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Robotic Primary RPLND for Stage I Testicular Cancer: a Review of Indications and Outcomes

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Abstract Patients diagnosed with stage I non-seminomatous germ cell tumor (NSGCT) face the task of selecting a management strategy. Whereas these options all offer excellent survival, unfortunately, each has drawbacks. Retroperitoneal lymph node dissection (RPLND) is a major operation with low, but significant risks of bleeding, chylous ascites, and retrograde ejaculation. Platinum-based chemotherapy is associated with a number of long-term side effects, not all of which are quantified, but include secondary malignancy and early cardiovascular disease. While surveillance minimizes the chances of exposure to unnecessary treatment, it is not infrequently salvaged with chemotherapy and requires a compliant patient willing to undergo serial imaging often with ionizing radiation. Although fewer than one-third of patients will relapse without intervention, the current guidelines propose treatment for stage I patients with high-risk features. New developments in minimally invasive techniques may mitigate the harms of RPLND and avoid the side effects of chemotherapy, making it an ideal option for this cohort of patients. Unlike laparoscopic RPLND, which was introduced as a staging procedure and heavily criticized for the advanced skill set required to achieve oncologic equivalence, robotic RPLND may offer the benefits of a minimally invasive technique without a steep learning curve and a true therapeutic operation in experienced hands.

Keywords RPLND · Robotics · Minimally invasive · Testis cancer

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Introduction

Germ cell tumors (GCTs) comprise 95 % of malignant neoplasms arising in the testicle and are the most common solid tumor found in men aged 20 to 34 years [1, 2]. In fact, the incidence of testicular GCTs is increasing [3–6]. Fortunately, only 10–30 % of men will present with distant disease [7]. GCTs can be further classified as seminoma or nonseminoma, which differ in terms of histology, serum tumor markers, metastatic potential, and management options [1]. For instance, non-seminomatous GCTs (NSGCTs) are believed to be more aggressive and are often treated with chemotherapy or surgery, while seminomas are often effectively treated with chemo- or radiotherapy [1]. For patients with clinical stage I NSCGTs, there are three main treatment options to consider: surveillance, platinum-based chemotherapy, and retroperitoneal lymph node dissection (RPLND) [1, 8].

Today, laparoscopic and robotic RPLND (L-RPLND, R-RPLND) are both options for minimally invasive management of stage I NSCGTs and are offered primarily in high-volume academic centers. While proponents hope to distinguish robotic RPLND as superior to laparoscopy, even if only in terms of the requisite learning curve, limited data exist to support this claim. In the following review, we describe the available published outcomes of R-RPLND that exist to date.

RPLND Versus Surveillance

For those considering surveillance as a management option, the risk of recurrence is a major concern. A contemporary surveillance cohort revealed a 5-year relapse rate of 30.6 % [9•]. Further, for patients without known high-risk features such as lymphovascular invasion (LVI), the recurrence rate was only 12 % [9•, 10]. Based on these outcomes, the authors promote surveillance to avoid overtreatment for the majority of patients. Yet, others interpret the numbers differently and recommend primary treatment with RPLND to provide definitive pathology and avoid salvage chemotherapy (see below for discussion on chemotherapy).

There are a number of benefits to primary RPLND in the management of clinical stage I NSGCT. These include local control of the retroperitoneum, complete staging, and removal of any chemo-resistant tumor elements. Traditionally, primary RPLND is performed through an open, midline approach. The risk of abdominopelvic recurrence after primary RPLND is extremely low (2 %) when done at an experienced center, and while recurrent cancer is effectively salvaged with chemotherapy, cure rates are high for patients with N1 disease without chemotherapy [11]. Downsides include peri- and post-operative complications and ejaculatory dysfunction due to injury to the sympathetic nerves as they course around the great vessels. In centers of excellence, the risks of excessive blood loss, bowel obstruction (1 %), chylous ascites (0.4 %), other visceral injuries, and long-term convalescence can be minimized [11, 12, 13•, 14–17]. In addition, template-based and nerve-sparing techniques preserve antegrade ejaculation in approximately 75 and 90 % of men, respectively [11, 12]. This involves active identification of the sympathetic chain and hypogastric plexus and avoiding electrocautery in these areas [18].

