

Surgery in Early Metastatic Seminoma: A Phase II Trial of Retroperitoneal Lymph Node Dissection for Testicular Seminoma With Limited Retroperitoneal Lymphadenopathy

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PURPOSE The long-term toxicities of chemotherapy and radiotherapy can represent a significant burden to testicular cancer survivors. Retroperitoneal lymph node dissection (RPLND) is an established treatment for testicular germ cell tumors with minimal late morbidity although little data exist on its efficacy in early metastatic seminoma. Surgery in early metastatic seminoma is a prospective phase II single-arm, multi-institutional trial of RPLND as first-line treatment for testicular seminoma with clinically low-volume retroperitoneal lymphadenopathy.

PATIENTS AND METHODS Twelve sites in the United States and Canada prospectively enrolled adult patients with testicular seminoma and isolated retroperitoneal lymphadenopathy (1-3 cm). Open RPLND was performed by certified surgeons with a primary end point of 2-year recurrence-free survival (RFS). Complication rates, pathologic up/downstaging, recurrence patterns, adjuvant therapies, and treatment-free survival were assessed.

RESULTS A total of 55 patients were enrolled, with a median (IQR) largest clinical lymph node size of 1.6 cm (1.3-1.9). RPLND pathology demonstrated a median (IQR) largest lymph node size of 2.3 cm (0.9-3.5); nine patients (16%) were pN0, 12 (22%) pN1, 31 (56%) pN2, and 3 (5%) pN3. One patient received adjuvant chemotherapy. With a median (IQR) follow-up of 33 months (12.0-61.6), 12 patients experienced recurrence, with a 2-year RFS of 81% and a recurrence rate of 22%. Of the patients who experienced recurrence, 10 were treated with chemotherapy and two underwent additional surgery. At last follow-up, all patients who experienced a recurrence were disease-free and the 2-year overall survival was 100%. Four patients (7%) experienced short-term complications, and four patients experienced long-term complications including incisional hernia (1) and anejaculation (3).

CONCLUSION RPLND is a treatment option for testicular seminoma with clinically low-volume retroperitoneal lymphadenopathy and is associated with low long-term morbidity.

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ASSOCIATED CONTENT

Appendix Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Long-term toxicities of chemotherapy and external beam radiotherapy (RT) represent a significant risk to many patients with germ cell tumors (GCTs) of the testis. These treatments are effective, with a disease-free survival of up to 90%,¹ but comprehensive population-based data reveal risks of late effects and diminished quality of life.² Toxicities include cardiovascular disease (RT Relative Risk [RR] 2.4, chemotherapy RR, 2.6),³ metabolic syndrome (chemotherapy RR, 2.2),⁴ secondary malignancies (chemotherapy RR, 1.8, RT RR, 2.0),⁵ and others.⁶ Cumulatively, the impact represents a burden to testicular cancer survivors with observed-to-expected mortality ratios ranging from 1.6 to 2.0 in those treated with RT or chemotherapy.^{7,8}

With excellent cure rates, the germ cell tumor investigative agenda has moved to focus on consistent delivery of guideline-directed strategies while limiting short- and long-term morbidities. In seminoma with retroperitoneal lymphadenopathy, investigations have modified chemotherapy or RT to potentially improve long-term safety. Single-agent carboplatin has not been adopted because of lower efficacy.⁹ Reducing RT fields or adding carboplatin to RT has been shown to provide oncologic control but unclear long-term benefits.^{10,11} Patients with early metastatic seminoma are typically managed with RT or chemotherapy, with good cure rates but elevated long-term risks.

Retroperitoneal lymph node dissection (RPLND) is an established and effective treatment for testicular GCT.

CONTEXT

Key Objective

Survivors of metastatic testicular seminoma can suffer long-term toxicities from radiotherapy or systemic chemotherapy.

This prospective phase II study examined whether retroperitoneal lymph node dissection (RPLND), which has minimal long-term risk, has efficacy in early metastatic seminoma. There were 55 patients who underwent RPLND at 12 different institutions for testicular seminoma with enlarged retroperitoneal lymph nodes.

Knowledge Generated

The estimated 2-year recurrence-free survival after surgery was 81%. The surgery was performed with a very low rate of complications.

