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Primary Retroperitoneal Lymph Node Dissection for Seminoma Metastatic to the Retroperitoneum

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Study Need and Importance: Primary surgical treatment with retroperitoneal lymph node dissection (RPLND) aims to accurately stage and treat patients with node-positive pure seminoma while avoiding long-term risks of chemotherapy or radiation.

What We Found: We report the outcomes of 45 patients treated with primary RPLND over a 10-year period for clinical stage II or relapsed clinical stage I pure seminoma. Among patients (n=29) managed with post-RPLND surveillance, the 2-year recurrence-free survival was 81% (95% CI 57-93; Figure). These outcomes corroborate recently reported phase II studies and support primary RPLND as a safe, highly effective treatment that may obviate the need for chemotherapy for most patients. In our series, all patients received an open bilateral template operation. There were no retroperitoneal recurrences, suggesting a potential benefit to this approach over modified template operations. We also provide the first report of outcomes among select patients receiving adjuvant chemotherapy (2 cycles of etoposide and cisplatin) following primary RPLND. In these patients, 2-year recurrence-free survival was 92% (95% CI 54-99). All patients are alive and free of disease following treatment regardless of adjuvant management strategy.

Limitations: Adjuvant management following RPLND was not standardized, and roughly one-third of the cohort elected for adjuvant 2 cycles of etoposide and cisplatin. Therefore, selection bias may have influenced our outcomes, as patients at higher risk for relapse may have been selected or self-selected for adjuvant chemotherapy. Additionally, the median follow-up for nonrelapsing patients managed with surveillance was 18.5 months, which is slightly shorter than the completed phase II studies.

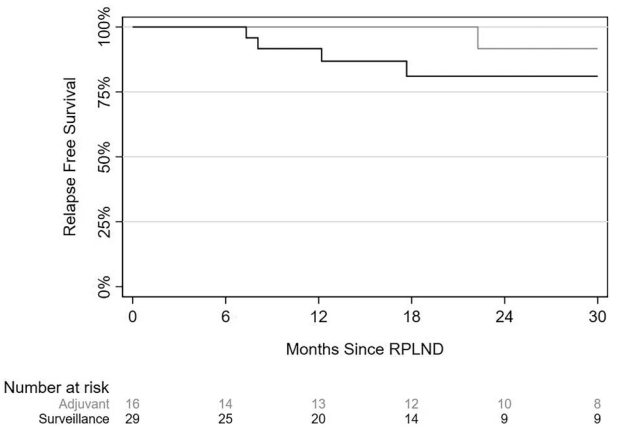

Figure. Relapse-free survival by postretroperitoneal lymph node dissection (RPLND) management strategy. The relapse-free survival estimate in the surveillance group at 24 months was 81% (95% CI, 57-93) and was 92% (95% CI, 54-99) in the adjuvant group.

Interpretation for Patient Care: Primary surgery is safe and effective for patients with testicular pure seminoma with low-volume metastases in the retroperitoneal lymph nodes. Most men treated with surgery in this series did not experience recurrence and were able to avoid chemotherapy or radiation treatment.

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Primary Retroperitoneal Lymph Node Dissection for Seminoma Metastatic to the Retroperitoneum

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Purpose: Primary surgical treatment with retroperitoneal lymph node dissection aims to accurately stage and treat patients with node-positive pure seminoma while avoiding long-term risks of chemotherapy or radiation, traditional standard-of-care treatments.

Materials and Methods: We reported the pathologic and oncologic outcomes of patients with pure seminoma treated with primary retroperitoneal lymph node dissection in a retrospective, single-institution case series over 10 years. The primary outcome was 2-year recurrence-free survival stratified by adjuvant management strategy (surveillance vs adjuvant chemotherapy).

Results: Forty-five patients treated with primary retroperitoneal lymph node dissection for pure testicular seminoma metastatic to the retroperitoneum were identified. Median size of largest lymph node before surgery was 1.8 cm. Viable germ cell tumor, all of which was pure seminoma, was found in 96% (n=43) of patients. The median number of positive nodes and nodes removed was 2 and 54, respectively. Median positive pathologic node size was 2 cm (IQR 1.4-2.5 cm, range 0.1-5 cm). Four of 29 patients managed with postoperative surveillance experienced relapse; 2-year recurrence-free survival was 81%. Median follow-up for those managed with surveillance who did not relapse was 18.5 months. There were no relapses in the retroperitoneum, visceral recurrences, or deaths. Among the 16 patients who received adjuvant treatment, 1 patient experienced relapse in the pelvis at 19 months.

