Curr Urol Rep (2013) 14:511–517
DOI 10.1007/s11934-013-0366-1

Critical Evaluation of Modified Templates and Current Trends in Retroperitoneal Lymph Node Dissection

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Published online: 2 August 2013

Abstract Retroperitoneal lymph node dissection (RPLND) is a critical aspect of staging and treatment of nonseminomatous germ cell tumors (NSGCTs) of the testis. RPLND achieves cure in a majority of patients with low-volume metastatic disease and minimizes the need for chemotherapy. Initial surgical approaches to RPLND, involving wide limits to dissection, were associated with high rates of retrograde ejaculation and significant overall morbidity. Evolving modified RPLND templates helped reduce rates of retrograde ejaculation but may be associated with a 3 %–23 % risk of unresected metastasis. Modified templates have become a standard of care in primary RPLND with low-volume metastatic disease. Only highly select patients at specialized centers should undergo modified template RPLND in the postchemotherapy setting, because risks of unresected disease are higher than in the primary setting. Bilateral RPLND optimizes cancer control and can preserve antegrade ejaculation if nerve sparing is performed. We also briefly discuss minimally invasive approaches to RPLND.

Keywords Retroperitoneal lymph node dissection · Modified template · Nonseminomatous germ cell tumor · Testicular cancer · Nerve sparing · Minimally invasive · Robotic · Retrograde ejaculation

Introduction

Interdisciplinary management of testicular cancer has led to a dramatic improvement in clinical outcomes, with 5-year survival rates increasing from 63 % in the 1960s to 96 % in 2002 [1], primarily attributable to the introduction of multiagent cisplatin-based chemotherapy and its appropriate integration with surgery. RPLND involves resection of the primary regions of lymphatic drainage from the testis and remains an essential component of the multimodal approach to successful treatment.

RPLND provides invaluable staging and prognostic information for patients with testicular cancer. Current imaging modalities have limited sensitivity and specificity for staging the retroperitoneum. Routine imaging with CT scan or MRI understages 20 %–25 % of patients with clinical stage I (CS I) and overstages 15 %–35 % of patients with CS IIA disease [2].

Another critical component of RPLND is its therapeutic value. For nonseminomatous germ cell tumors (NSGCTs) of the testes with low-volume nodal disease (pN1), 85 %–90 % durable cure rates can be achieved with surgery alone [3], obviating the need for chemotherapy in these patients. Routine surveillance imaging of the retroperitoneum after RPLND is not required, because local recurrences after RPLND are rare, as compared with the purported risk of radiation-induced malignancy associated with imaging [4].

Surgery has the potential to minimize the need for additional treatments such as adjuvant chemotherapy. The short- and long-term morbidity associated with RPLND, when performed by an experienced surgeon, is minimal, as compared with the risk of neurologic sequelae, cardiovascular disease, and secondary malignancy associated with chemotherapy [2]. The main risks of RPLND include a 1 %–2 % incidence of small bowel obstruction and 5 %–30 % of retrograde ejaculation, depending on the size and location of retroperitoneal (RP) disease [5, 6].

A better anatomic understanding of the lymphatic drainage of the testes and the pertinent neuroanatomy of the retroperitoneum has led to the development of modified surgical templates and prospective nerve sparing during RPLND, both of which intend to limit the ejaculatory morbidity of the

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operation. The effect of modified templates and nerve sparing on oncologic outcomes remains an area of active research, although existing data in *appropriately selected* patients suggest that these approaches do not compromise oncologic efficacy. In recent years, there has also been a growing interest in minimally invasive approaches to RPLND for testicular cancer.

Natural History of Testicular Germ Cell Tumors

Germ cell tumors (GCTs) typically exhibit a very predictable pattern of lymphatogenous spread from the testis to the RP lymph nodes and, subsequently, to the lung parenchyma and/or posterior mediastinum. RP nodes are the first site of lymphatic spread in 90 %–95 % of GCTs. As compared with other histologic subtypes, pure choriocarcinoma has a predilection for hematogenous routes of metastasis [7].

