Management of Pelvic Metastases in Patients With Testicular Cancer

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OBJECTIVE To evaluate the clinicopathologic features and predictors of pelvic metastasis in patients with germ cell tumors.

METHODS Between 1990 and 2009, 2722 patients undergoing retroperitoneal lymph node dissection (RPLND) were prospectively included in our institution's testis cancer database. Patients with pelvic disease were identified and clinicopathologic features were analyzed.

RESULTS Of the 134 patients, 14.5% had a history of prior groin surgery. At the time of referral, 98% had received prior chemotherapy, 19.4% had undergone prior RPLND, and 24% presented as late relapse. Surgery consisted of pelvic excision alone in 37 (27.6%) and pelvic excision with primary RPLND in 2 (1.5%) or with postchemotherapy RPLND in 95 (70.9%). Median pelvic mass size was 6.5 cm. Pathology of pelvic disease revealed teratoma in 74 (55%), nonseminomatous germ cell tumor in 28 (21%), sarcoma in 8 (6%), and necrosis in 22 (16.5%). Patients with pelvic metastases had a statistically higher initial stage of presentation (P <.001) and had a higher incidence of prior groin surgeries (P <.001).

CONCLUSION Pelvic metastasis in testicular cancer is uncommon and can be a site of late relapse. These patients tend to present with high-volume retroperitoneal disease or a history of prior groin surgeries. Surgery is curative in most patients, and pelvic pathology was teratoma in more than half. UROLOGY ■■: ■■–■■, 2016. © 2016 Elsevier Inc.

Germ cell tumors (GCT) follow a predictable pattern of metastases along the lymphatic system from the testicle to the retroperitoneal lymph nodes. As identified in early mapping studies, the first level of lymph nodes draining the right testis is located in the interaortocaval area, followed by the precaval and preaortic nodes. The primary landing zone for left-sided tumors includes the periaortic and preaortic lymph nodes.[1] Various surgical templates have been developed accordingly and have excluded the pelvic lymph nodes.[2,3]

Although pelvic disease is less common than retroperitoneal disease, a small number of centers have reported its incidence in GCT. Ray et al reported the rate of external iliac nodal metastases to be less than 5%.[4] Donohue et al later confirmed a similar incidence of 5%.[1] Despite these early reports, pelvic disease and management strategies are poorly understood.

We seek to better characterize the incidence, risk factors, and management of pelvic disease as well as determine the clinical and pathologic features of pelvic metastases in patients with GCT.

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METHODS

From 1990 to 2009, 2722 patients undergoing retroperitoneal lymph node dissection (RPLND) were prospectively included in our institution's testis cancer database. Of these, 134 (5.0%) had pelvic metastases. After obtaining institutional review board approval, a retrospective review of these patients was performed. Recorded information included patient's background information, previous treatment, serum tumor markers, preoperative imaging, details of surgery, pathology reports, surgical complications, relapse history, and current status.

Prior groin surgery was defined as previous inguinal hernia repair or orchiopexy. Scrotal contamination was defined as a scrotal incision at time of orchiectomy with or without tumor spillage. Late relapse was defined as disease recurrence 2 years after complete remission.

Clinical features at initial presentation were compared between those with and those without eventual pelvic metastasis using Pearson chi-square tests. A P value ≤.05 was considered significant. Statistical analysis was performed with IBM SPSS Statistics 19.

RESULTS

Among the 134 patients with pelvic metastases, 88 (65.7%) patients initially presented with clinical stage IIC or III

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Table 1. Demographics at presentation

Characteristic	No. (%)
Initial clinical stage	N = 134
I	14 (10.5)
IS	3 (2.2)
IIA, IIB	29 (21.6)
IIC, III	88 (65.7)
Prior groin surgery	18 of 124 (14.5)
History of undescended testes	7 of 127 (5.5)
Scrotal contamination	2 of 115 (1.7)
Histology of primary tumor	N = 134
Seminoma	28 (21)
Nonseminoma	106 (79)
Size of testicular mass	N = 134
Unknown	62 (46.3)
<5 cm	47 (35)
≥5 cm	25 (18.7)
Site of primary tumor	N = 134
Right testicle	63 (47)
Left testicle	63 (47)
Bilateral	1 (0.7)
Extragonadal	7 (5.3)