Furthermore, proponents note that criticisms of open RPLND derive primarily from historical complication data. One contemporary 2014 series of open RPLND reported a complication rate of just 9 % and length of stay (LOS) of only 4 days [19]. What is clear is that if the complications of surgical management could be minimized, this would obviate much of the discussion on the optimal modality for stage I non-seminomas. Laparoscopic RPLND was introduced to accomplish this, citing small incisions, shorter hospital stay, and decreased blood loss, but initially faced heavy criticism as oncologically inferior [20].

Surveillance does offer an excellent survival outcome for clinical stage I NSGCTs, exceeding 95 % [21]. The problem is that many patients on surveillance do go on to progress and then may suffer the side effects of chemotherapy. Recently published 5-year progression-free survival rates were 74.1 % for surveillance, as compared to 92.3 % for chemotherapy, and 100 % for RPLND [10]. In this series, risk factors for progression on multivariable analysis included patient age, cryptorchidism, and LVI. Interestingly, a 2011 SEER population study found the use of RPLND for stage I NSGCTs had decreased over time from 39 % in 1988–1995 to 18 % in 2004–2006 [22]. This may be secondary to the preference for surveillance for stage IA disease based upon the most recent NCCN guidelines [1].

While surveillance avoids overtreatment for many patients, it necessitates a significant radiation burden due to follow-up imaging. The current NCCN guidelines call for a total of nine abdominal (plus minus pelvic) CTs over 4 years of surveillance for stage IB [1]. Looking at this, a 2009 study compared the surveillance protocol to the radiation of a single scan after RPLND [23]. Strikingly, they found that the relative risk of a secondary malignancy is 15.2, with a lifetime cancer risk of 1–2 %. More recently, a study from Columbia University revealed that this is still a problem, finding that in excess of 75 % of testicular cancer patients in surveillance for 5 years exceeded standard safety limits for radiation exposure [24]. Additionally, compliance with frequent follow-up may be an issue in this young and often mobile population of patients.

RPLND Versus Chemotherapy

In general, GCTs are very susceptible to platinum-based chemotherapy, making this a useful management option to have available, especially for patients with advanced disease [25]. However, as previously stated, stage I NSGCTs are associated with excellent survival in excess of 95 % [21]. Chemotherapy has many serious negative consequences, which is the reason why many in the United States feel it is inappropriate for stage I disease and why it is not an option for stage IA disease according to the NCCN guidelines [1]. Specifically, there are associations with secondary malignancies and cardiac risks [23, 26]. In fact, a quarter of patients treated with cisplatin-based chemotherapy will have sub-clinically impaired renal function, and in one study, a statistically significant 2.59 (95 % CI 1.15 to 5.84; $P = .022$) relative risk of having a cardiac event [26, 27]. Furthermore, patients with the teratoma subtype of NSGCT will receive no benefit from chemotherapy, due to its chemo-resistant nature [28]. Notably, there is some evidence that chemotherapy may be superior to RPLND. One study randomnized clinical stage I NSCGT patients to one cycle of chemotherapy versus RPLND, and they found a statistically significant improvement in 2-year recurrence-free survival from 91.87 % with RPLND to 99.46 % for chemotherapy [29].

Laparoscopic RPLND

At its inception, L-RPLND was very controversial, and in early adaptations, this technique was used simply as a staging procedure [30, 31]. There was no retrocaval or retroaortic dissection, and the case was often aborted if disease was encountered [28, 30–32]. Over time, this changed, and the goal of L-RPLND was to perform an oncologically equivalent dissection to its open counterpart [28, 33, 34]. There have been no randomized controlled trials of open versus L-RPLND, yet in many retrospective series, the minimally invasive method has been shown to offer a shorter hospital stay, less blood loss, and shorter convalescence [16, 20, 28, 35–38] Table 1.