Conclusions: Primary retroperitoneal lymph node dissection for pure seminoma with low-volume metastases to the retroperitoneum is safe and effective, allowing most patients to avoid long-term toxicities from chemotherapy or radiation.

Key Words: neoplasms, germ cell and embryonal; lymph node excision; testicular neoplasms

Patients with clinical stage II (CSII) and relapsed clinical stage I (CSI) pure seminoma have traditionally been managed with radiation to the retroperitoneum (RP) or first-line chemotherapy.[1] These well-established treatment modalities provide excellent recurrence-free and overall survival[2-5] but are associated with significant risk of short-term toxicities and long-term adverse effects. Survivors exposed to radiation, chemotherapy, or both have higher rates of cardiovascular disease, metabolic syndrome, secondary cancers, and worse overall survival compared to age-matched

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Data Availability: The data sets generated during and/or analyzed during the current study are not publicly available due to being drawn from our institutional database of routinely collected patient data but are available from the corresponding author on reasonable request.

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controls.[6-11] Since long-term cure is an expectation among these patients, focus has shifted toward strategies that can limit these risks while maintaining excellent cancer control outcomes.

The predictable patterns of metastatic spread seen in patients with testicular seminoma make primary retroperitoneal lymph node dissection (RPLND) an attractive alternative to chemotherapy or radiation for disease isolated to the RP. When performed at high-volume centers by experienced surgeons, primary RPLND has the benefit of definitively staging the patient and potentially curing them with reduced long-term side effects.[12] Although primary RPLND has been a standard postorchiectomy treatment option in patients with CSII nonseminomatous germ cell tumor (GCT) and those with CSI at high risk of relapse,[13,14] primary surgery for patients with suspected metastatic seminoma isolated to the RP has not traditionally been used. There are several ongoing and recently completed studies including the multicenter United States SEMS trial,[15] the European PRIMETEST study,[16] and the COTRIMS trial.[17] While there are nuanced differences in these studies' approaches, the overall goal of performing primary RPLND in low-volume RP-only metastatic seminoma is to mitigate the long-term risks of chemotherapy or radiation while maintaining a low overall treatment burden and the expectation of cure.

For >10 years, we have used primary RPLND as a treatment option for select patients with low-volume RP-only metastatic pure seminoma. Recently, indications for this approach have expanded, and utilization has increased at Memorial Sloan Kettering Cancer Center (MSK) based on maturing data from clinical trials, our own growing experience, and patient preference. We report our contemporary 10-year series of patients treated with multidisciplinary care as a real-world benchmark of primary RPLND for seminoma.

MATERIALS AND METHODS

Data Source and Patients

All patients undergoing surgery at MSK for testicular GCTs are included in our prospectively collected clinical database. Data include patient demographic details, staging and treatment information, and short- and long-term oncologic and adverse effect outcomes. As a standard for staging, all patients at MSK receive CT of the chest, abdomen, and pelvis with contrast (CT CAP) and standard serum tumor marker (STM) assessment at the time of initial diagnosis. Further surveillance imaging and STM assessments are conducted according to standard protocols.[13,14] Prior to any primary RPLND, patients are restaged with CT CAP and STMs around the time of surgery. All orchiectomy and surgical pathology data were reviewed by an experienced genitourinary pathologist.

Following Institutional Review Board approval (IRB No. 16-554), the database was queried for patients who underwent curative intent primary surgery for initial (incident) CSII or relapsed CSI seminoma isolated to the RP over 10 years (January 1, 2013-March 31, 2023). Patients were excluded if they received any adjuvant postorchiectomy therapy prior to RPLND for their current testicular cancer episode or if they had any α-fetoprotein elevation before or after orchiectomy.