Table 2. Characteristics at time of referral

	N = 134
Late relapse	32 (24)
Prior chemotherapy	131 (98)
Prior RPLND	26 (19.4)
Marker status at time of surgery	
Elevated AFP (>20 ng/mL)	20 of 125 (16)
Elevated BHCG (>5 mU/mL)	17 of 125 (13.6)
Location of pelvic disease	
Right-sided	53 (40)
Left-sided	70 (52)
Bilateral	11 (8)
Size of pelvic disease	
<5 cm	34 (25)
≥5 cm	100 (75)
Size of associated RP disease	
N/A	3 (2)
Negative	32 (24)
<5 cm	15 (11)
≥5 cm	84 (63)
Pelvic pathology	
Teratoma	74 (55)
NSGCT	28 (21)
Seminoma	2 (1.5)
Necrosis	22 (16.5)
Sarcoma	8 (6)

AFP, alpha-fetoprotein; BHCG, beta-human chorionic gonadotropin; N/A, not applicable; NSGCT, nonseminomatous germ cell tumor; RPLND, retroperitoneal lymph node dissection.

disease. Prior groin surgery, a history of undescended testes, and documented scrotal contamination were noted in 14.5%, 5.5%, and 1.7% of cases, respectively. Histology of the primary tumor was seminoma in 21% of pelvic masses, whereas 79% were nonseminomatous GCT. The site of the primary tumor was evenly distributed between right- and left-sided testicular tumors, with the remaining 5.3% originating from extra gonadal sites (Table 1). Four patients presented with a retroperitoneal primary tumor, 1 strangely presented with a thigh mass and bilateral normal testes, 1 presented with pelvic disease only, and 1 presented with a pineal gland GCT.

One hundred thirty-one (98%) of the patients with pelvic disease had prior chemotherapy. Sixty-eight percent presented with synchronous retroperitoneal and pelvic disease at time of referral. Thirty-two (24%) pelvic recurrences presented as late relapse. Twenty-six patients had undergone prior RPLND. Sixteen percent had an elevated alpha-fetoprotein, and 13.6% had an elevated human chorionic gonadotropin at the time of pelvic dissection. Sixteen (11.7%) had pelvic disease with a contralateral primary tumor. Retroperitoneal mass size was ≥5 cm in 63% of patients.

Surgical management of pelvic disease consisted of pelvic excision alone in 37 (27.6%), pelvic excision with primary RPLND in 2 (1.5%), and pelvic excision with postchemotherapy (PC)-RPLND in 95 (70.9%). Additional surgical procedures required at time of pelvic mass excision included iliac vascular patch or graft in 5 (3.7%), ureteral excision in 4 (3%), and bowel resection in 2 (1.5%). Complications included 1 ureteral stricture, 1 small bowel obstruction requiring adhesiolysis, 1 ileus managed conservatively, 1 partial femoral nerve injury, 1 deep venous thrombosis, and 1 chylous ascites.

Pathology of pelvic disease revealed teratoma in 74 (55%), nonseminomatous GCT in 28 (21%), sarcoma in 8 (6%), and necrosis in 22 (16.5%). Median pelvic mass size was 6.5 cm. Most patients had received chemotherapy before pelvic dissection. Seventy-five percent of patients had bulky pelvic disease, and 63% of patients had bulky retroperitoneal disease (Table 2).

The 2-year overall survival based on pathology for teratoma was 90.2%, nonseminoma GCT was 59%, seminoma was 50%, necrosis or fibrosis was 100%, and sarcoma was 43% (Table 3). Only 2 patients had seminoma on final pathology after pelvic dissections. Therefore, concluding that seminoma on final pathology precludes worse outcomes is inappropriate.

Compared with the 2722 without pelvic metastasis, the group of 134 patients had a statistically higher initial stage of presentation (P <.001), had a higher incidence of prior groin surgeries (P <.001), and had a higher incidence of undescended testes (P .0327). Furthermore, a comparison of groups did not show a statistical difference in history

Table 3. Survival based on pelvic pathology from available data

	Overall Survival (2 y)
Teratoma	90.2%
Active cancer	
NSGCT	59%
Seminoma	50%
Sarcoma	43%
Necrosis or fibrosis	100%