Relevance (M.A. Carducci)

This report of a sizable clinical trial to assess the utility of primary RPLND for patients with stage II-A/B seminoma did not meet its end point as designed. Yet, the results in total clearly demonstrate that primary RPLND is an option for the management of Stage II seminoma with adenopathy <3 cm given the potential to avoid long-term toxicity of radiation and chemotherapy.

*Relevance section written by JCO Associate Editor Michael A. Carducci, MD, FACP, FASCO.

RPLND is a standard, well-studied option in stage I-II B nonseminomatous GCT (NSGCT) and is used for both seminoma and NSGCT with postchemotherapy residual masses.^{12,13} Ample data demonstrate that long-term impacts of primary RPLND are limited to ejaculatory dysfunction (<10%), incisional hernia (4%), bowel obstruction (2%), and ureteral obstruction (1%).¹⁴⁻¹⁷ Patients with stage IIA-B NSGCT treated with primary RPLND have cure rates of approximately 80%, which represents a significant reduction in chemotherapy cycles and associated morbidities.¹⁸ Seminoma spreads in a more predictable lymphatic pattern compared with NSGCT, making the rationale for primary RPLND in lymph node–positive seminoma logical.¹⁹ The Surgery in Early Metastatic Seminoma (SEMS) trial evaluated the efficacy and safety of RPLND for seminoma with clinically low-volume retroperitoneal adenopathy.

PATIENTS AND METHODS

SEMS was a single-arm, prospective phase II clinical trial (ClinicalTrials.gov identifier: [NCT02537548](https://clinicaltrials.gov/ct2/show/study/NCT02537548)) evaluating the efficacy of RPLND in testicular seminoma. The study was initiated at the University of Southern California, included 11 other institutions in the United States and Canada (Appendix [Table A1](#) [online only]), and approved by all local sites' IRB. All patients provided written informed consent.

Eligibility

SEMS enrolled adult patients with pure testicular seminoma after radical orchiectomy with isolated retroperitoneal lymphadenopathy 1-3 cm in greatest dimension. No more than two lymph nodes could be enlarged radiographically, and lymph nodes needed to be within the ipsilateral RPLND template. The lymph node enlargement could be synchronous (stage IIA or IIB) or metachronous (stage I with recurrence). Abdominal/pelvic imaging (computed tomography [CT] scan, positron

emission tomography [PET] scan, or magnetic resonance imaging [MRI]) and negative chest imaging were required within 6 weeks of RPLND. The inclusion criteria for maximum lymph node size were increased from 2 to 3 cm on August 1, 2018 (after 31 patients enrolled), to improve accrual and align with guidelines at the time of defining bulky adenopathy as >3 cm.²⁰ When the accrual goal of 46 was reached, several institutions had not had an opportunity to enroll patients. To allow for more sites to accrue patients and improve the generalizability of the results, the goal was increased to 55.

Eligibility included an Eastern Cooperative Oncology Group performance status of <2, serum tumor marker (alpha fetoprotein, human chorionic gonadotropin, and lactate dehydrogenase) elevation ≤1.5 times upper limit of normal, and evidence of regional adenopathy only. Exclusion criteria were second primary malignancy, previous RT or chemotherapy, or comorbidities that precluded surgery.

Treatment

Open RPLND was performed by certified surgeons who performed ≥8 open RPLND surgeries in the year before site initiation or at least 25 open RPLND surgeries within the past 3 years.

Minimum recommended surgery was a nerve-sparing, modified ipsilateral template dissection. Surgeon discretion allowed for resection of postganglionic sympathetic nerves if needed for oncologic control and dissection outside of the recommended template. Templates of dissection were consistent with previously described modified templates, with the lateral limits of the right template being from right ureter to left ureter above the inferior mesenteric artery and right ureter to the anterior aorta below the inferior mesenteric artery.²¹ Left template lateral limits were from the anterior aspect of the inferior vena cava to the left ureter above the

inferior mesenteric artery and the anterior aspect of the aorta to the left ureter below the inferior mesenteric artery.

Follow-Up

Evaluations were performed postoperatively to assess short-term complications using the Clavien-Dindo classification and pathology review.²² Adjuvant chemotherapy was not recommended. After RPLND, patients were followed every 4 months for year 1, every 6 months for years 2 and 3, and then annually up to 5 years. Patients were assessed for complications and recurrence at each visit with history including queries regarding sexual health and ejaculatory function, physical examination, serum tumor markers, CT or MRI imaging of the abdomen/pelvis, and chest imaging (chest x-ray preferred). Management of disease recurrence was at the discretion of the treating physician.

