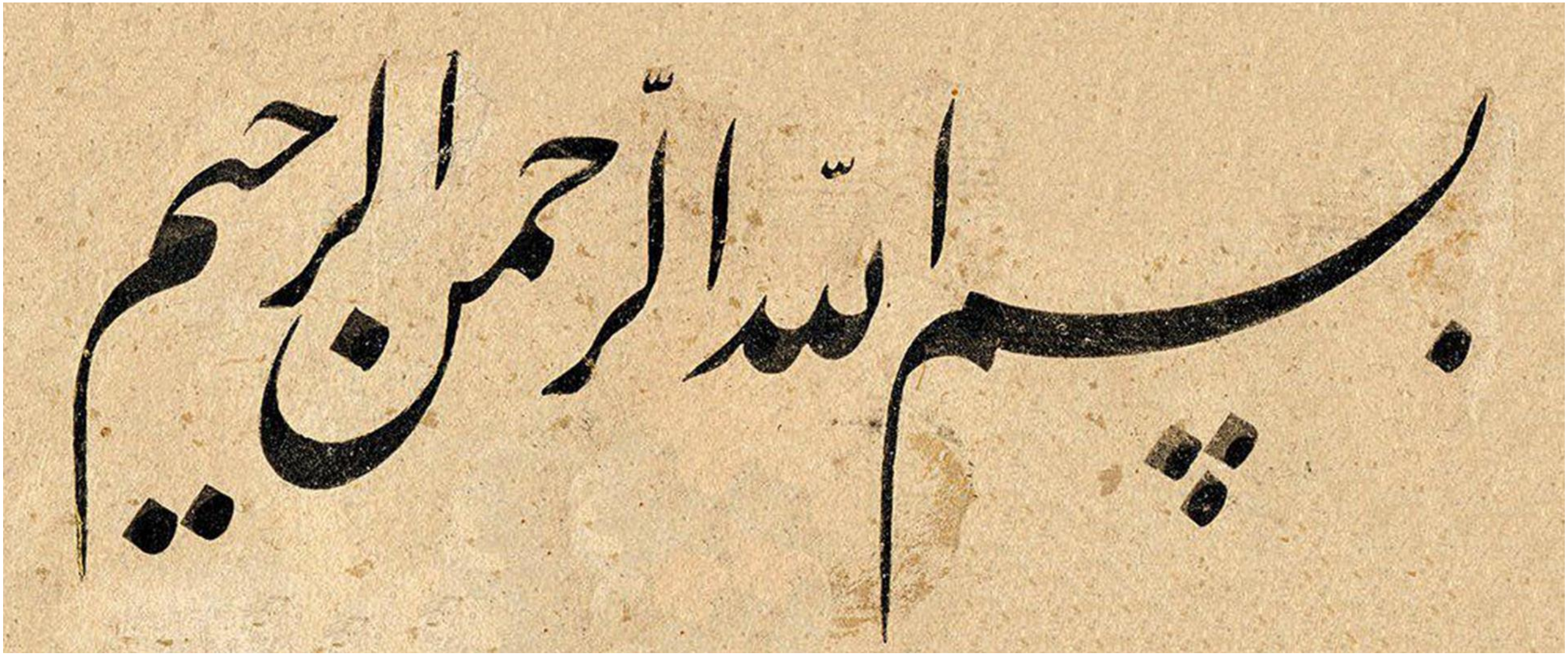
بسم الله الرحمن الرحيم

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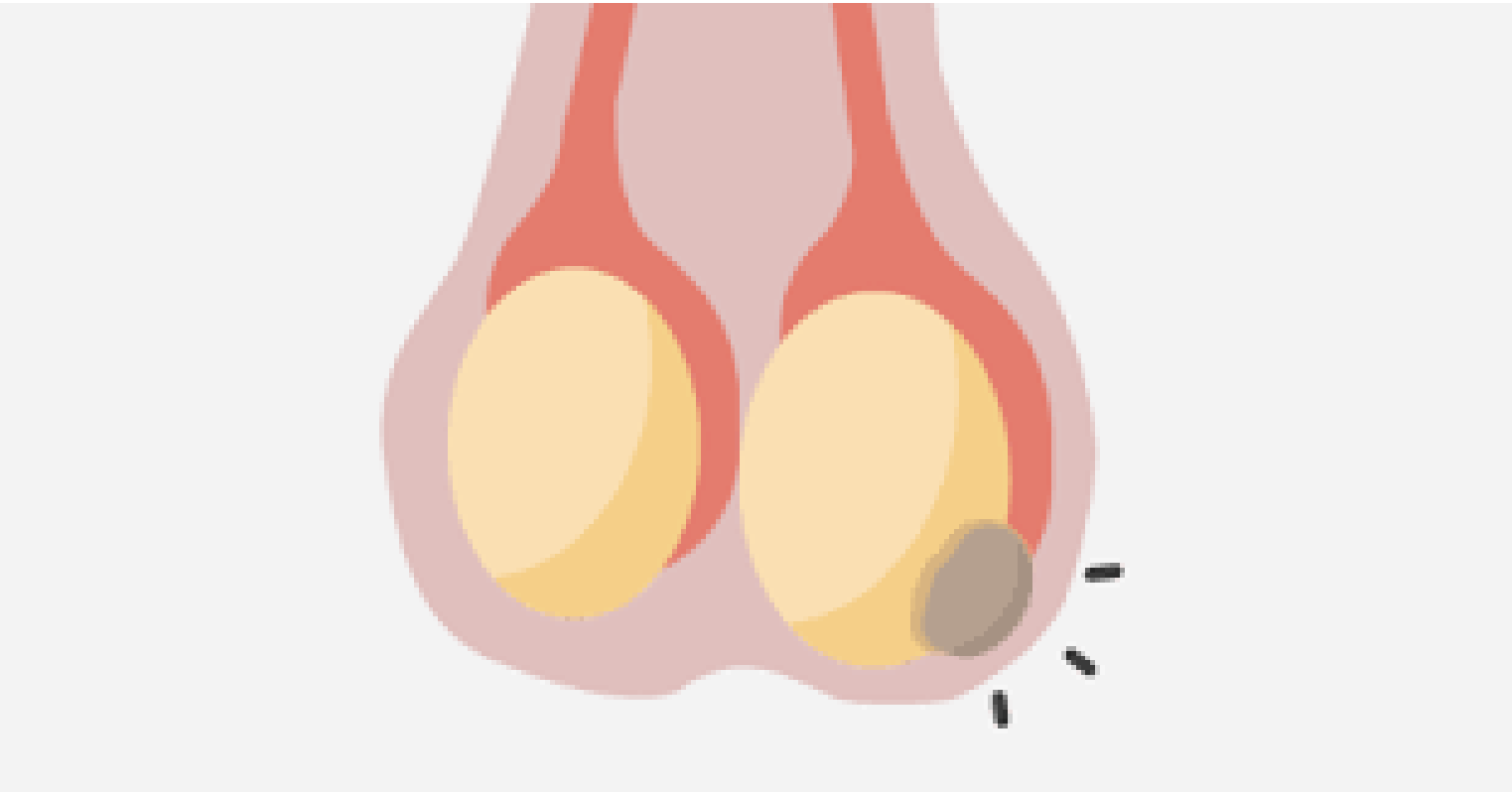
Management of stage I non-seminoma testicular cancer



- Radical inguinal orchiectomy is the first step for diagnosis and initial treatment (except for men who present with widely disseminated disease requiring emergent treatment).

- If there is no evidence of regional or distant metastases and serum tumor markers are normal after orchiectomy, patients are defined as having clinical stage I nonseminomatous germ cell tumor (NSGCT)

- The majority (75%) of clinical stage I NSGCTs are cured with orchiectomy alone and do not require further treatment.

- However, it is difficult to identify which patients with stage I NSGCT are at highest risk for recurrence and thus have the most to gain from adjuvant treatment.

- Adjuvant treatment might be unnecessary (over treatment).
- Although the risk of recurrence is approximately 25% for men undergoing surveillance, treatment at the time of recurrence is almost always curative.

- Long-term disease-specific survival exceeds 99 percent regardless of whether patients undergo surveillance, chemotherapy, or retroperitoneal lymph node dissection.

- Men with persistently elevated postorchiectomy serum tumor markers and normal imaging studies are defined as having clinical stage IS disease.
- Persistently elevated markers generally indicate the presence of metastatic disease.

RISK STRATIFICATION

- The most widely used risk factors for recurrence in men undergoing surveillance following orchiectomy for clinical stage I disease include the following:

- Lymphovascular invasion (LVI).
- Predominance of an embryonal carcinoma (EC) component in the primary tumor.
- Pathologic tumor stage T3 or T4

These risk factors can stratify men with testicular NSGCT by risk of relapse:

- Low risk: Tumors with **none** of these risk factors (relapse rates 10 to 14%).
- High risk: Tumors with **one or more** of these risk factors.

Recurrence rate:

- Predominance of EC alone (no LVI): 20-40%.
- LVI alone (no EC): 40-55%
- Both a predominance of EC and LVI: >50%

There are limited data for relapse rates in patients with T3 or T4 disease due to the rarity of these tumors and their exclusion from most surveillance series.