Patient Selection and Operative Approach

Since 2013, patients at MSK have been offered primary surgical treatment for incident or relapsed pure seminoma metastatic only to the RP. Patients with any evidence of disease in the chest or with bulky RP disease (>3 cm largest node) were treated with standard-of-care first-line chemotherapy. All patients underwent bilateral full-template open RPLND. Nerve-sparing was performed when indicated for fertility preservation. Postoperative assessment of antegrade ejaculation was not systematically collected in a standardized fashion throughout the study period so is not included as an outcome. Patients were also treated with pelvic lymph node dissection (LND) for equivocal or clinically enlarged pelvic lymphadenopathy found on preoperative imaging or discovered at the time of surgery. The extent of pelvic LND was at the surgeon discretion. Two surgeons contributed patients to this cohort (J.S. and R.M.).

Decision for Adjuvant Treatment

Before surgery, patients were also seen by a genitourinary medical oncologist with GCT expertise as part of a multidisciplinary consultation. Patients met with the medical oncologists again after primary RPLND to discuss the risks and benefits of adjuvant chemotherapy relative to their final pathology. Decisions for adjuvant treatment were made by individual patients and were influenced by pathologic factors and potential risks of further relapse with and without adjuvant treatment extrapolated from the nonseminomatous GCT literature after shared decision-making.

Patients treated with RPLND underwent CT CAP once 3 to 4 months after RPLND and were followed serially with STM assessments and chest X-rays according to established surveillance protocols.[13,14] Additional cross-sectional imaging was ordered for cause (symptoms, STM elevation, concern for complications) or at the treating physician's discretion based on relapse risk. Patients treated with adjuvant chemotherapy were followed with a single postoperative CT scan and subsequently with STM assessments and chest X-rays, given the low risk of relapse.

Outcomes and Statistical Analysis

Our primary outcome of interest was 2-year recurrence-free survival calculated from the date of RPLND. Recurrence was defined as radiographic or STM evidence of relapse after RPLND that subsequently prompted treatment. Patients who did not experience a relapse were censored at the time of their last follow-up clinic visit that included imaging or STM. Secondary outcomes included RPLND pathology, location of relapse, and perioperative surgical outcomes. Patient characteristics were reported

using descriptive statistics. Frequency of pN stage was compared between adjuvant treatment groups (surveillance vs chemotherapy) using Fisher's exact test. Time-to-event analysis was performed using the Kaplan-Meier method for relapse-free survival (RFS) among all patients and stratified by adjuvant management strategy. All analyses were performed using Stata, version 15.0.

RESULTS

Patient and Disease Characteristics

Forty-five patients treated with primary RPLND for pure testicular seminoma metastatic to the RP were included over the study period. All patients except 2 were treated for their first diagnosis of testicular GCT. One patient had a metachronous testicular cancer (pure seminoma) approximately 7 years prior, received adjuvant radiation to the RP, and was followed without recurrence until their second primary testicular tumor was discovered on routine self-exam. The other had synchronous bilateral testicular cancers (both seminoma).

Median patient age was 36 at the time of RPLND (IQR 32-43), and 60% (n = 27) had left-sided primary testicular tumors. Most patients (73%) had CSI pure seminoma at diagnosis that subsequently relapsed prior to RPLND, and 27% had incident CSII seminoma. Median testicular primary tumor size was 4 cm, 18% had lymphovascular invasion, and 58% had rete testis invasion in the orchiectomy specimen. Prior to RPLND, the median size of the largest measurable retroperitoneal node was 1.8 cm (IQR 1.4-2.2, range 1.1-3.4 cm). Median time from orchiectomy to RPLND was 2.2 months (IQR 1.0-2.7 months) for those with CSII and 13.3 months (IQR 8.6-20.5 months) for those with relapsed CSI seminoma (Table 1). All patients had normal STMs before surgery other than 1 with a lactate dehydrogenase level of 258 U/L (MSK upper limit of normal is 250 U/L) and 1 with a human chorionic gonadotropin (hCG) level of 21.8. This patient had significant fluctuation of hCG in the 12 months preceding surgery.

RPLND and Pathologic Outcomes

All patients underwent bilateral full-template primary RPLND, and 71% of these operations were nerve sparing. Six patients concurrently received a unilateral pelvic LND on the ipsilateral side of the primary tumor. No patients required additional adjunctive procedures. Five patients experienced minor (Clavien-Dindo III or less) complications 30 days following surgery: 2 had chylous ascites requiring bedside paracentesis, 2 had *Clostridium difficile* infections that resolved with oral antibiotics, and 1 experienced a superficial wound breakdown that healed by secondary intention after conservative treatment.