The USC Data and Safety Monitoring Committee reviewed the complication and recurrence rate to ensure that these remained below predefined thresholds.

Statistical Analysis

The sample size of this study was based on the Brookmeyer-Crowley method using the online tool.²³ The power analysis showed that with a sample size of 41 (anticipating five patients lost to follow-up), the trial would achieve 90% power to detect a 2-year recurrence-free survival (RFS) rate of 0.9 after RPLND compared with a baseline 2-year RFS of 0.75 assuming the significance level at 0.1 one-sided. The study was open for accrual from August 2015 to April 2019. Accrual per site is listed in Appendix Table A1.

The primary end point of the analysis was 2-year RFS. Patients who were lost to follow-up and the patients who were still alive at the date of data cutoff were censored at the date the patient was last known alive or the cutoff date, whichever occurred first. Similar survival analysis techniques were applied to the treatment-free survival (TFS). To remain consistent with study design, we provided one-sided 90% CI, that is, the lower bound for the 2-year RFS point estimator. Furthermore, to describe the RFS, the survival probability was estimated using the Kaplan-Meier method with its 95% CI plotted over time. In a post hoc analysis, the Kaplan-Meier method was used to estimate RFS stratified by stage, the log-rank test was applied to compare these group survival differences, and the overall *P* values were reported. Fisher's exact test was used to assess the association between recurrence status and four variables of interests. Descriptive statistics were provided for patient demographics and clinical factors. Intention-to-treat analysis was performed including patients who had nonseminomatous components on pathology, pNO, or clinical node size >3 cm or underwent adjuvant therapy.

RESULTS

Fifty-five patients were enrolled (Table 1). For patients presenting with stage I disease, the median (IQR) time from

orchiectomy to disease recurrence was 13.7 (8.2-20.1) months. The most recent axial imaging was performed at a median (IQR) of 12 (5-28) days before the RPLND. All patients except for one had pre-RPLND lymph nodes measuring ≥ 1 cm and ≤ 3 cm. The exception was a patient who underwent RPLND for what was initially assessed as a 3-cm lymph node, which, on review, was measured at 3.5 cm in maximal dimension.

All patients underwent RPLND by 19 certified surgeons. Six patients underwent surgery that excised fewer lymph nodes than recommended: five underwent a left template RPLND without interaortocaval lymphadenectomy and one underwent a right template RPLND without para-aortic lymphadenectomy. Nerve-sparing within the template was performed in 48 (87%) patients. Of the seven who did not have nerve-sparing, four underwent modified template dissections and one patient underwent bilateral

TABLE 1. Patient Demographics and Clinical Factors at Study Entry

Clinical Characteristic	Total (N = 55)
Median age, years (range)	34 (20–64)
Race/ethnicity, No. (%)	
Non-Hispanic White	44 (80)
Hispanic	6 (11)
Unknown	5 (9)
Performance status, No. (%)	
ECOG 0	53 (96)
ECOG 1	2 (4)
Serum tumor markers (AFP, HCG, and LDH), No. (%)	
Normal	47 (85)
Elevated (up to 1.5× upper limit)	8 (15)
Clinical stage, No. (%)	
Stage I with recurrence (1-2 cm)	27 (49)
Stage I with recurrence (>2 cm)	9 (16)
Stage IIA	17 (31)
Stage IIB	2 (4)
No. of clinically enlarged lymph nodes, No. (%)	
One	40 (73)
Two	15 (27)
Median size of first enlarged LN (range), cm	1.6 (1.0-3.5)
Median size of second enlarged LN (range), cm	1.3 (1.0-2.3)
Time between abdominal imaging and RPLND, No. (%)	
0-4 weeks	42 (76)
>4 weeks	13 (24)

Abbreviations: AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; LN, lymph node; RPLND, retroperitoneal lymph node dissection.

non-nerve-sparing surgery in part due to a history of RPLND over 15 years before study enrollment. The median (IQR) blood loss was 150 (100-300) mL, and no patient required blood transfusion. The median (IQR) duration of surgery was 233 (178-313) minutes, and the median (range) length of hospital stay was 3 (1-7) days.