Historical Perspective on RPLND

For much of the 19th century in the developed world (and currently in many regions of the world), radical orchiectomy was the only available treatment for patients with GCTs of the testes. Without adjunctive options such as radiation, chemotherapy, or RPLND, long-term survival rates were as low as 20 % [8]. Initial attempts at RPLND were made at the turn of the century for large bulky abdominal masses and resulted in unacceptably high rates of major complications and incomplete resections [9]. Two small series from the first few decades of the 20th century, one from Europe and the other from Johns Hopkins, demonstrated a 15 %–17 % long-term survival rate in a subset of patients with stage II NSGCT following RPLND [10]. The therapeutic role for RPLND was eventually established by a large series of 167 military men treated for NSGCT at Walter Reed Medical Center following World War II. In their experience, 48 % of clinical stage II patients were cured following radical orchiectomy and RPLND, while all patients treated with orchiectomy and radiation eventually died from their disease [11].

An improved understanding of vascular, lymphatic, and neural anatomy during the 20th century allowed for safer and more effective RPLND. Dr. Most was the first to accurately describe the lymphatic drainage of the testis in 1899 [12], detailing drainage from the testis to its area of embryologic origin, the lymph nodes adjacent to the great vessels. In 1963, the original human lymphangiographic studies were performed with spermatic cord injections and demonstrated reproducible crossover from right to left in the RP nodes, rare crossover from left to right, and frequent ascension to the suprahilar region [13]. These anatomic findings provided the rationale for wide surgical resections, including the suprahilar, paracaval, precaval, para-aortic, preaortic, interaortocaval, and common iliac regions (Fig. 1). With complete resections of these areas, cure rates improved but were associated with high rates of chylous ascites, injury to foregut structures, nephrectomy, and near universal retrograde ejaculation [14].

Development of RPLND Templates

On the basis of the Indiana University (IU) experience with suprahilar dissection and low cure rates with surgery alone when disease was present in this region, the standard bilateral RPLND evolved to include the area inferior to the renal hilum, bounded laterally by the ureters, and extending caudally to the common iliac region and proximal one third of the external iliac. As surgical experience grew, a refined approach to clinical staging and surgical management of patients with NSGCTs was guided by detailed mapping studies of lymph node metastases in these patients [15–17].

As early as 1955, Whitmore at Memorial Sloan Kettering Cancer Center (MSKCC) began performing a "modified template RPLND." This modified approach omitted contralateral iliac nodes, caudal two thirds of the paraortic nodes for right-sided primaries, and paracaval nodes for left-sided primaries (Fig. 1, Table 1). Ray and Whitmore published their experience in the first large retrospective anatomic mapping series of 283 patients who had undergone RPLND, demonstrating a side-specific preference for infrahilar metastasis [15]. Additionally, among patients with a solitary metastasis, right-sided primary tumors were associated with variable sites of the metastasis, while left-sided primaries almost universally spread to the left lateral para-aortic region. This study provided valuable data but was limited by a lack of clinical outcomes and a limited sampling of RP regions, since 69 % of patients underwent a modified template RPLND.

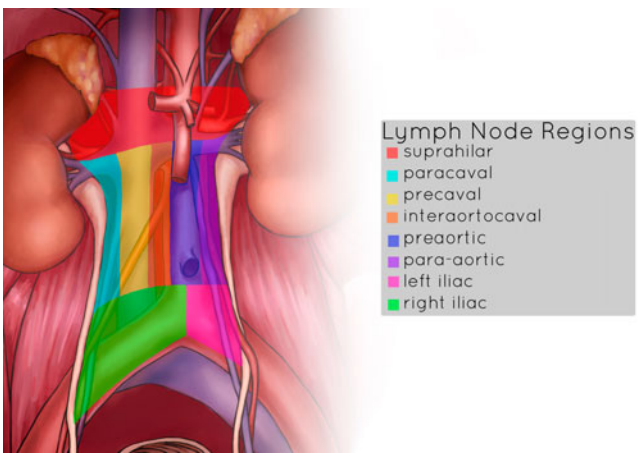

Fig. 1 Retroperitoneal anatomy with lymph node regions

Table 1 Various modified RPLND templates

Lymph Node Regions	Wide Resection	Standard Bilateral	IU Modified Template	MSKCC	TTSG
Right					
Suprahilar	X				
Paracaval	X	X	X	X	X
Precaval	X	X	X	X	X
Interaortocaval	X	X	X	X	X
Preaortic	X	X	X	X	X
Para-aortic	X	X		X	
Ipsilateral iliac	X	X	X	X	X
Contralateral iliac	X	X			
Gonadal vein	X	X	X	X	X
Left					
Suprahilar	X				
Paracaval	X	X			
Precaval	X	X		X	
Interaortocaval	X	X	X	X	
Preaortic	X	X	X	X	X
Para-aortic	X	X	X	X	X
Ipsilateral iliac	X	X	X	X	
Contralateral iliac	X	X			
Gonadal vein	X	X	X	X	X