Viable GCT was found in 96% (n = 43) of patients, all of which was pure seminoma. The median number of positive nodes was 2 (IQR 1-3, range 0-15); the median positive node size was 2 cm (IQR 1.4-2.5 cm, range 0.1-5 cm). The median number of nodes removed was 54 (IQR 42-71, range 25-159). Final pathological staging was pN0 for 4%, pN1 for 22%, pN2 for 67%, and pN3 for 4% (Table 2). One patient had cancer in the pelvic lymph nodes and was pM1. Twenty (44%) patients were upstaged

Table 1. *Patient Demographics, Testicular Cancer Details, and Staging Information for Cohort of Patients Undergoing Primary Retroperitoneal Lymph Node Dissection for Pure Seminoma (n = 45)*

Age at RPLND, median (IQR) [range], y	36	(32-43) [22-66]
CS at initial diagnosis, No. (%)		
IA	26	(58)
IB	7	(16)
IIA	11	(24)
IIB	1	(2.2)
Side of orchiectomy, No. (%)		
Bilateral (synchronous)	1	(2.2)
Left	27	(60)
Right	17	(38)
Prior ipsilateral groin surgery, No. (%)	11	(24)
Time from orchiectomy to RPLND, median (IQR), mo	2.2	(1.0-2.7)
Initial CSII	13.3	(8.6-20.5)
Relapsed CSI		
Tumor size on orchiectomy, median (IQR) [range], cm[a]	4.0	(3.0-5.0) [1-8]
LVI, orchiectomy specimen, No. (%)	8	(18)
Rete testis invasion, orchiectomy specimen, No. (%)	26	(58)
Size of largest pre-RPLND lymph node, median (IQR) [range], cm	1.8	(1.4-2.2) [1.1-3.4]
Time from CT scan to RPLND, median (IQR) [range], d	14	(7-21) [2-37]

Abbreviations: CS, clinical stage; CT, computed tomography; IQR, interquartile range; LVI, lymphovascular invasion; RPLND, retroperitoneal lymph node dissection.
[a] n = 44; 1 patient had a "burnt out" tumor, and no size estimate was possible.

Table 2. *Retroperitoneal Lymph Node Dissection Surgical Details and Pathology Outcomes*

RPLND estimated blood loss, median (IQR) [range], mL	200	(100-300) [50-700]
Nerve-sparing RPLND, No. (%)	32	(71)
Pelvic LND performed, No. (%)	6	(13)
Any 30-d complication, No. (%)	5	(11)
Histology at RPLND, No. (%)		
Benign	2	(4)
Seminoma	43	(96)
NM stage at RPLND, No. (%)[a]		
pN0	2	(4.4)
pN1	10	(22)
pN2	30	(67)
pN3	2	(4.4)
pM1a	1	(2.2)
Extranodal extension, No. (%)	25	(58)
Node size at RPLND, median (IQR) [range], cm	2.0	(1.4-2.5) [0.1–5.0]
No. positive nodes at RPLND, median (IQR) [range]	2	(1-3) [0-15]
No. nodes removed at RPLND, median (IQR) [range]	54	(42-71) [25-159]

Abbreviations: IQR, interquartile range; LND, lymph node dissection; NM, node metastasis; RPLND, retroperitoneal lymph node dissection.
[a] One patient was pN0M1a due to seminoma being found in deep pelvic lymph node only.