Seminoma was detected in 45 of 55 (82%) specimens (Table 2). One specimen was found to have a small component of NSGCT within a linear 12-cm matted nodal mass. Nine patients (16%) had no evidence of cancer (pN0). All these patients had clinical (radiographic) lymph node size from 1 to 1.5 cm. Twenty-nine patients had clinical lymph nodes of size 1-1.5 cm. Although downstaging was observed, pathologic upstaging (44%) was the most common outcome. The median clinical versus pathologic lymph node size increased from 1.6 to 2.3 cm.

In post-RPLND follow-up, one patient received a single cycle of carboplatin for pN2 disease (two lymph nodes with extra-nodal extension and largest lymph node 5 cm). This patient was free of disease at last follow-up. All other patients were managed with surveillance. The median (range) follow-up after RPLND was 33 (12.0-61.6) months. The 2-year follow-up was completed in 52 of 55

patients (95%), with three patients lost to follow-up after 12, 12, and 17 months. The overall recurrence rate was 22% with a median (range) time to recurrence of 10.2 (7.3-31.6) months. The 2-year RFS was estimated to be 81% with the one-sided 90% CI, and the lower bound was 0.75. The 2-year TFS was estimated to be 83%, with the one-sided 90% CI, and the lower bound was 0.77. Figure 1 demonstrates the survival patterns over time using the Kaplan-Meier method. The 2-year overall survival was 100%.

Table 3 shows a detailed description of the patients (n = 12) who experienced disease recurrence after RPLND. All had pathologically positive lymph nodes at the time of RPLND. Five in-field retroperitoneal recurrences were seen, with other recurrences being retroperitoneum out-of-field, pelvis, peritoneum, and mediastinum. Two patients were treated with surgical resection, and all others received systemic chemotherapy. Two patients experienced a second relapse (one after retroperitoneal mass resection and the other after salvage chemotherapy). One was treated with a third surgical resection, and the other with high-dose chemotherapy. All patients were disease-free at last follow-up.

Rates of recurrence within the cohort were compared in a post hoc analysis. For clinical N1 and N2 diseases, the 2-year RFS [95% CI] was 86% [0.76 to 0.97] and 64% [0.41 to 0.99], respectively. The survival probability of clinical N1 and cN2 over time (Fig 2A) was significantly different ($P = .039$, log-rank). The 2-year RFS on the basis of the pathologic stage was pN0 100%, pN1 92% [0.77 to 1], pN2 74% [0.60 to 1], and pN3 67% [0.30 to 1]. The survival probabilities for pathologic stages N0, N1, N2, and N3 (Fig 2B) were not significantly different ($P = .36$, log-rank). The association analysis from Fisher's exact test provided the following findings: patients with abdominal imaging >4 weeks before RPLND experienced a higher recurrence rate compared with those who had more recent imaging (54% v 12%, $P = .0037$). Variables not significantly associated with recurrence were those with stage I disease with recurrence versus stage IIA/IIB disease (25% and 16%, respectively, $P = .52$), bilateral dissection versus modified template (26% and 19%, respectively, $P = .73$), and serum tumor elevation preoperatively versus normal serum tumor markers (12.5% and 31%, respectively, $P = .67$).

Four patients (7%) experienced a total of five Clavien-Dindo grade I-III complications (Table 4). Long-term complications were noted in four (7%) patients. One had an asymptomatic incisional hernia detected radiographically and not treated at the time of last follow-up. Three (5%) patients, who all underwent non-nerve-sparing surgery, experienced anejaculation.

DISCUSSION

Our prospective multi-institutional trial evaluated the efficacy of RPLND as a primary treatment for metastatic seminoma and found a 2-year RFS of 81%. When excluding patients

TABLE 2. Pathology at RPLND

Operative/Pathologic Characteristic	Total (N = 55)
RPLND template, No. (%)	
Bilateral	19 (35)
Left modified	25 (45)
Right modified	11 (20)
RPLND approach, No. (%)	
Intraperitoneal	40 (73)
Extraperitoneal	15 (27)
Median No. of LN removed (range)	29 (8-76)
Median No. of positive LN (range)	1 (0-12)
Median size of largest positive LN (range), cm	2.30 (0.03-12.30)
ENE, No. (%)	
Yes	13 (24)
Median No. of nodes (if with ENE)	2 (1-8)
Pathologic nodal stage, No. (%)	
pN0	9 (16)
pN1	12 (22)
pN2	31 (56)
pN3	3 (5)
Clinical N staging > pathologic stage, No. (%)	
Downstage	11 (20)
No change	20 (36)
Upstage	24 (44)

Abbreviations: ENE, extranodal extension; LN, lymph node; RPLND, retroperitoneal lymph node dissection.