One systematic review of L-RPLND included more than 800 patients from 34 series spanning 1992–2008, with 63-month follow-up. The complication rate was 15.6 %, with 2 % retrograde ejaculation. In fact, OR time was longer than open RPLND, at 204 min (versus 186 min, $P < 0.05$). They found no difference in oncologic outcomes compared to open surgery, with local relapse of 1.4 % and distant relapse rate 3.3 % [14]. Yet, critics say that contemporary open series have similar outcomes, with one group demonstrating a 7 % complication rate for primary RPLND, with operative time 188 min [20]. Other comparisons investigated in the metaanalysis include length of stay, which was shorter at 3.3 days for laparoscopic vs 6.6 days for open surgery, and on sub-analysis of the most contemporary series, laparoscopic patients required 33–50 % less analgesic than their open surgery counterparts [14].

Robotic RPLND

Robotic RPLND was first described in a case report from 2006 [39]. Since, the body of literature encompasses several small case-series (Table 1). An early three-patient series published in 2011 by Williams et al. reported a 2-day length of stay, zero perioperative complications, and lymph node count of 25 [19]. As was the case for laparoscopic RPLND, the first major hurdle to overcome for the robotic modality is demonstrating equivalence. In 2015, Harris et al. published the first comparative analysis of robotic and laparoscopic RPLND to evaluate perioperative outcomes and safety [40••]. In this single-surgeon series of 16 R-RPLND and 21 L-RPLND, equivalence was found in terms of operative time, blood loss, lymph node yield, and ejaculatory status [24]. Still, it remains to be demonstrated that R-RPLND offers a specific benefit over L-RPLND.

Most notably, a recent multi-institutional experience combining data from four centers was presented, with a total of 56 patients [41••]. Estimated blood loss was only 50 mL, and median length of stay was just one day. There was one open conversion (2 %) and a 9 % perioperative complication rate. Antegrade ejaculation was preserved in 96 % of patients. Importantly, this series also contains oncologic outcomes: With 15-month median follow-up, the recurrence-free rate was 98 %.

While direct comparative evidence across modalities is limited, proponents of R-RPLND would put forth that it offers the benefits of minimally invasive surgery without demanding an advanced skill set. In the first report of R-RPLND by Davol et al. in 2006, the authors justified their novel approach by citing the advanced skill set necessary to adequately perform an L-RPLND, and need for alternatives [39]. In general, it is accepted that robotic surgery has a faster learning curve than laparoscopic surgery [42]. Still, any RPLND represents a challenging operation that should be performed in high-volume centers of excellence for optimal results. In addition to primary RPLND, post-chemotherapy RPLND is another arena where robotic RPLND is emerging. Though expected to be technically more difficult, post-chemotherapy R-RPLND is feasible. From the Mayo Clinic, a series of 18 patients had zero major complications, and 15 of 18 were able to be completed robotically [13•].

With increasing scrutiny of health care spending, a cost comparison of surgical modalities is prudent. While information specific to RPLND is limited, this topic has recently been addressed in the setting of robotic nephrectomy. One group performed model-based cost analysis, assuming 55 % higher costs for patients who suffered surgical complications related to open surgery [43]. With this assertion, robot-assisted partial nephrectomy was cost-effective by virtue of its ability to prevent additional complications. Separately, a more concrete analysis was performed based on the Maryland Health Services Cost Review Commission total hospital charge to patients [44]. Interestingly, robotic partial nephrectomy was less expensive than laparoscopic partial, while robotic radical was more costly than laparoscopic partial. Granularly, savings for robotic partial nephrectomy were due to decreased room and board charges. More study is needed specifically for RPLND, but clearly length of stay and complication rate are important drivers of cost, which may offset the price tag of newer surgical technologies.

