Anita Philyaw. *Conversation in Key* (detail), 1999. Acrylic on canvas, 48″ × 34″.
Courtesy of Stella Jones Gallery, New Orleans, La.

The current indications for retroperitoneal lymph node dissection in the therapy of testicular cancer are reviewed.

Current Status of Retroperitoneal Lymph Node Dissection and Testicular Cancer: When to Operate

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Background: *Historically, retroperitoneal lymph node dissection (RPLND) has been used in the therapy of both low-stage and high-stage testicular cancer after chemotherapy. As other therapies have developed, the role of RPLND has also evolved.*

Methods: *The authors review the current indications for RPLND in the therapy of testicular cancer.*

Results: *Metastatic testicular cancer can be cured in 50% to 75% of cases by surgical removal using RPLND, depending on the volume of metastasis. In postchemotherapy disease, the surgical removal of teratoma or carcinoma also confers a therapeutic benefit to the patient.*

Conclusions: *The therapeutic capability of RPLND in low-stage testicular cancer is underappreciated. In postchemotherapy disease, this therapeutic capability is retained if the patient has carcinoma or teratoma in the metastatic tumor. In postchemotherapy disease, efforts continue to appropriately select patients preoperatively who have only fibrosis and necrosis in the specimen and therefore do not derive therapeutic benefit from RPLND.*

Introduction

It is well recognized that cisplatin-based chemotherapy is highly effective in the treatment of metastatic testicular cancer. Indeed, the development of cisplatin-based chemotherapy was one of the great success stories in the treatment of metastatic cancer.[1] Clearly, testicular cancer is one of the most chemosensitive tumors.

Metastatic testis cancer is also highly amenable to curative surgical therapy. Most cancers are, in fact, sys-

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temic when spread to a lymph node is noted and verified. Therefore, the removal of involved lymph nodes is not curative in most cancers as the majority of these patients have distant micrometastatic disease. Testicular cancer is different in this regard. The spread of testis cancer is by and large predictable and sequential; hence, the surgical removal of metastatic tumor is curative 30% to 75% of the time depending on the clinical situation, site of metastasis, and volume of metastatic disease.[2]

Testis cancer is not only one of the most chemosensitive tumors, but also one of the most "surgery-sensitive" tumors. This review discusses the indications and outcome of retroperitoneal lymph node dissection (RPLND) in the therapy of testis cancer, and it enumerates the indications for surgical therapy on a stage-by-stage basis. The discussion of surgical therapy is relevant for nonseminomatous disease; the few indications for surgery in metastatic seminoma are discussed separately.

RPLND in Low-Stage Disease

Clinical Stage I

After radical inguinal orchiectomy for a solid intratesticular mass, the patient undergoes a staging workup that includes determination of serum alpha fetoprotein (AFP), beta human chorionic gonadotropin (hCG), and computed tomography (CT) scans of the abdomen, pelvis, and chest. If the CT scans are normal and the markers normalize after radical inguinal orchiectomy or, alternatively, are falling appropriately based on the half-life of AFP of 4½ days and beta hCG of 1½ days, the patient is classified as having clinical stage I disease.[3] Approximately 30% of patients who are clinical stage I, in fact, have occult metastatic disease.[4] Patients in this circumstance are managed by either surveillance or nerve-sparing RPLND. No prospective randomized trial has compared these two methods of management, but many series of RPLND and surveillance from around the world have shown that the chance for cure is essentially the same with either method of management and is approximately 99%.[5,6]

The surveillance scheme employs a careful paradigm of follow-up using chest radiographs, physical examinations, marker determinations, and CT scans in order to diagnose those patients with metastatic disease early when the tumor burden is low. Patients who are found to have growing metastatic tumor are then managed with cisplatin-based chemotherapy, with approximately one third of patients who are treated with chemotherapy requiring subsequent postchemotherapy RPLND.[7] The major advantage of a surveillance approach is that patients who have no metastatic disease undergo no therapy, and patients diagnosed with metastatic tumor are treated appropriately with cisplatin-based chemotherapy. Disadvantages of the surveillance scheme include the psychological burden on the patient, the higher probability of receiving chemotherapy compared to management with RPLND, and a higher probability of patients requiring postchemotherapy RPLND, a procedure with higher morbidity than primary RPLND.[8]

The advantages of managing a patient with clinical stage I nonseminoma with nerve-sparing RPLND include the immediate determination of whether metastatic retroperitoneal tumor exists, the chance for cure with surgical removal of involved lymph nodes of 50% to 75% (depending on the volume of metastasis), and the elimination of the need for monitoring a patient postoperatively with CT scans. Additionally, the initial follow-up after RPLND is only 2 years, whereas the follow-up requirement after surveillance is at least 5 years.