Note. IU, Indiana University; MSKCC, Memorial Sloan Kettering Cancer Center; TTSG, Testicular Tumor Study Group

These results were supported and elaborated upon when John Donohue and his group at IU published an RPLND series of 104 patients with pathologic stage II NSGCT undergoing a bilateral dissection template from the suprahilar zones extending caudally to the bifurcation of the common iliac vessels (Fig. 1). This series elegantly demonstrated that the initial landing zone for lymphatic metastases from right-sided tumors is typically the interaortocaval nodes, followed by the precaval and preaortic nodes. Primary deposits of metastatic disease from left-sided tumors involved the para-aortic and preaortic nodes, followed by the interaortocaval nodes [16].

Weissbach et al. provided support to these studies with a pathologic review of 214 consecutive patients from multiple institutions undergoing bilateral RPLND, including the suprahilar region [17]. Among patients with pN1 disease, positive nodes were almost always ipsilateral, in the interaortocaval region for right-sided primaries and the para-aortic for left-sided tumors. Only 9 % of right-sided tumors and 6 % of left-sided tumors were associated with solitary metastases in atypical locations (i.e., suprahilar/preaortic for right side primary and precaval/interaortocaval for left side). Unfortunately, because clinical outcomes were not available in the first two studies [15, 16] and all patients with metastatic disease in the Weissbach study received chemotherapy [17], these mapping studies did not demonstrate the true rate and location of RP recurrences. Despite these important limitations, these anatomic studies led to common use of modified surgical templates, particularly for patients with clinical stage I disease.

Preservation of Antegrade Ejaculation

The RP neurologic structures responsible for antegrade ejaculation include the two paravertebral sympathetic trunks and the postganglionic sympathetic fibers, which travel dorsal to the inferior vena cava and ventral to the aorta (Fig. 2). These fibers converge in the hypogastric plexus on the anterior aorta just caudal to the origin of the inferior mesenteric artery (IMA) [18]. A more complete understanding of RP sympathetic neuroanatomy and the previously described anatomic mapping studies suggested two strategies for improving antegrade ejaculation rates following RPLND. One strategy to reduce the 65 %–90 % retrograde ejaculation rate following bilateral RPLND is to limit contralateral dissection and naturally preserve neural pathways contralateral to the primary tumor. This is the goal of modified dissection templates. An alternative strategy is the nerve-sparing approach, wherein the surgeon prospectively identifies, dissects, and preserves sympathetic nerves while maintaining the possibility of performing a full bilateral template.

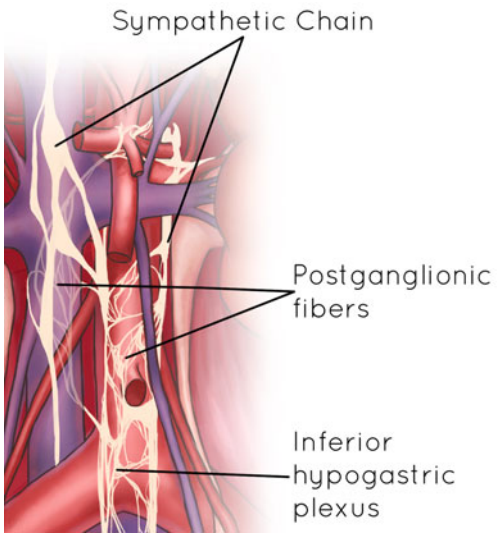

Fig. 2 Retroperitoneal neuroanatomy

Development of Modified Templates and Nerve-Sparing RPLND

Various side-specific modified templates for patients with low-stage NSGCT were subsequently proposed. They all included the ipsilateral lymph nodes inferior to the renal hilum extending caudally to the bifurcation of the common iliac artery. Right-sided templates invariably must include the interaortocaval region, due to the relatively high incidence of metastatic disease in this region (Fig. 1). The final common theme in the modified templates was avoidance of dissection in the region of the contralateral sympathetic trunk and eliminating contralateral dissection below the IMA.