Robotic RPLND Technique

At our institution, a transperitoneal approach is performed, and nerve-sparing is based upon surgeon preference. A modified node dissection template is used as previously described [12, 45–47]. Ports include a 12-mm camera port, three robotic ports, and additional ports for liver retraction and the assistant. Two positioning methods are used, dorsal lithotomy and flank position with a slightly flexed bed. For dorsal lithotomy, the patient is placed in Trendelenburg, and the robot is docked over the left shoulder. First, the colon is mobilized, and a two hitch stitches are used to tack the peritoneum to the anterior abdominal wall, exposing the retroperitoneum. For the nodal dissection, the superior border is the renal hilum and laterally, the ureter. The gonadal vein is also removed. For left templates, separate nodal packets removed include the left common iliac, pre-aortic, para-aortic, and retroaortic. Occasionally, interaortocaval nodes are removed. For right

Table 1 Perioperative outcomes of notable series of open, laparoscopic, and robotic RPLND

Modality	Year	Group	Number	EBL (mL)	Operative time (min)	Lymph node count	Complication rate (%)	LOS (days)	Recurrence rate (%)	Antegrade ejaculation (%)	Follow-up time (months)
Open	2010	Williams [19]	190	294	206	–	9	4	–	–	–
Open (metaanalysis)	1992–2008	Rassweiler [14]	524	–	186	19	33	6.6	1.3 (RP) 3.3 (distant)	–	63
Laparoscopic (metaanalysis)	1992–2008	Rassweiler [14]	499	–	204	14	15.6	3.3	1.4 (RP) 3.3 (distant)	–	63
Laparoscopic	2005	Albquami [16]	162	144	217	–	2.5	3.6	1.2 (RP) 2.5 (distant)	–	5
Laparoscopic	2006	Abdel-aziz [36]	22	159	313	17	18.2	1.2	4.5	–	12
Laparoscopic	2008	Steiner [34]	42	–	323	–	0 (intraop)	–	0 (RP) 2.4 (distant)	85.7	17.2
Laparoscopic	2011	Gardner [37]	59	184	291	21.6	8.5	–	1.7	–	21.3
Laparoscopic	2012	Hyams [38]	91	200	–	26.1	4.3 (intraop) 9.8 (postop)	2.1	5.5 (distant)	95.7	38.0
Laparoscopic	2015	Harris [40••]	21	125	294	22	0	–	–	76.2 (unknown in 14.3)	2.8
Robotic	2015	Harris [40••]	16	75	270	30	6.3	–	–	100	13.5
Robotic	2011	Williams [19]	3	150–200	150–240	25	0	2	–	–	–
Robotic	2015	Pearce [41••]	56	50	239	24	4	–	2	96	15
Robotic (post-chemo)	2015	Cheney [13•]	18	103	329	22	0 (major) 17 (minor)	2.4	0 (RP) 12 (distant)	91	22

EBL estimated blood loss, *RP* retroperitoneal templates, right common iliac, paracaval, precaval, retrocaval, interaortocaval, and pre-aortic nodes are sent separately.

Conclusion

Patients with clinical stage I NSGCT have a number of excellent management options, each with benefits and side effects. Robotic RPLND offers patients the opportunity to avoid the long-term side effects of chemotherapy, and for patients undergoing surveillance, it obviates the need for serial imaging with ionizing radiation and the anxieties related to surveillance. With promising early oncologic outcomes and improved perioperative outcomes, robotic RPLND may offer a truly effective management strategy for men with early stage NSGCT.

Compliance with Ethical Standards

Conflict of Interest Heather J. Chalfin, Wesley Ludwig, Phillip M. Pierorazio, and Mohamad E. Allaf each declare no potential conflicts of interest.

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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•• Of major importance

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