



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 (bHCG), lactate dehydrogenase (LDH), and alpha-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

Funding: Harvard-wide Pediatric Health Service Fellowship. BV is supported by NICHD grant number T32HD075727. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Approval: Approval for this project was waived by Boston Children's Hospital Institutional Review Board.

From the Department of Urology, Boston Medical Center, Boston, MA; the Department of Urology, Boston Children's Hospital, Boston, MA; the Division of Urology, Beth Israel Deaconess Medical Center, Boston, MA; and the Department of Surgery, Harvard Medical School, Boston, MA

Address correspondence to: Richard S. Lee, M.D., Department of Urology, Boston Children's Hospital, 300 Longwood Avenue, Hunnewell 390, Boston, MA 02115. E-mail: richard.lee@childrens.harvard.edu

Submitted: July 16, 2018, accepted (with revisions): October 15, 2018

Table 1. Summary data on 2 patients treated with multimodal therapy for paratesticular rhabdomyosarcoma

	Patient 1	Patient 2
Age at diagnosis (Years)	14	15
Primary tumor Pathology	7 cm, Right-sided Embryonal ptRMS	9.5 cm, Left-sided Embryonal ptRMS
Pathologic features	Epididymal involvement, no LVI	Epididymal, spermatic cord, testicular invasion with extensive LVI
Metastatic disease on imaging	No evidence	1.1 cm interaortocaval node on CT
RPLND technique	Open, bilateral nerve-sparing, modified template	Robot-assisted laparoscopic, bilateral nerve-sparing, modified template
Nodal disease	0 of 32 total nodes positive	2 of 43 total nodes positive
COG stage and group	Stage 1, Group 1	Stage 1, Group 2
Adjuvant treatment	8 cycles VAC	4 cycles VAC 4 cycles VA Retroperitoneal XRT (41.4 Gy)
Oncologic outcome	No evidence of disease recurrence at 4yrs	No evidence of disease recurrence at 18 months
Treatment related Side effects	Peripheral neuropathy Retrograde ejaculation	Peripheral neuropathy Retrograde ejaculation
Time to return of ejaculatory function (from completion of all therapies)	1 year	1 year

COG, Children's Oncology Group; ptRMS, paratesticular rhabdomyosarcoma; RPLND, retroperitoneal lymph node dissection; VAC, vincristine, actinomycin, cyclophosphamide; VA, vincristine, actinomycin.

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.³ 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 EF in these patients.

EF preservation rates after traditional nonnerve sparing RPLND for NSGCT have been reported at 25%, with improvement to 95%-100% with nerve sparing for low stage NSGCT.^{7,8} The vast majority of outcome data in this population however were not collected using validated questionnaires and typically did not describe the time to recovery of 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.⁹ 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.^{10,11}

Although the acute and long-term side effects associated with chemotherapy are well reported, ejaculatory dysfunction has not been examined.¹⁰

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.¹²⁻¹⁴ 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.¹⁵ There are limited data on the side effects of radiation in this population, with

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.¹⁶ 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.¹⁷⁻¹⁹ Unlike our patients, spontaneous recovery to pretreatment function has not been reported.²⁰ Although, data from patients age 55-78 with associated comorbidities and a diagnosis of prostate cancer may not be comparable to adolescent males with ptRMS, 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.^{21,22} 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 ptRMS. Retrograde ejaculation is a known side effect of RPLND and may be exacerbated by chemotherapy and radiation. Urologists managing patients with ptRMS 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

1. Ahmed H, Arya M, Muneer A, Mustaq I, Sebire N. Testicular and paratesticular tumors in the prepubertal population. *Lancet Oncol*. 2010;11:476-483.