Table 4. Comparison of groups from available data

	Pelvic Mets No. (%)	No Pelvic Mets No. (%)	*P* Value
Initial clinical stage			<.001
IA, IB	14 (10.2)	1132 of 2570 (44.0)	
IS	3 (2.2)		
IIA, IIB	29 (21.9)	564 of 2570 (22)	
IIC, III	91 (66.4)	874 of 2570 (34.0)	
Prior groin surgery*	18 of 124 (14.5)	15 of 2498 (0.6)	<.001
History of undescended testes	7 of 127 (5.5)	55 of 2535 (2.2)	.0327
Scrotal contamination	2 of 115 (1.7)	47 of 2352 (2.0)	NS
Vascular or lymphatic invasion	34 of 98 (34.7)	820 of 2169 (37.8)	NS
Site of primary tumor			NS
Gonadal	127 of 134 (95)	2468 of 2553 (97)	
Extragonadal	7 of 134 (5)	85 of 2553 (3)	
Size of testicular mass			NS
N/A	62	1543	
<5 cm	47 (35)	698 (27)	
≥5 cm	25 (34.2)	329 (31.6)	

* Includes all patients who had previously undergone an inguinal hernia repair or orchiopexy.

of scrotal contamination, size of testis primary, site of primary tumor, or lymphovascular invasion (Table 4).

DISCUSSION

In this retrospective study, the incidence of pelvic metastasis in patients with testicular cancer is 5%. Patients with pelvic involvement are more likely to present with bulky disease and a history of prior groin procedures. These factors may explain the etiology of lymphatic involvement of the iliac lymph nodes: caudad in bulky retroperitoneal disease or cephalad in cases with prior groin surgery with presumed lymphatic disruption.

To our knowledge, this is the largest series on pelvic metastasis in GCT. The Memorial Sloan Kettering Cancer Center (MSKCC) reported on 44 patients who underwent a pelvic lymph node dissection. In their series presented in abstract form in 2013, 19 (43%) patients had either teratoma or viable cancer in the pelvic specimen. Of the 44 patients, 17 (38.6%) were found to have teratoma and 2 (4.5%) were found to have viable cancer. Interestingly, no patients reported a history of inguinal or scrotal surgery.[5] Similar to the MSKCC experience, we found that a large proportion of pelvic disease was teratoma. On the other hand, we observed a higher percentage of non-teratoma GCT in the pelvis (30%) and only 16.5% with necrosis. Moreover, we found an association between pelvic disease and prior inguinal surgery. This variability is likely owing to selection bias and the difference in size between the 2 series. Aside from our series and the MSKCC series, we are unaware of any other literature specifically focused on pelvic disease in GCT. However, there are select papers that describe the incidence of pelvic disease in various settings. Early mapping studies in the pre-cisplatin era showed up to a 5% incidence of pelvic lymph node involvement.[1,4] In the reoperative RPLND setting, 16.8% of patients were found to have pelvic disease.[6] In late-relapse patients, the pelvis is a site of recurrence 7%-8% of the time.[7,8]

Limitations of this study include its retrospective design and small sample size. However, this is the largest series to date describing pelvic disease in GCT. The testis cancer database is prospectively maintained, which presumably does limit some of the bias associated with retrospective studies. The purpose of this study is mainly to describe a rare clinical occurrence in testicular cancer and to inform practice. Although it is rare, clinicians will encounter patients who have or are at risk of pelvic disease. Because of the small sample size, broad generalizations cannot be made regarding our observations. However, we share our institutional experience to aid clinical decision making especially because there have been no publications directly addressing this issue.

These data currently do inform our practice and care for these patients. For example, surveillance patients only receive an abdominal computed tomography scan because patients with bulky retroperitoneal disease extending to the pelvis will be diagnosed on abdominal imaging. However, if a patient has a known history of prior groin surgery or an undescended testicle, the patient will receive abdominal and pelvic computed tomography scans during surveillance. Although there is a statistically significant association between pelvic disease and groin surgery, at this point we do not subject these patients to a pelvic lymph node dissection unless they have known pelvic disease. Performing pelvic lymph node dissection on patients at risk of lymphatic drainage disruption could be a future area of study. However, this specific patient population is extremely small. Moreover, adding morbidity to this subset of patients is unlikely to improve outcomes especially because a large percentage of patients will have teratoma. However, inquiring about prior groin surgery or an undescended testicle is an important part of the history and physical examination in patients with testicular cancer, which does help guide the clinician's suspicion for pelvic disease. If patients are found to have bulky retroperitoneal disease, we recommend obtaining full pelvic imaging.