IU published much of the seminal literature describing modified templates for RPLND. They initially described the extended bilateral suprarenal RPLND though a midline transabdominal approach in 1977 [14]. The first modification was elimination of the suprahilar dissection based on previous anatomic mapping studies. Subsequent series of bilateral infrahilar RPLND confirmed equivalent efficacy with shorter operative time and less perioperative morbidity through this approach [16]. Beginning in 1981, Indiana began employing a modified unilateral RPLND template for patients with clinical stage I disease (Fig. 1, Table 1) [19••]. Indiana's modified template for right-sided tumors included the paracaval, precaval, interaortocaval, preaortic, right-iliac, and right-gonadal regions. The template for left-sided tumors included the para-aortic, preaortic, interaortocaval, left-iliac, and left-gonadal regions (Fig. 1, Table 1). These templates preserved antegrade ejaculation in about 90 % of patients without any appreciable compromise of oncologic outcomes [19••].

Concurrently, in 1988, Jewett et al. described the feasibility and effectiveness of a nerve-sparing RPLND for preservation of antegrade ejaculation. They reported a series of 30 consecutive patients, of which nerve sparing was technically feasible in 20. Of the 20 patients, 18 (90 %) were able to ejaculate normally, and there was no increased risk for recurrence at a median follow-up of 19 months [20]. Donohue et al. at IU also demonstrated acceptable oncologic outcomes and 100 % preservation of antegrade ejaculation, utilizing a similar nerve-sparing approach in a series of 75 patients [21].

On the basis of anatomical mapping data from 214 patients, the Testicular Tumor Study Group (TTSG) proposed side-specific templates designed to incorporate >95 % of metastases. These templates were very similar to the templates used at IU, aside from eliminating dissection in the interaortocaval and ipsilateral iliac regions for left-sided tumors (Fig. 1, Table 1) [17].

Other investigators also described their experience with modified templates. Pizzocaro et al. reported a unilateral lymphadenectomy in 61 consecutive patients with intraoperative stage I NSGCT between 1978 and 1981. The boundaries of dissection extended from the ipsilateral diaphragmatic crus to the inguinal ligament. This approach eliminated dissection of the para-aortic region for right-sided tumors and the interaortovacal, precaval, and paracaval regions for left-sided tumors (Fig. 1). While antegrade ejaculation was preserved in 82 % of patients, 15 % of pathologic stage I patients recurred, as compared with a 6 % recurrence rate observed at the same institution following standard bilateral RPLND. Additionally, 10 % of the patients thought to be stage I intraoperatively had evidence of microscopic metastases on final pathology [22]. The elevated relapse rates suggest suboptimal surgery or a limitation of the proposed template.

Richie et al. described a series of 85 patients with clinical stage I NSGCT who underwent RPLND between 1982 and 1989. A full bilateral dissection was performed above the IMA, with only a unilateral dissection inferior to the IMA (Fig. 1). Antegrade ejaculation was achieved in 94 % of the patients, with relapse in 6 % of pathologic stage I patients and 15 % of pathologic stage IIA patients at a median follow-up of 38 months [23].

To date, only one prospective trial has compared a modified template RPLND with bilateral RPLND in patients with pathologic stage I NSGCT. This was a multiinstitutional study with 168 patients undergoing a modified template dissection and 67 patients undergoing a full template dissection. No differences were found in relapse rates, RP relapse, and complications. A modified template was associated with an over twofold improvement in the rate of antegrade ejaculation (74 % vs. 34 %) [24]. This study does have significant limitations in that it was not randomized, only assessed pathologic stage I patients, included data from multiple centers and surgeons, and had higher recurrence rates and much lower ejaculation rates than would typically be seen by an experienced surgeon.

Role of Postchemotherapy RPLND

Postchemotherapy RPLND (PC-RPLND) is a crucial treatment modality for many patients with metastatic NSGCT. Indications for PC-RPLND are variable. Some have argued that all patients should undergo PC-RPLND because there are no reliable pre- or postchemotherapy clinical or radiologic parameters that can predict the presence of viable malignant GCT in RPLND specimens [25]. Alternatively, others have argued that patients with a complete radiographic response and normal serum tumor markers after chemotherapy can be observed, because the risk of recurrence in International Germ Cell Cancer Collaborative Group low-risk patients is ~5 % [26].