2. Heyn R, Raney RB, Hays DM, et al. Late effects of therapy in patients with paratesticular rhabdomyosarcoma. Intergroup Rhabdomyosarcoma Study Committee. *J Clin Oncol*. 1992;614-623.
3. Wiener ES, Anderson JR, Ojimba JI, et al. Controversies in the management of paratesticular rhabdomyosarcoma: is staging retroperitoneal lymph node dissection necessary for adolescents with resected paratesticular rhabdomyosarcoma. *Semin Pediatr Surg*. 2001;10:146-152.
4. Baniel J, Foster RS, Rowland RG, Bihle R, Donohue JP. Complications of primary retroperitoneal lymph node dissection. *J Urol*. 1994;152:424-427.
5. Nonomura N, Nishimura K, Takaha N, et al. Nerve-sparing retroperitoneal lymph node dissection for advanced cancer after chemotherapy. *Int J of Urol*. 2002;9:539-544.
6. Donohue JP, Foster RS, Rowland RG, Bihle R, Jones D, Geier G. Nerve-sparing retroperitoneal lymphadenectomy with preservation of ejaculation. *J Urol*. 1990;144:287-292.
7. Pettus J, Carver B, Masterson T, Stasi J, Sheinfeld J. Preservation of ejaculation in patients undergoing nerve-sparing post-chemotherapy retroperitoneal lymph node dissection for metastatic testicular cancer. *Urology*. 2009;73:328-332.
8. Narayan P, Lange PH, Fraley EE. Ejaculation and fertility after extended retroperitoneal lymph node dissection for testicular cancer. *J Urol*. 1982;127L:685-688.
9. Kihara K. Nerve-sparing retroperitoneal lymph node dissection: control mechanism, technique for nerve sparing and reconstruction. *Int J Urol*. 2000;52-55.
10. Maurer HM, Gehan EA, Beltangady M, et al. The intergroup rhabdomyosarcoma study-II. *Cancer*. 1993;71:1904-1922.
11. Crist W, Gahan EA, Ragab AH. The third intergroup rhabdomyosarcoma study. *J Clin Oncol*. 1995;610-630.
12. van den Berg MH. Vincristine-induced peripheral neuropathy in children with cancer: a systematic review. *Crit Rev Oncol Hematol*. 2017;114:114-130.
13. Gidding CE, Kellie SJ, Kamps WA, de Graaf SS. Vincristine revisited. *Crit Rev Onc/Heme*. 1999;29:267-287.
14. Gomber S, Dewan P, Chhonker D. Vincristine induced neurotoxicity in cancer patients. *Indian J Pediatr*. 2010;77:97-100.
15. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study IV: results for patients with nonmetastatic disease. *J Clin Oncol*. 2001;19:3091-3102.
16. Delanian S, Lefaix JL, Pradat PF. Radiation-induced neuropathy in cancer survivors. *Radiotherapy Onc*. 2012;105:273-282.
17. Sullivan J, Sember D, Deveci S, Akin-Olugbade Y, Mulhall JP. Ejaculation profiles of men following radiation therapy for prostate cancer. *J Sex Med*. 2013;10:1410-1416.
18. Choo R, Long J, Morton G, Gardner S, Danjoux C. Prospective survey of sexual function among patient with clinically localized prostate cancer referred for definitive radiotherapy and the impact of radiotherapy on sexual function. *Support Care Cancer*. 2010;18:715-722.
19. Siglin J, Kubicek GJ, Leiby B, Valicenti RK. Time of decline in sexual function after external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2010;76:31-35.
20. Hughes LL, Baruzzi MJ, Ribeiro RC, et al. Paratesticular rhabdomyosarcoma: delayed effects of multimodality therapy and implications for current management. *Cancer*. 1994;73:472-482.
21. Syndberg KK, Lampic C, Arvidson J, Helström L, Wettergren L. Sexual function an experience among long-term survivors of childhood cancer. *Eur J Cancer*. 2011;47:397-403.
22. Zebrack BJ, Foley S, Wittmann D, Leonard M. Sexual functioning in young adult survivors of childhood cancer. *Psychooncology*. 2010;19:814-822.