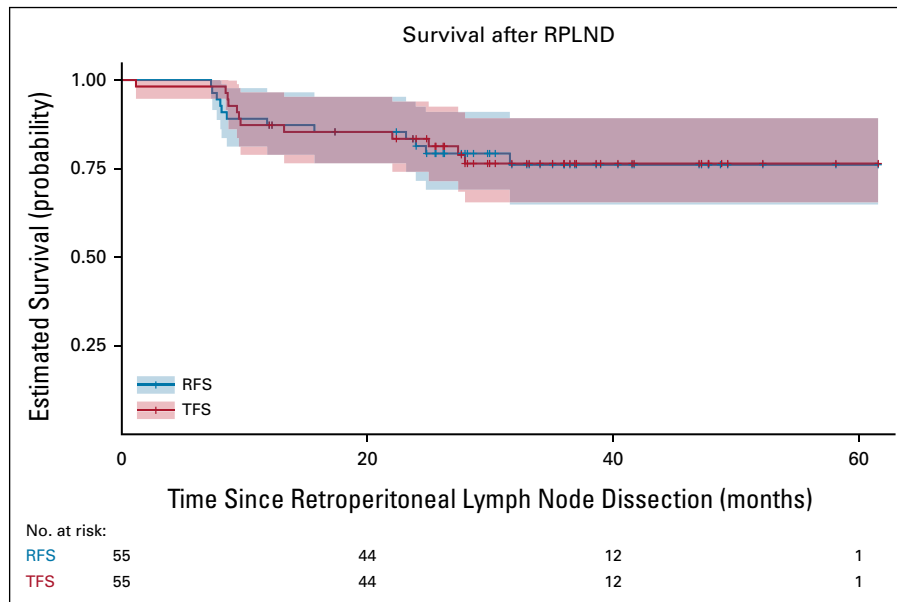


FIG 1. RFS and TFS after RPLND. RFS, recurrence-free survival; RPLND, retroperitoneal lymph node dissection; TFS, treatment-free survival.

who did not have cancer in the retroperitoneum (pN0), the recurrence rate was 26% as compared with 22% for the entire cohort. These early efficacy data of RPLND, which provide accurate pathologic diagnosis and staging, must be compared against established treatments in seminoma based solely on clinical staging. The 5-year RFS for stage IIA and IIB seminoma treated with RT has been noted between 89%-95% and 69%-89%,^{11,24-26} respectively, whereas the 3- or 5-year RFS for stage IIA/IIB seminoma after multiagent cisplatin-based chemotherapy ranges between 87% and 100%.^{24,27,28} As worse oncologic outcomes are associated with higher-stage disease, it should be noted that 20% of patients in SEMS had clinical N2 disease, which corresponds to stage IIB disease. At the time of surgery, pN2 (56%) and pN3 (5%) diseases comprised 61% of the patients and over a third (35%) of patients had bulky disease (>3 cm) on pathology.¹³

The rate of pN0 disease was 16%, comparable with that seen in stage IIA NSGCT (13%-35%) and presumably similar to those with seminoma treated with chemotherapy or RT.²⁹ The finding of pN0 disease exclusively in patients with clinical lymph nodes ≤ 1.5 cm is unique and an area that warrants further research such as with emerging liquid biomarkers (ie, miRNA-371) or short-interval repeat imaging. However, moving the current 1.0 cm threshold for therapeutic interventions above 1.5 cm would miss 69% of patients who had retroperitoneal involvement with GCT < 1.5 cm. Furthermore, five of 12 (42%) patients who experienced recurrence after RPLND had clinical lymph nodes ≤ 1.5 cm.