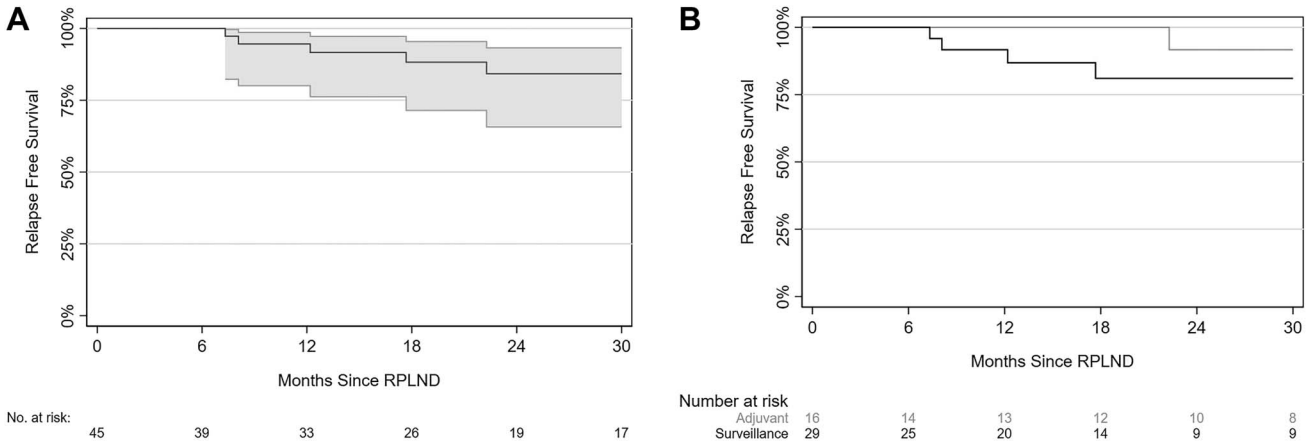

Figure. A, Relapse-free survival for the entire cohort. Relapse-free survival at 12 and 24 months was 95% (95% CI, 80-99) and 84% (95% CI, 66-93), respectively. B, Relapse-free survival by postretroperitoneal lymph node dissection (RPLND) management strategy. The relapse-free survival estimate in the surveillance group at 24 months was 81% (95% CI, 57-93) and was 92% (95% CI, 54-99) in the adjuvant group.

from cN1 to pN2-3, and 3 (6.7%) patients were downstaged from cN2 to pN0-1 (Supplemental Table 1, https://www.jurology.com). Extranodal extension was identified in 58% (n=25) of patients. The 2 patients with benign (pN0) pathology both had initial CSIIA disease at diagnosis (Patient A—2 RP nodes [1.4×1.1 and 1.7×1.0]; patient B—1 RP node 1.1×0.8 cm on preoperative imaging). Time from orchiectomy to RPLND was 26 days for Patient A and 80 for Patient B.

Adjuvant Management and Relapse Outcomes

There were no standard criteria applied to adjuvant treatment decision-making, but after consultation with our medical oncology team, 29 patients elected to pursue surveillance after RPLND, and 16 chose adjuvant chemotherapy. There were no statistically significant differences in the distribution of pN stage between those who did or did not choose adjuvant chemotherapy ($P = .3$; Supplemental Table 2, https://www.jurology.com). Patients who elected for adjuvant chemotherapy received 2 cycles of etoposide and cisplatin (EP×2).

Overall, 5 patients experienced a relapse, and RFS for all patients was 95% (95% CI, 80-99) and 84% (95% CI, 66-93) at 12 and 24 months, respectively (part A of Figure). Four patients whose disease was managed with post-RPLND surveillance relapsed, and the Kaplan-Meier 2-year RFS was 81% (95% CI, 57-93; part B of Figure) for those patients. The 2-year RFS for patients with pN1 and pN2 managed with surveillance was 75% (95% CI, 13-96) and 80% (95% CI, 50-93), respectively. All relapses were detected primarily with cross-sectional imaging; 2 patients had detectable hCG (1.1 and 2.0 mIU/mL), and 1 had an elevated lactate dehydrogenase (524 U/L) concurrently. There were no visceral or retroperitoneal relapses. Patients who relapsed on surveillance are all alive, having completed or currently undergoing treatment with 4 cycles of etoposide and cisplatin (EP×4). Median follow-up for those who did not experience a relapse in the surveillance group was 18.5 months (IQR: 10.4-34.3). Details about relapse location, timing, and detection method can be found in Table 3.

In the adjuvant chemotherapy group, 1 patient experienced relapse in the pelvis 22 months after EP×2. Therefore, the 2-year RFS was 92% (95% CI, 54-99). This patient received salvage chemotherapy (4 cycles of paclitaxel, ifosfamide, and cisplatin) and has no evidence of disease at last follow-up. Median follow-up time for those who did not experience relapse in the adjuvant group was 30.1 months (IQR, 17.1-45.6). There were no deaths during the follow-up period in either cohort.

