Delayed Return of Ejaculatory Function in Adolescent Males Treated With Retroperitoneal Lymph Node Dissection and Adjuvant Therapy for Paratesticular Rhabdomyosarcoma

James T. Rague, Briony K. Varda, Andrew A. Wagner, and Richard S. Lee

Due to the rarity of the disease, adverse events related to ejaculatory function following the management of paratesticular rhabdomyosarcoma with multimodal therapy in adolescents are rarely discussed. Two patients, age 14 and 15 at time of diagnosis were treated with multimodal therapy with nerve-sparing retroperitoneal lymph node dissection, chemotherapy, and radiotherapy. Each developed ejaculatory dysfunction during the treatment period, which resolved 1 year after completion of all therapies. We sought to assess the role of each component of multimodal therapy on the observed side effect and the potential for delayed recovery of function after cessation of all therapies. UROLOGY 124: 254 -256, 2019. © 2018 Elsevier Inc.

Paratesticular rhabdomyosarcoma (ptRMS) accounts for 12% of all pediatric scrotal tumors.1 With primary tumor resection and multimodal therapy, 5-year survival reaches >80%. Treatment with retroperitoneal lymph node dissection (RPLND), chemotherapy, and radiation are not without risk.2 Retroperitoneal (RP) therapy may have adverse effects on ejaculatory function (EF), which is important as patients approach reproductive years.

The Children’s Oncology Group recommends staging RPLND in all males >10 years of age.3 While traditional RPLND has an associated risk of long-term ejaculatory dysfunction, nerve sparing techniques have greatly improved outcomes.4-7 There are limited data on delayed return of EF after RPLND. Moreover, little is known about the cumulative effect of adjuvant chemotherapy and radiation therapy on ejaculatory dysfunction in males with ptRMS.

CASE REPORT

Two patients, ages 14 (Patient 1) and 15 (Patient 2) presented with scrotal swelling (Table 1). Each patient underwent scrotal ultrasound revealing a para-testicular mass. Tumor markers were normal in both patients (human chorionic gonadotropin (hHCG), lactate dehydrogenase (LDH), and alph-fetoprotein (AFP)). Patient 1 had negative imaging for metastatic disease and patient 2 was found to have a 1.1 cm lymph node in the interaortocaval region.

Each patient underwent radical inguinal orchiectomy identifying embryonal para-testicular rhabdomyosarcoma (pathologic features listed in Table 1). Chest computed tomography, positron emission tomography scan, bone scan, and bone marrow aspirate and biopsy were negative for metastatic disease in both.

Patient 1 underwent open bilateral NS-RPLND (nerve-sparing retroperitoneal lymph node dissection), demonstrating 0 of 32 total positive nodes. Patient 2 underwent robot-assisted laparoscopic NS-RPLND identifying 2 of 43 total positive nodes. Ten days postoperatively, each patient started adjuvant chemotherapy with vincristine, actinomycin, and cyclophosphamide. Patient 1 underwent 8 cycles while patient 2 underwent 4 cycles of vincristine, actinomycin, and cyclophosphamide followed by 4 cycles of vincristine and actinomycin. The chemotherapy course was complicated by lower extremity neuropathy which resolved after chemotherapy completion in both patients. Patient 2 received additional adjuvant radiotherapy to the periaortic and ipsilateral pelvic nodes given nodal disease on RPLND.

Postoperatively after RPLND and during chemotherapy treatment course, each was asked to classify degree of sexual desire, erectile function, EF, and ability to orgasm as compared to preoperative baseline. At all postop visits (3, 9, and 12 months), each patient endorsed normal
sexual function except loss of normal antegrade ejaculation since the time of surgery.

One year after completion of all therapies, each reported return of normal preoperative EF. Chemotherapy related neuropathy had also resolved by that time. They are now 4 years and 18 months, respectively from their last cycle of chemotherapy with no imaging evidence of disease recurrence and with continued normal EF.

COMMENTS
We describe 2 adolescent males treated with multimodal therapy for ptRMS who developed transient ejaculatory dysfunction after NS-RPLND that resolved 1 year after completion of adjuvant therapy. Ejaculatory dysfunction is typically a result of injury to RP nerves; however, the multimodal adjuvant therapy likely played a role in transient dysfunction. There is no literature reporting delayed return of EF in this patient population and we discuss the possible contribution of each treatment modality to the described side effect.

Retroperitoneal Lymph Node Dissection
Approximately 25% of patients with ptRMS present with RP disease with adolescent males more likely to have RP disease compared to younger infants. As in adult males with nonseminomatous germ cell tumor (NSGCT), staging NS-RPLND is the preferred operative technique in ptRMS, however there are no existing data regarding disease recurrence and with continued normal EF.