The results of this trial should be interpreted in the context of other investigations aimed at limiting the long-term morbidity

in seminoma. In the PRIMETEST trial, Albers and colleagues reported on 33 patients treated with open or robotic RPLND for lymph node-positive seminoma including patients with lymph nodes up to 5 cm and some treated with carboplatin chemotherapy.³⁰ With a median follow-up of 32 months, they observed a 70% progression-free survival (95% CI, 51 to 84), which did not reach its estimated primary end point. Another group from the United Kingdom is evaluating stage IIA seminoma treated with minimally invasive RPLND and adjuvant carboplatin. Their interim analysis reported one recurrence in 20 patients with a median follow-up of 41 months.³¹ In the COTRIMS trial, Heidenreich et al reported on 21 patients who underwent RPLND for clinical stage IIA/B seminoma with two recurrences observed at a mean follow-up of 21 months (9.5%).³²

Nonsurgical attempts at de-escalation efforts in seminoma include the SAKK 01/10 trial that explored single-dose carboplatin followed by RT with a 3-year PFS rate of 94%.³³ A multicenter, phase 2 SEMITEP trial aimed to reduce the number of cycles of multiagent chemotherapy by using early FDG-PET/CT as an indicator of response and found similar recurrence outcomes between the two arms.³⁴ Results of these clinical investigations are just becoming available although uncertain is whether these different treatment algorithms will lead to diminished therapeutic outcomes, delayed recurrences, or any appreciable reduction in late toxicities.

SEMS initially hypothesized that primary RPLND was associated with a 2-year RFS of > 0.75 and with one-sided 90% CI, the lower bound overlapped right on 0.75, and the study just missed the formal statistical end point. However, the statistical results do not detract from the major clinical

TABLE 3. Detailed Description of Patients Who Experienced Recurrence After RPLND

Patient	Initial Presentation		RPLND				Recurrence			Survival	
	Stage (if stage I, time from orchiectomy to RPLND)	Largest Clinical Lymph Node, cm	RPLND Template	Largest Size of Positive Node, cm	Positive Nodes, No.	Extranodal Extension	Method of Detection	Time from RPLND to Recurrence, months	Location(s)	Treatment	Disease-Free, Y/N
1	I (37 months)	2.7	Bilateral	0.03	1	N	Radiographic	7.2	Retroperitoneal (in-field para-aortic and preaortic)	Bleomycin, etoposide-cisplatin × 3	Y
2	I (10 months)	1.9	Left modified (no interaortocaval)	3.0	3	N	Radiographic	7.3	Retroperitoneal (out-of-field lower interaortocaval)	Bleomycin, etoposide-cisplatin × 3	Y
3	IIA	1.8	Left modified	1.0	8	Y	Radiographic	7.7	Retroperitoneal (in-field retrocaval, interaortocaval) Retroperitoneal (out-of-field) Peritoneal Pelvic	Bleomycin, etoposide-cisplatin × 3	Y
4	I (20 months)	1.6	Right modified	3.5	1	Y	Serum marker elevation Radiographic	8.0	Retroperitoneal (in-field out-of-field) Peritoneal Pelvic	Bleomycin, etoposide-cisplatin × 4	Y
5	IIB	2.4	Left modified (no interaortocaval)	6.1	1	N	Radiographic	8.1	Retroperitoneal (in-field para-aortic)	Etoposide-cisplatin × 4	Y
6	IIA	1.2	Bilateral	1.1	4	Y	Radiographic	8.5	Pelvic	Etoposide-cisplatin × 4	Y
7	I (9 months)	1.5	Right modified (no preaortic or para-aortic)	3.5	1	Y	Radiographic	11.8	Pelvic	Bleomycin, etoposide-cisplatin × 3	Y
8	I (9 months)	1.2	Left modified	3.6	4	N	Radiographic	15.6	Retroperitoneal (in-field interaortocaval)	Surgical resection	Y
9	I (35 months)	3	Bilateral	3.7	5	N	Radiographic	16.9	Mediastinal	Bleomycin, etoposide-cisplatin × 3	Y
10	I (19 months)	1.1	Bilateral	1.5	8	N	Radiographic	23.1	Mediastinal Pelvic	Bleomycin, etoposide-cisplatin × 3	Y
11; first recurrence after RPLND	I (6 months)	1.4	Left modified	5.0	3	N	Radiographic	24.7	Mediastinal	Bleomycin, etoposide-cisplatin × 3	N
11; second recurrence after RPLND							Radiographic	31.7	Mediastinal	High-dose carboplatin-etoposide × 2	Y
12; first recurrence after RPLND	I (19 months)	1.8	Bilateral	1.5	2	N	Radiographic	31.5	Retroperitoneal (in-field interaortocaval)	Surgical resection	N
12; second recurrence after RPLND							Radiographic	46.7	Retroperitoneal (in-field preaortic)	Surgical resection	Y

Abbreviation: RPLND, retroperitoneal lymph node dissection.