PC-RPLND is technically challenging and associated with higher peri-operative complication rates due to large residual masses and chemotherapy-related tissue changes [27]. A review of 472 patients undergoing PC-RPLND at IU between

1988 and 1995 demonstrated that nerve sparing can be performed in about 20 % of patients with low-volume residual disease without compromising recurrence rates. Nerve sparing in the postchemotherapy setting resulted in a 77 % rate of antegrade ejaculation [28]. In a more contemporary series, MSKCC reported a series of 341 patients between 1995 and 2005, with 40 % of all patients undergoing nerve sparing and antegrade ejaculation achieved in 79 % [6].

In order to further improve antegrade ejaculation rates, attempts have been made to apply modified templates to the PC-RPLND. A retrospective review of the IU testicular cancer database found that between 1991 and 2004, 10 % of patients undergoing PC-RPLND were deemed candidates for a modified template dissection if they had normal serum tumor markers and radiographic disease confined to the primary landing zone before and after chemotherapy. The template utilized was identical to the previously described side-specific templates from IU. Disease-free survival was 95 % at 2 and 5 years, and all relapses occurred outside the boundaries of a full bilateral RPLND [29]. Steiner et al. utilized modified templates in the postchemotherapy setting in 102 patients with an overall 98 % antegrade ejaculation rate, and there were only three recurrences at a median follow-up of 102 months [30]. These studies support feasibility and improved antegrade ejaculation rates with nerve sparing and modified templates in *highly select* patients undergoing PC-RPLND. Because patients with teratoma at PC-RPLND have a significant risk for late recurrence >2 years after surgery, more long-term data are necessary to support oncologic equivalence of modified templates in the postchemotherapy setting [31]. It is also essential to recognize that the selection of patients for modified template PC-RPLND represents a small proportion of all patients undergoing PC-RPLND and these series are from highly experienced centers.

Minimally Invasive RPLND

With the goal of reducing the morbidity associated with RPLND, several investigators have examined the role of laparoscopic RPLND (L-RPLND) in the management of clinical stage I/IIA and low-volume postchemotherapy residual disease. The approach has been shown to be technically feasible and has several advantages, including faster convalescence, better cosmetic outcomes, less blood loss, and shorter length of hospital stay, as compared with the open approach [32, 33].

Hyams et al. recently described their experience with 91 patients undergoing L-RPLND for clinical stage I NSGCT at Johns Hopkins University from 1995 to 2010. The authors performed a modified bilateral template dissection with nerve sparing unless there were abnormally enlarged nodes encountered during the operation, in which case a full bilateral template dissection was performed. This study was unique in that 66 % of patients with pN1 disease received adjuvant chemotherapy, significantly lower than rates in other L-RPLND series but notably higher than most open RPLND series. The blood loss, length of stay, and complication rates compared favorably to most open series. The recurrence rate for patients with pN0 disease was 8 %, with no recurrences in the retroperitoneum, and there were no relapses in the pN1 and pN2 cases [34•]. Unfortunately, no direct comparative trials have been performed, and in recent years, the morbidity, blood loss, and hospital stay associated with open RPLND has also significantly declined [35].

The oncologic efficacy of L-RPLND for clinical stage I NSGCT remains difficult to assess because most patients with positive nodes, regardless of tumor burden, receive chemotherapy after L-RPLND. A recent meta-analysis, which included 140 patients with positive nodes following L-RPLND, found that 90 % received adjuvant chemotherapy [36]. Indiscriminate use of chemotherapy is unnecessary in most patients with pN1 disease, since historical data have shown that 85 %–90 % of these patients are cured with surgery alone. There is a great deal of inconsistency in the literature with regard to performance of L-RPLND with diagnostic, as compared with therapeutic, intent. Additionally, L-RPLND is associated with lower node counts than an open RPLND. Node counts were lower in patients with pathologic stage II disease than in patients with pathologic stage I disease, potentially indicating a less extensive dissection in patients with more significant disease [37]. Concerns have also been raised about high rates of chylous ascites [38], heterogeneity with regard to the templates of dissection, extent of dissection, and unusual patterns of recurrence following L-RPLND. L-RPLND, which can be performed with or without robotic assistance, should not be considered standard. Its application should be limited to experienced minimally invasive surgeons in the setting of formal prospective study until more data are available.