Spontaneous return of EF after iatrogenic injury is not well described in the literature. While neuropraxia and neuro-regeneration of peripheral nerves is well understood, similar processes for autonomic nerve fibers are limited to proposed mechanisms in animal models. In our patients, nerves were preserved bilaterally, but both patients started chemotherapy within 10 days of NS-RPLND. Assessment of EF immediately after surgery was not able to be ascertained. It is difficult to determine if nerve preservation was inadequate, particularly given the eventual return of function after completion of therapy.

Chemotherapy
The use of chemotherapy for all patients with ptRMS has led to a dramatic increase in overall survival compared to those patients who received surgical resection alone.

Although the acute and long-term side effects associated with chemotherapy are well reported, ejaculatory dysfunction has not been examined.

One proposed mechanism for delayed return of EF in our patients is the addition of vincristine; generally described as leading to mixed sensory-motor peripheral neuropathy. Autonomic nerve dysfunction with bowel and bladder dysfunction, constipation and impotence has been reported as well, and we propose this drug could also affect post-RPLND EF. Interestingly, both of our patients suffered from peripheral neuropathy and ejaculatory dysfunction, both of which resolved after completion of chemotherapy.

Radiotherapy
Given high rates of localized disease at time of diagnosis, the role of radiotherapy is often limited and recommended in those with locally advanced disease or nodal involvement discovered during RPLND. There are limited data on the side effects of radiation in this population, with

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (Years)</td>
<td>14</td>
</tr>
<tr>
<td>Primary tumor Pathology</td>
<td>7 cm, Right-sided Embryonal ptRMS</td>
</tr>
<tr>
<td>Pathologic features</td>
<td>Epididymal involvement, no LVI</td>
</tr>
<tr>
<td>Metastatic disease on imaging</td>
<td>No evidence</td>
</tr>
<tr>
<td>RPLND technique</td>
<td>Open, bilateral nerve-sparing, modified template</td>
</tr>
<tr>
<td>Nodal disease</td>
<td>0 of 32 total nodes positive</td>
</tr>
<tr>
<td>COG stage and group</td>
<td>Stage 1, Group 1</td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td>8 cycles VAC</td>
</tr>
<tr>
<td>Oncologic outcome</td>
<td>No evidence of disease recurrence at 4yrs</td>
</tr>
<tr>
<td>Treatment related Side effects</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Time to return of ejaculatory function (from completion of all therapies)</td>
<td>Retrograde ejaculation</td>
</tr>
</tbody>
</table>

COG, Children’s Oncology Group; ptRMS, paratesticular rhabdomyosarcoma; RPLND, retroperitoneal lymph node dissection; VAC, vincristine, actinomycin, cyclophosphamide; VA, vincristine, actinomycin.
reports of small bowel obstruction and bile duct stricture, however no reports of ejaculatory dysfunction.

Radiation therapy causes microvascular injury with fibrosis, axonal injury, and demyelination in peripheral nerves in a stepwise and progression fashion after therapy. Conversely, in our cases there was recovery as opposed to loss of function over time.

Loss of normal antegrade ejaculation has been described after radiation in adults with prostate cancer with worsening function with time from therapy. Unlike our patients, spontaneous recovery to pretreatment function has not been reported. Although, data from patients age 55-78 with associated comorbidities and a diagnosis of prostate cancer may not be comparable to adolescent males with pRMS, these studies do suggest that radiation therapy to the pelvis may alter the microvascular environment with potential for detrimental effects on EF.

**Cancer Experience**

Cancer diagnosis and treatment in the adolescent population have been linked to mood and psychosexual development with decreased sexual satisfaction, interest, and orgasmic difficulty reported in up to 10% childhood cancer survivors. In our patients, EF did not return until the treatment course was complete and patients were known to be in remission based on follow-up imaging. We therefore propose that a psychological component affected EF in these patients. We based our finding of delayed return of function on direct questioning alone, and with a validated questionnaire, we may have found different results and determined different time frames of recovery. Such questionnaires are rarely used in the pediatric population to assess sexual function and greater utilization would be helpful in the future.

**CONCLUSION**

Multimodal therapy with surgery, chemotherapy, and radiation is important for maximal survival benefit in patients with pRMS. Retrograde ejaculation is a known side effect of RPLND and may be exacerbated by chemotherapy and radiation. Urologists managing patients with pRMS should remain hopeful that delayed return of EF is possible in the adolescent population. Validated questionnaires, which are rarely used in this population, would be valuable to assess and track sexual dysfunction pre-operatively and during follow-up.

**References**