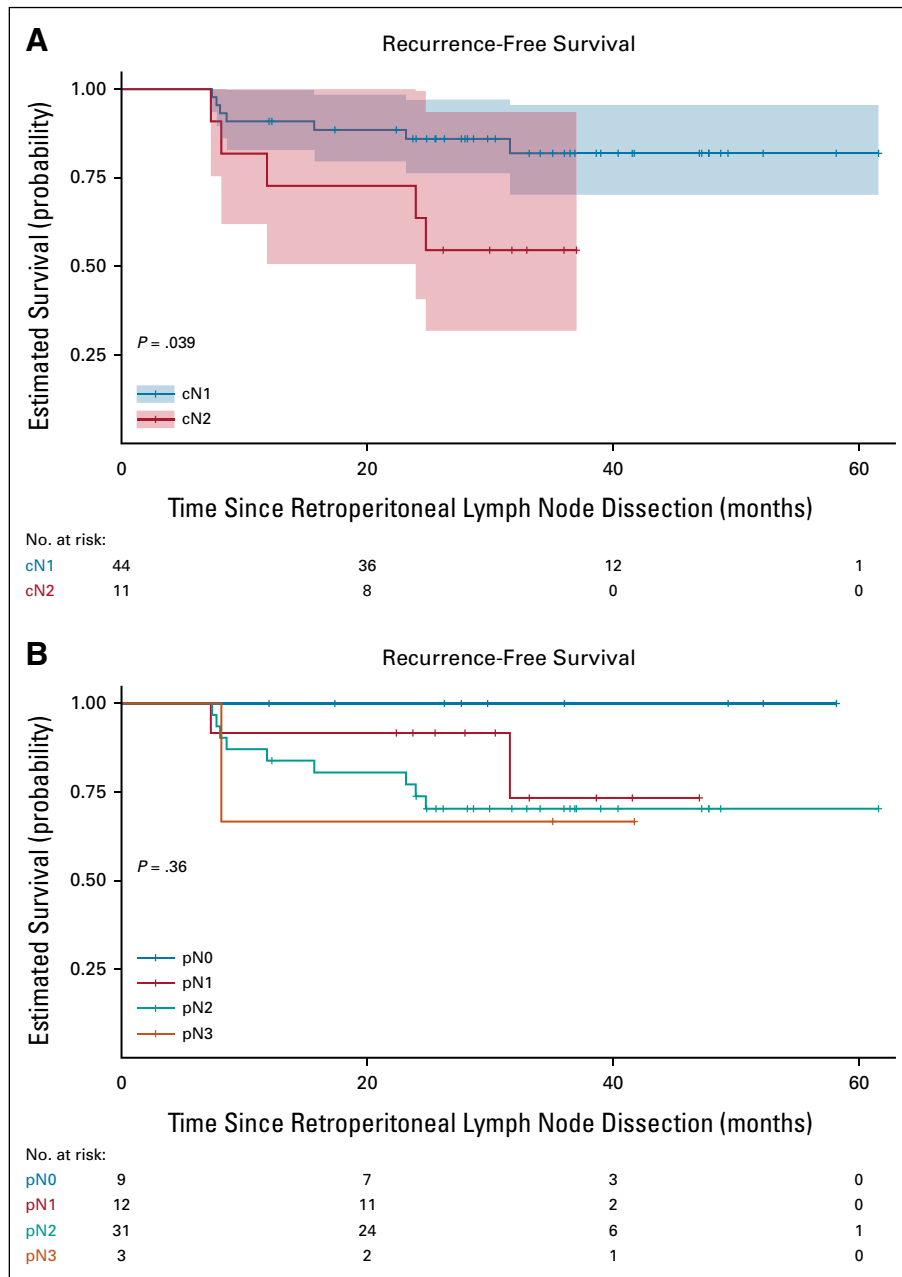


FIG 2. Survival stratified by (A) clinical and (B) pathologic lymph node size.

