA-79; mtDNA-220	Short length, simple structure	Y	N
CircDNA	—	Same methylation pattern as tumor cells	Y	N
CpG island hypermethylation	Gene silencing (APC, GSTP1, p14, p16, PTGS2, RASSF1A)	Easy to detect methylation; techniques already established	Y	N
CTC	—	Easy to detect; molecular techniques	Y	Y

Abbreviations: CircDNA, cell-free circulating plasma DNA; CTC, circulating tumor cell; mRNA, messenger RNA; mtDNA, mitochondrial DNA; N, no; Y, yes.