Table 3. *Relapse Details for All Patients Who Experience Relapse*

Patient	Initial stage	pN status	Adjuvant chemotherapy	Time to relapse (mo)	Location of relapse	STM elevation at relapse
1	CSIA	pN2	No	7	Supraclavicular, retrocrural	LDH 523
2	CSIA	pN2	No	17	Portal LN, pelvis	hCG 2.0
3	CSIA	pN1	No	12	Left suprahilar, SMA	hCG 1.1
4	CSIIA	pN2	No	8	Left inguinal lymph node	None
5	CSIA	pN2	Yes	22	Pelvis	hCG 0.6

Abbreviations: CS, clinical stage; hCG, human chorionic gonadotrophin; LDH, lactate dehydrogenase; LN, lymph node; pN, pathological nodal; SMA, superior mesenteric artery; STM, serum tumor marker.

DISCUSSION

In this single-institution series of patients undergoing primary surgery for pure seminoma metastatic to the RP, we report excellent oncologic outcomes and minimal significant adverse events following surgery. Notable findings include low overall rates of recurrence that corroborate recently reported studies and the absence of any RP recurrences among patients receiving bilateral template RPLND. Our results add to the growing evidence supporting primary RPLND as a safe and highly effective treatment when performed at high-volume centers for patients with pure seminoma.

There are several ongoing or completed trials assessing outcomes of primary surgery for seminoma metastatic to the RP. To contextualize and compare findings from these cohorts with ours, it is important to understand the similarities and differences of patient disease characteristics and the surgical approach used in each study. In our series, the majority (73%) of patients were CSI at diagnosis and experienced relapse only in the RP, with a median node size of 1.8 cm. In the SEMS trial, 65% of patients had relapsed CSI, most of whom had recurrences between 1-2 cm.[15] In PRIMETEST, 58% of patients experienced relapse, but 15% had received adjuvant carboplatin following orchiectomy, which is known to alter the natural history of relapse.[18,19] Although it is not clear if there are biologic or long-term oncologic differences in patients who relapse vs those who present with initial CSII seminoma, data from an Indiana University series showed patients who were initially managed with a 12-month period of surveillance after orchiectomy had better RFS than those with upfront surgery when treated with primary RPLND.[20] Our cohort included 1 patient who had received retroperitoneal radiation for a metachronous (7 years prior) first primary GCT, as well as 1 patient with a late relapse who had M1a pelvic disease at the time of RPLND which introduced a marginal level of heterogeneity.

Another consideration when comparing outcomes across studies is the effect each cohort's pN0 rate may have had on risk of subsequent recurrence. The predictable patterns of metastatic spread with seminoma make it unlikely these patients would experience a recurrence within or outside of the RP following surgery. Accordingly, 16% and 9% of patients were pN0 in SEMS and PRIMETEST, respectively. Since these patients are probably at very low risk of recurrence, the RFS rate in these studies may be artificially improved compared to those with lower pN0 rates, like our series. Relapses in our series and others are too infrequent to draw meaningful conclusions about factors associated with recurrence; however, future meta-studies using pooled patient-level outcomes can help illuminate these factors.

The differences in the operative approach and completeness of the retroperitoneal resection may have influenced outcomes across studies. In our series, all patients received an open bilateral template operation, but both SEMS and PRIMETEST allowed for modified template operations. In SEMS, only high-volume surgeons were included, but ~10% of patients received dissections below what was recommended by the protocol and only 35% received a bilateral template surgery.[15] PRIMETEST included patients who modified template resections, only. There were no RP recurrences in any of the 29 patients managed with surveillance in our series, while both SEMS and PRIMETEST had several patients experience RP recurrences. Any recurrence in the RP, whether "in field" or "out of template," is a surgical failure, usually avoidable with a bilateral template dissection. Furthermore, in the Indiana series, 9 of 67 patients (13%) had disease on the contralateral side of a templated dissection, suggesting bilateral template dissection should be the standard for primary RPLND in seminoma.[20] Notably, the prevalence of extra-template disease is similar to prior mapping studies of template dissections.[21-23]