Limitations of Modified Template RPLND

Modified template RPLND offers many advantages by limiting the extent of dissection, decreased operative times, and improved antegrade ejaculation rates. However, limited resection templates could potentially increase the risk of disease recurrence and necessitate further surgery or chemotherapy. A retrospective analysis of 500 patients at MSKCC undergoing bilateral infrahilar primary RPLND identified the anatomic location of metastases and RP recurrences [39•]. Five commonly utilized modified RPLND templates were then applied. Rates of extratemplate disease ranged from 1 % to 5 % for patients with clinical stage I tumors, 1 % to 11 % for pathologic stage IIA disease, 4 % to 25 % for left-sided primaries, and 2 % to 28 % for right-sided primaries. Resecting all of the

infrahilar nodes with exception of the contralateral iliac nodes would have decreased the rate of unresected disease to <3 %.

A similar study design was applied to patients who underwent PC-RPLND at MSKCC [40]. Of the 532 men who underwent PC-RPLND between 1989 and 2003, 269 had either viable GCT or teratoma present in the RPLND specimen. Depending upon the template utilized, 7 %–32 % of patients had evidence of extratemplate disease. The size of the residual RP mass on preoperative imaging was also associated with the incidence of extratemplate disease. Extratemplate disease was found in 8 % of men with a residual mass <1 cm, as compared with 25 % of men with a residual mass >5 cm. The most common sites for extratemplate disease were the interaortocaval and paracaval regions for left-sided primary tumors and the preaortic and para-aortic regions for right-sided primary tumors. Inclusion of all infrahilar nodal regions except for the contralateral iliac nodes again would have minimized the rate of extratemplate disease to 4 %.

These two studies suggest that modified templates may inadequately treat the retroperitoneum. This could increase risk for recurrence and subject them to further treatment, such as chemotherapy or reoperative RPLND. Modified templates can still be effectively applied to select patients with minimal risk of unresected extratemplate disease, including clinical stage I patients. Interestingly, the rates of extratemplate disease demonstrated in these two studies are much higher than clinical recurrence rates seen in trials of modified template RPLND. This could be explained by the natural history of recurrent disease. Only a proportion of unresected teratomas are capable of growth, and that growth can be at a very slow pace. This suggests that true recurrence rates likely lie somewhere between the underestimates provided by clinical trials and the overestimates from histological studies. It is feasible that long-term follow-up of patients after modified template RPLND will detect more recurrences. Additionally, many patients with unresected disease may be cured by overutilization of adjuvant chemotherapy.

The significance of unresected disease cannot be overstated. Patients with unresected viable GCT will invariably experience recurrence, leading to further treatment. Unresected RP teratoma can have a more indolent course, followed by dedifferentiation and aggressive local growth. Subsequent reoperative surgery is associated with poor outcomes. Late relapses most commonly occur in the retroperitoneum, are defined as occurring after a 2-year disease-free interval, and are associated with a 5-year survival rate of only 40 %–60 % [41]. Furthermore, many patients who experience relapse after RPLND will require cisplatin-based chemotherapy, which is associated with cardiovascular sequelae, high rates of peripheral sensory neuropathy, auditory damage, renal insufficiency, and an increased risk of secondary cancers [42]. Because the consequences of recurrence are so high, we must continue to critically assess the application of modified templates to ensure optimal oncologic control.

Conclusions

The traditional bilateral RPLND achieved optimal cancer control at the expense of near universal ejaculatory dysfunction. Surgical techniques evolved to optimize rates of antegrade ejaculation without impairing oncologic efficacy through modified template-based resections and prospective nerve sparing. Many centers now consider the modified unilateral template as the standard surgical approach for low-stage testicular cancer. However, evidence of nodal involvement intraoperatively should, in general, lead to a bilateral dissection. The standard of care for PC-RPLND remains a full bilateral RPLND, although there is evidence that a modified template can be considered in *highly select* patients with a small residual radiographic mass without compromising 2- and 5-year progression-free survival rates [29]. Nerve sparing can be performed with any resection template and results in favorable antegrade ejaculation rates.

While intermediate term outcomes for patients undergoing modified template RPLND in the primary or postchemotherapy setting appear favorable, longer term follow-up and larger cohorts are necessary to assess recurrence rates, especially in patients not receiving adjuvant chemotherapy. Similarly, longer term follow-up is needed to assess outcomes following minimally invasive RPLND.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Shane Pearce, Zoe Steinberg, and Dr. Scott Eggener reported no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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