Interpreting studies of the prognostic significance of EC is complicated by the fact that different studies have used different measures to pathologically characterize EC:

- whether EC is present or absent
- whether it is predominant (>40%, >50% percent, or representing a greater proportion of the tumor than any other individual germ cell tumor type)
- whether it is pure.

- Mere presence of EC is a significant risk factor for relapse
- Both the presence and predominance of EC are significant prognostic risk factors.
- Regardless, EC is a weaker predictor of relapse than LVI

TREATMENT APPROACHES

- Surveillance
- Adjuvant chemotherapy
- Retroperitoneal lymph node dissection (RPLND)

Each approach is associated with a 99% rate of long-term disease-specific survival.

Active surveillance

- **British Columbia Cancer Agency**
- included 209 men with high-risk clinical stage I NSGCT (60 with LVI, 109 EC-predominant tumors, and 40 with both).
- Median follow-up of over four years:
- Disease-specific survival was 100 percent

- The relapse rate was 50 percent among men with LVI (30 of 60 relapsed) and 55 percent for men with LVI and EC-predominant tumors.
- In contrast, it was <20 percent for men with EC-predominant tumors but no evidence of LVI.

- Despite the high rate of relapse, all but one patient had good-risk disease at relapse, and only 17 (8 percent) required postchemotherapy resection of residual masses.
- No patients required second-line chemotherapy.

Adjuvant chemotherapy

- The data that adjuvant chemotherapy may be preferable to active surveillance come from the SWENOTECA Management Program.
- Men with LVI present (n = 227) were recommended to proceed with one cycle of BEP (although they could choose active surveillance or two cycles of BEP)

- The relapse rate was higher among men managed with surveillance compared with one or two cycles of BEP adjuvant chemotherapy (42 vs 3 and 0%, respectively).
- There were no relapses among the 70 patients who chose to receive two cycles of BEP.
- Still, the mortality rate in the entire cohort was 1 percent

One versus two cycles of BEP

- Disease-specific survival is over 99% with either approach
- BEP is associated with dose-dependent long-term toxicity.
- Two cycles of therapy in patients with stage IB disease is a reasonable alternative (T3 or T4 tumors)

Retroperitoneal lymph node dissection

- RPLND remains a reasonable alternative to chemotherapy, particularly for men with a teratoma-predominant tumor and for those patients who are not comfortable with active surveillance and decline chemotherapy for whatever reason.

Low-risk disease

- Reasonable options include surveillance or adjuvant chemotherapy.
- Prognosis is excellent
- surveillance avoids the complications and toxicity of chemotherapy.

- Although surveillance is appropriate for most patients with low-risk disease, not all men will be comfortable with surveillance, even if their risk of relapse is "only" 10-15%.

- For men who express a preference for treatment at the time of initial diagnosis, adjuvant chemotherapy is also reasonable.
- Men whose disease is comprised predominantly of teratoma are ideal candidates for RPLND.

SWENOTECA trial

Swedish and Norwegian Testicular Cancer Project

- 1998-2005
- 745 men in Sweden and Norway
- Treated prospectively for clinical stage I NSGCTs.
- Active surveillance for men without LVI (n = 491)
- Median follow-up of 4.7 years:

- The relapse rate was higher among men who underwent surveillance rather than BEP chemotherapy (12 vs 1.3% with one cycle of BEP or 0% with two cycles of BEP).
- The overall mortality rate was only 1 percent, and none of these deaths was due to progressive testicular cancer.

High-risk disease

- Adjuvant chemotherapy, active surveillance, and RPLND (if an appropriately experienced urological surgeon is available).
- All 3 options are associated with a >99 disease-specific survival
- There is no single best option for all patients.

- For those rare men with teratoma with somatic malignant transformation, RPLND is the preferred treatment option.
- Surveillance or primary chemotherapy are not recommended.

- Psychological stress must be taken into account

if placing high-risk patients on surveillance.

- Worrying about relapse
- Psychological trauma if relapse occurs and patient's life must be put on hold on short notice and at an unpredictable time.

- One appeal of adjuvant chemotherapy after orchiectomy is the near certainty it provides that the disease has been cured, particularly in this high-risk group.

- Decision of which modality to use should be based on patient preference:
- In high-risk NSGCTs, active surveillance is a highly effective strategy with regard to long-term survival, although it leaves the patient with a substantial risk of recurrence (which would require treatment) at some point in the subsequent two to three years.

- Roughly half of men with high-risk disease will relapse, and approximately one-fourth of those (ie, one-eighth of high-risk men undergoing surveillance) will require additional treatment (eg, RPLND in addition to three or four cycles of chemotherapy).

- In light of these statistics, some men may reasonably choose to proceed with chemotherapy after orchiectomy in order to nearly eliminate the risk of needing such aggressive treatment in the future.