and patient significance seen in this study. The major advantage for RPLND, which overshadows other therapeutic approaches and any potential decrement in relapse-free survival, is the opportunity to avoid chemotherapy or RT. Taking an intention-to-treat approach among our 55 enrolled patients, a total of 33 cycles of chemotherapy were administered to the study population (44 of 55 receiving no chemotherapy), whereas the standard chemotherapy management for 55 patients with good-risk seminoma would include at least 165 cycles of chemotherapy. This potential 80% reduction in the number of patients receiving chemotherapy will have a

significant impact when extrapolated for prolonged survivorship. The most sensible comparator for RPLND in seminoma would be with the performance of primary RPLND in isolated retroperitoneal nonseminoma, an approach that has been globally accepted and practiced for decades. Two recent large updates from Indiana University and Princess Margaret demonstrate comparable long-term disease control of RPLND, between 73% and 80%, while sparing these patients from chemotherapy.^{35,36}

The pattern of relapses observed after RPLND provides insight into the biology of metastatic seminoma. All recurrences were of a local or lymphatic route, and two patients experienced

TABLE 4. Complications After RPLND

Short-term (Clavien-Dindo Grade)
Incision ulceration (I)
Ileus (II)
Ileus (II) ^a
Pulmonary embolism (II) ^a
Chylous ascites (III)
Long-term (>30 days)
Incision hernia—radiographic
Anejaculation—bilateral dissection, non-nerve-sparing
Anejaculation—bilateral dissection, non-nerve-sparing
Anejaculation—left modified template, non-nerve-sparing

Abbreviation: RPLND, retroperitoneal lymph node dissection.

^aSame patient.

diffuse disease in the abdomen and pelvis. This preponderance of lymphatic and retroperitoneal/pelvic recurrences is similar to described patterns after regional RT in seminoma and in the PRIMETEST trial.^{30,37} This pattern differs from that seen with primary RPLND in NSGCT, where retroperitoneal recurrences are uncommon, but should still draw attention to propensity of seminoma to spread via lymphatic channels and local tissue planes.³⁵ In both our study and PRIMETEST, there are a limited number of recurrences, which makes it difficult to draw firm conclusions on clinical or surgical factors that may contribute to this. Although our study did not find that a bilateral dissection was associated with lower recurrence rates, the recurrence patterns seen in SEMS and PRIMETEST

(in which patients were treated with unilateral RPLND) argue for bilateral RPLND in this population with meticulous attention to oncologic principles.

Limitations to this study include a minimum of 2-year follow-up, and we recognize the possibility of additional relapses with further follow-up. RPLND templates differed within the study in part due to controversies regarding the optimal RPLND template and allowances for surgeon discretion. Conversely, including surgery performed at 12 institutions with 19 experienced surgeons improves generalizability although this will not likely apply to centers without extensive surgical experience and multidisciplinary teams in testicular cancer. The inclusion criteria for the study must be emphasized as only those with 1-2 enlarged lymph nodes within the ipsilateral template of dissection were included. Therefore, the results may not be translatable to patients with more enlarged lymph nodes or those with atypical patterns of disease.

Our next planned GCT trial integrating RPLND will be a large, multicenter trial of expert primary RPLND in low-volume, marker-negative stage II seminoma and NSGCT with the addition of the blood-based biomarker, microRNA-371a-3p, to address earlier diagnosis of relapse and the relatively high rate of false-positive clinical assessments and possibly assist in decision making regarding post-RPLND adjuvant therapy.^{38,39}

In conclusion, RPLND is a treatment option for testicular seminoma with clinically low-volume retroperitoneal lymphadenopathy, is associated with low long-term morbidity, and offers the majority of such patients the opportunity to be cured without chemotherapy or radiation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Surgery in Early Metastatic Seminoma: A Phase II Trial of Retroperitoneal Lymph Node Dissection for Testicular Seminoma With Limited Retroperitoneal Lymphadenopathy**

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No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Institutional Accrual

Institution	Enrolled Patients, No. (%)
Indiana University	19 (34.5)
USC Norris Comprehensive Cancer Center	12 (21.8)
Mayo Clinic	6 (10.9)
British Columbia Cancer Agency	5 (9.1)
University of Texas Southwestern	4 (7.3)
Stanford University	3 (5.5)
Loma Linda University	1 (1.8)
Emory University	1 (1.8)
Madigan Army Medical Center	1 (1.8)
University of Chicago	1 (1.8)
University of Oklahoma	1 (1.8)
Johns Hopkins	1 (1.8)