CONCLUSION

Pelvic metastasis in testicular cancer is rare but can be a site of primary disease, relapsed disease, or late-relapse disease. These patients tend to present with high-volume retroperitoneal disease and a history of prior groin surgeries or an undescended testicle. Surgery is curative in most patients and pelvic pathology was teratoma in more than half.

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EDITORIAL COMMENT

In this issue of *Urology*, Jacob et al present their experience at Indiana University with pelvic lymph node dissection (PLND) for germ cell tumor (GCT). The authors provide several insights with important clinical implications.

Although a PLND at the time of retroperitoneal lymph node dissection (RPLND) is relatively uncommon in GCT, the data suggest that a subset of patients benefit from the procedure. Of 2722 patients undergoing RPLND at Indiana University, 4.9% underwent a synchronous PLND. This is slightly higher than the 2% rate reported by the Memorial Sloan Kettering Cancer Center.[1] The rate of PLND at these institutions is similar to the 5% positive nodal rate seen in nonseminomatous GCT mapping studies,[2] and to the 4% pelvic recurrence rates seen in clinical stage 1 seminoma treated with only a para-aortic strip radiation portal.[3]

Although pelvic involvement of GCT may occur in up to 5% of patients with GCT, the over-representation of teratoma, redo-RPLNDs, and late relapse seen in Jacob et al's study highlights the importance of identifying patients most likely to benefit from a PLND. Jacob et al confirmed that bulky retroperitoneal disease is also a risk factor that can result in pelvic involvement, usually by retrograde spread. Importantly, the authors also identified prior inguinal surgery as another potential risk factor of pelvic involvement with GCT. Inguinal surgery can disrupt the typical lymphatic drainage patterns, resulting in aberrant metastatic dissemination to the ipsilateral pelvic nodes. Interestingly, scrotal violation was not associated with an increased rate of pelvic involvement. Although the present study noted that a history of undescended testis was associated with pelvic involvement on univariate analysis, it is difficult to distinguish undescended testis from the effect of an orchiopexy as a risk factor impacting lymphatic drainage patterns.

We agree with Jacob et al's suggestion that prophylactic pelvic dissection warrants investigation in the postchemotherapy setting for patients with prior inguinal surgery, even when overt disease is not present. Furthermore, we propose a PLND for patients who had pelvic disease present before chemotherapy, even if they experienced a radiographic complete response. We would also add that wide excision of the spermatic cord is prudent when operating on patients whose lymphatic drainage is potentially altered.[4] Given the potential for aberrant lymphatic drainage, a primary RPLND in patients with prior inguinal surgery should either be avoided in many cases or include an ipsilateral PLND. Although the decision for prophylactic PLND during RPLND should be individualized, the study by Jacob et al provides very useful guidelines in identifying those patients at highest risk of pelvic involvement who would thus benefit from a PLND.

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AUTHOR REPLY

In reply to the submitted commentary, we would like to clarify a few points that we believe are important to the discussion regarding pelvic disease in germ cell tumors.

Firstly, we describe 4.9% of our retroperitoneal lymph node dissection (RPLND) cohort that were found to have synchronous **or** metachronous pelvic disease. It is important to note that only 68% of these patients presented with synchronous pelvic disease. Twenty-four percent of patients presented with pelvic disease in the late-relapse setting. Approximately 19% of patients had previously undergone an RPLND.

Additionally, we do not propose a pelvic dissection in the setting of a complete response to chemotherapy. This is similar to our recommendation against prophylactic postchemotherapy RPLND for patients with complete remission in the retroperitoneum. This is based on 15-year follow-up data in patients with a complete

response to induction chemotherapy who did not get a postchemotherapy RPLND, demonstrating a cancer-specific survival of 97%.[1] If visible disease in the pelvis remains following chemotherapy, a pelvic lymph node dissection should be included during the RPLND. It is important to recall that although prior groin surgery was statistically associated with pelvic disease, only 14.5% of patients with pelvic disease had a history of prior groin surgery.

The goal of our study is to determine which patients are at risk of pelvic disease. Our primary message is to have a higher suspicion for pelvic disease in patients with a history of groin surgery, in patients with bulky retroperitoneal disease, and in patients with late relapse. If pelvic disease is identified on imaging, it can be resected with good long-term outcomes.

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