Management of Low-Stage Testicular Seminoma

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KEYWORDS

• Seminoma • Stage I • Stage II • Surveillance • Chemotherapy • Radiotherapy

KEY POINTS

- Initial staging evaluation of seminoma after orchiectomy with serum tumor markers and imaging of chest, abdomen, and pelvis is critical.
- Disease-specific survival approaching 100% achieved for low-stage seminoma with active surveillance, adjuvant radiotherapy, or adjuvant single-agent carboplatin.
- Patient selection depends on specific patient and cancer characteristics.
- Risk of unnecessary treatment and sequelae of adjuvant therapy must be weighed against pitfalls of active surveillance such as poor compliance.
- Further research is needed to guide patient selection for adjuvant therapy and to optimize active surveillance protocols.

INTRODUCTION

Epidemiology

Although testicular cancer is the most commonly diagnosed cancer among men aged 14 to 44 years worldwide, it is a rare disease accounting for only 1% to 2% of malignancies.[1,2] Over the last 40 years, for unknown reasons, the global incidence of testicular cancer has doubled. In the United States, there will be an estimated 8820 new cases of testicular cancer in 2014, accounting for 380 deaths.[3] Testicular cancers are classified as seminomatous or nonseminomatous, with a nearly 1:1 incidence ratio. Among testicular cancer diagnoses, seminoma accounts for 46% to 60%.[4]

Histologic Subtypes

Classic or typical seminoma accounts for 95% of seminomas. Gross pathology reveals a white or tan tumor with lobulations. Microscopic examination demonstrates large uniform cells in a sheetlike distribution with a characteristic "fried egg" appearance. Syncytiotrophoblasts may be present, which accounts for the 10% to 15% of seminomas that produce abnormally high levels of human chorionic gonadotropin (hCG).[5] Immunohistochemistry plays a limited role in the diagnosis of seminoma, but nearly all seminomas stain strongly positive for placental alkaline phosphatase (87%–100% of cases). However, placental alkaline phosphatase staining is not specific for seminoma.[5]

Histologic variants of seminoma include tubular seminoma, which histologically mimics Sertoli cell tumor, and anaplastic seminoma.[6] Anaplastic seminoma is a subtype of historical significance referring to seminomas with high mitotic activity. Both tubular and anaplastic seminomas have a

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similar prognosis and clinical management strategy as classic seminoma.[5,7]

Spermatocytic seminoma is rare (<1% of germ cell tumors [GCTs]), originates from more mature germ cells compared with classic seminoma, and has entirely different genetic and morphologic signatures.[8,9] These tumors are also unique because cryptorchidism is not a risk factor and they typically present in older men (mean age at diagnosis, 54 years).[10] Microscopy shows 3 distinct cell types (small, medium, and large) with round nuclei and no placental alkaline phosphatase expression.[11] Spermatocytic seminomas have very low malignant potential and are usually cured with radical orchiectomy followed by surveillance, with the exception of rare cases containing sarcomatous differentiation.[12]

Patterns of Spread

Classic seminoma metastasizes via lymphatic spread to the retroperitoneum if lymphatic flow has not been altered, such as after previous inguinal or scrotal surgery. The primary landing zone for right-sided tumors is the interaortocaval retroperitoneal nodes, compared with left-sided tumors, which typically spread initially to the left paraaortic (PA) nodes. Lymphatic spread within the retroperitoneum tends to be from right to left. Although rare, advanced seminoma presents with supradiaphragmatic lymphadenopathy or visceral metastases in the lung, liver, brain, and other sites. Even advanced seminoma has a relatively favorable prognosis and only liver and brain metastasis have been associated with an adverse prognosis.[13]

CLINICAL EVALUATION

Presentation and Initial Evaluation

Seminoma incidence peaks between 34 and 45 years, approximately 10 years later than other GCTs.[14] Most patients with testicular cancer will present with a painless mass. If present, pain may be owing to rapid growth of the tumor, hemorrhage, or infarction. Symptoms are observed more commonly with nonseminomatous GCTs compared with seminomas, because seminomas tend to have a more indolent disease course. Gynecomastia and infertility can rarely be presenting symptoms. Additionally, a small percentage of cases present with symptoms of metastatic disease, such as abdominal or flank pain, back pain, palpable mass of the abdomen or neck, lower extremity swelling, or a unilateral right-sided varicocele.[15,16] There is a well-recognized diagnostic delay between the onset of symptoms and diagnosis of seminoma, with a mean delay of 4.9 months.[17]

Clinicians should assess for GCT risk factors when taking a history from patients with a testicular mass. A history of undescended testicle is the most significant risk factor for testicular GCT with a relative risk of between 2.7 and 8. Prepubertal orchiopexy seems to result in a significant reduction in the relative risk of testicular GCTs.[18] Orchiopexy seems to reduce specifically the risk of seminoma, evidenced by a 74% incidence of seminoma among malignant tumors arising from uncorrected cryptorchid testicles compared with a 29% incidence of seminoma among GCTs arising after orchiopexy.[18,19] Other established risk factors that should be assessed include a family history of testicular cancer, personal history of testicular cancer, presence of intratubular germ cell neoplasia, or a history of other urogenital abnormalities such as hypospadias.[20,21]

The initial evaluation of a patient presenting with a testicular mass should routinely involve scrotal ultrasonography as an extension of the physical examination. Both testes should be examined. Ultrasonography will usually reveal a solitary, hypoechoic lesion. Seminomas tend to have a more homogenous appearance compared with nonseminomatous GCTs. They can also seem to be lobulated or multinodular with cystic spaces.[22,23]

Serum Tumor Markers

Before radical orchiectomy, serum tumor markers such as α-fetoprotein (AFP), hCG, and lactate dehydrogenase should be obtained. The presence of syncytiotrophoblastic elements in approximately 10% to 15% of classical seminomas account for the increased hCG level in this subset of seminomatous GCTs.[24,25] When hCG is increased, it is typically less than 500 IU/mL. Although increased tumor markers do play a role in the staging of testis cancer (**Table 1**), patients with hCG-producing seminomas do not have a worse prognosis compared with nonsecretors.[26] In contrast with nonseminomatous GCTs, tumor markers are not utilized in the International Germ Cell Cancer Collaborative Group risk stratification schema (**Table 2**) for seminomas.[27] Detection of lactate dehydrogenase does not aid in the differential diagnosis of seminomatous or nonseminomatous GCTs, although levels may reflect overall disease burden.[28] Pure seminoma never secretes AFP; therefore, an increased AFP level indicates a nonseminomatous component or the presence of liver metastases, even when the primary tumor is pure seminoma on final histology.[29] Several recent