Six patients also received a formal unilateral pelvic LND in our cohort, only 1 of which had seminoma in the pelvic nodes. Most series have reported a low proportion of patients who relapse in the pelvis only,[16,20,24] and a 4% rate of pelvic disease, and therefore relapse, can be inferred from historic radiation studies.[25] Since only 1 patient had disease found in the pelvis lymph nodes, and there were no isolated pelvic LN recurrences among patients managed with surveillance, it is not clear what therapeutic benefit or influence on the risk of relapse pelvic LND may have when used selectively or universally. The possible influence prior ipsilateral inguinal surgery may have on the risk of relapse and/or the need for pelvic LND due to aberrant lymphatic drainage also requires further investigation.

Although primary RPLND alone will not cure all patients in this setting, the goal of avoiding chemotherapy to mitigate the risk of cardiovascular complications and second primary malignancies remains. Deescalation strategies are similarly being explored with combination stereotactic radiation and "lesser" chemotherapy in the form of carboplatin, as recently reported in SAKK 01-10.[26] However, if all patients with RP node-positive pure seminoma were managed with primary surgery, assuming an 80% cure rate with surgery alone, only 20% would

require chemotherapy. Assuming no routine adjuvant chemotherapy, each patient would receive either EP×4 or 3 cycles of bleomycin, etoposide, and cisplatin on relapse. However, the number of patients exposed to full-dose first-line chemotherapy could be further reduced with judicious use of adjuvant chemotherapy in those at highest risk of relapse.[27] Taken together, routine use of primary surgery for the majority of patients with RP-only metastatic seminoma will significantly reduce the overall burden of chemotherapy received in this patient population and should be adopted as a standard option. Better understanding of who is at highest risk of relapse after primary RPLND will help guide indications and counseling for surgery and adjuvant treatment.

Negative (pN0) pathology at the time of RPLND should be avoided when possible, as this is another form of potential overtreatment. Mitigating this risk may be possible through short interval repeated imaging prior to surgery or the use of adjunctive diagnostics (eg, microRNA.) Although the clinical utility of microRNA is yet to be fully determined, there is evidence that it may provide additional information about active disease beyond our current standards and would therefore help with clinical decision-making.[28-31]

In our series, there are limitations and other factors that must be considered for proper interpretation. First, there was a nonstandard adjuvant management strategy with roughly one third of the cohort electing for adjuvant EP×2. Since many of our patients had previously relapsed on surveillance, many did not want to experience another recurrence and elected for adjuvant chemotherapy after extensive counseling. Selection bias may have influenced our outcomes, as those at higher risk for relapse may have been selected or self-selected for adjuvant chemotherapy, artificially lowering our recurrence rates compared to other studies. However, there was no significant statistical difference in the distribution of pN stages among those given adjuvant chemotherapy and those in the surveillance group though both patients with pN3 disease received adjuvant EP×2. The cohort also has inherent selection bias since all patients had to be considered good surgical candidates with a high chance of surgical cure based on the clinical burden of disease. Although our selection criteria were not as strictly delineated as in SEMS or PRIMETEST, the preoperative node size and multiplicity of enlarged nodes on preoperative imaging were quite similar to the inclusion criteria of those studies. Our median follow-up for nonrelapsing patients managed with surveillance was 18.4 months. This period is slightly shorter than the completed Phase 2 studies, both of which have near-complete 2-year follow-up for all patients. Additionally, our post-RPLND surveillance regimen was consistent with our routine clinical practice (1 CT scan 3-4 months after surgery) and not as intensive as most of the clinical trial protocols. These factors could lead to an underestimation of the true number of recurrences, but our data are consistent with historical institutional RP-only relapse rate of $<1\%$ after RPLND.

CONCLUSIONS

In this series of patients with metastatic pure seminoma limited to the RP and treated with primary RPLND, 2-year RFS for those who did not receive adjuvant chemotherapy was 81%. Among these patients, there were no retroperitoneal relapses, suggesting a potential benefit to bilateral template surgery that should be further explored.

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EDITORIAL COMMENTS

The therapeutic landscape for stage 2 seminoma is evolving as we reassess traditional standards of care to optimize cancer control and minimize treatment-related morbidity. Seminoma comprises over half of all testicular germ cell tumors, and stage 1 seminoma is the most common presentation, with 15% to 20% of men experiencing relapse if managed with surveillance alone. Given decreasing use of adjuvant chemotherapy in stage 1 and growing implementation of serum microRNA-371a-3p for earlier detection of relapse, the proportion of patients presenting with low-volume retroperitoneal metastatic recurrence will likely increase. This underscores the need to refine treatment strategies for stage 2 seminoma.

Several institutional series have explored primary retroperitoneal lymph node dissection (RPLND) as an alternative to chemotherapy with or without radiotherapy for stage 2 seminoma.[1] Differences in surgical technique/template, use of adjuvant chemotherapy, patient selection, and length of follow-up make direct comparisons challenging. Nevertheless, these initial prospective trials have demonstrated promising 2-year recurrence-free survival rates of 70% to 95% with surgery alone, and successful salvage with chemotherapy for those recurring which may indeed lead to a decrease in treatment burden overall.[2]

The current study by Matulewicz et al adds a valuable long-term retrospective cohort to this evidence base.[3] Over 10 years at a high-volume center, 45 patients underwent primary bilateral full template RPLND for stage 2 seminoma. The clinical stage was primarily 2a with a median lymph node size of 1.8 cm (IQR 1.4-2.2, range 1.1-3.4 cm). Seminoma was confirmed in 96% which underlines the well-performed selection and only limited overtreatment. The 2-year RFS was 84% but adjuvant chemotherapy was given in 16 patients. Notably, there were no retroperitoneal recurrences.

In conclusion, data supporting primary RPLND as a treatment option for stage 2 seminoma are emerging, but longer follow-up to confirm the

oncological efficacy and selection nuances to decrease overtreatment (pN0) is important. In addition, surgical quality assurance will be integral before guideline endorsement as even in high-volume centers surgical and medical complications may happen leading to short- and long-term adverse events in this young patient population. For now, primary RPLND in stage 2 seminoma should only be performed in prospective cohorts with quality monitoring in expert centers. Further research to define criteria for patient selection (eg, restaging after 6 to 8 weeks or incorporating microRNA-371a-3p) is planned, and we appreciate being contacted by international interested centers for such studies.

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Cisplatin-based chemotherapy regimens and radiation therapy to the regional lymph nodes are well-established options to treat men with low-volume metastatic seminoma to the retroperitoneum (stage IIA/B). Though cure rates approach and/or exceed 90% with either approach, these therapies may be associated with long-term toxicities including pulmonary fibrosis, ototoxicity, nephrotoxity, cardiotoxicity, and increased risk for secondary cancers. In this distinctively young population where long-term survival should be an expectation, treatments have focused on minimizing morbidity. Retroperitoneal lymph node dissection (RPLND) has been proposed as an alternate treatment strategy for patients with low-volume metastatic seminoma because of its established efficacy, safety, and few long-term complications in the nonseminoma population when performed by high-volume providers at experienced centers.

The role of primary RPLND in early metastatic seminoma has recently been clarified by data from several prospective phase II trials (SEMS, PRIMETEST, COTRIMS). Though the inclusion criteria (number and size of lymph nodes), surgical approach, and templates varied according to trial, recurrence-free survival was 78%, 70%, and 90% at median follow-up of 33 months, 32 months, and 21 months in the SEMS, PRIMETEST, and COTRIMS trials, respectively.[1-3]

In the present study, investigators from Memorial Sloan Kettering Cancer Center report a retrospective review of their 10-year experience in treating 45 men with testicular seminoma metastatic to the retroperitoneum.[4] Taking into account that almost 20% of men with pN1 disease received adjuvant chemotherapy in this cohort despite having undergone an RPLND, this experienced group from Memorial Sloan Kettering report outcomes (2-year recurrence-free survival of 81%) analogous to those reported in prospective trials. Anejaculatory rates following RPLND were not reported, though ejaculatory dysfunction rates post-RPLND reported in SEMS trial appear low (5%).[1]

Taken together, data from this study add to the emerging literature corroborating the early oncologic efficacy and low complication rate of primary RPLND for patients with early metastatic seminoma.

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