As surgical therapy for metastatic testicular cancer has evolved, the full bilateral RPLND used in the past evolved first to a template-type dissection and then to a nerve-sparing modification with a unilateral template (Fig 1). The evolution of this procedure has resulted in low acute and long-term morbidity.[9,10]

For patients with a right-sided testicular primary, right modified nerve-sparing RPLND is performed by first dissecting the efferent sympathetic fibers that control emission and ejaculation, followed by a template removal of lymphatic tissue in the right paracaval, precaval, and interaortocaval areas (Fig 2). This removal of lymphatic tissue is an en bloc removal and not a "node

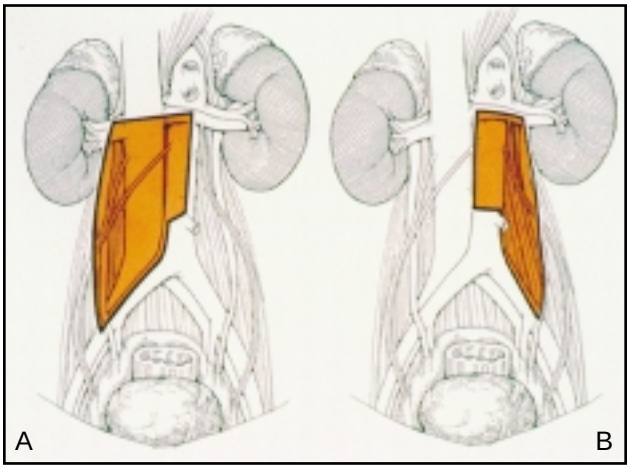

Fig 1. — The templates of dissection for a right-sided (A) and left-sided (B) testicular primary. Reprinted with permission from the Indiana University Office of Visual Media.

plucking" removal of involved lymph nodes. Careful removal of involved lymph nodes is important since testis cancer has the capability of implanting intraperitoneally if tumor is spilled at the time of the procedure.

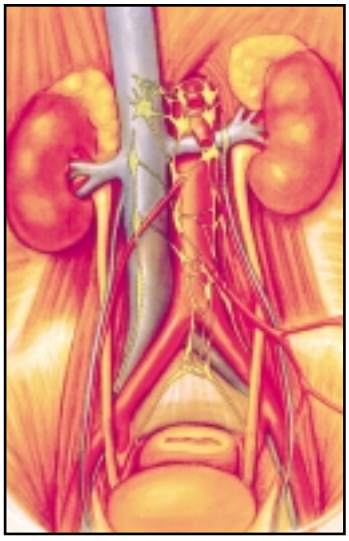

Fig 2. — The anatomy of retroperitoneal sympathetics shown in relation to the aorta and vena cava. Reprinted with permission from the Indiana University Office of Visual Media.

For patients with a left-sided primary, left modified nerve-sparing RPLND is performed by first dissecting efferent sympathetic fibers from the left side of the retroperitoneum, followed by en bloc removal of lymphatic tissue in the left para-aortic and pre-aortic areas.

The modified nerve-sparing RPLND is performed through a midline incision. At our institute, the current operative time is approximately 2 hours and the hospitalization is about 3½ days. Transfusions are not necessary, and the long-term morbidity includes a 1% to 2% chance of a small bowel obstruction due to adhesions and a less than 5% chance of an incisional hernia. Return to full physical activity is possible in 3 to 6 weeks.

The chance for cure with removal of involved lymph nodes is 50% to 75%.[4,11] Patients with minimal microscopic spread to the retroperitoneum are cured at the 75% level; those with more significant involvement experience surgical cure approximately 50% of the time. Patients who recur after RPLND are usually found to have either serologic recurrence with elevation of hCG or AFP, or documentation of chest metastasis on chest radiograph. These patients are curable at the 99% level with three courses of bleomycin, etoposide, and cisplatin (BEP) or four courses of etoposide and cisplatin.[12] An option for patients who undergo modified nerve-sparing RPLND and are found to have metastatic retroperitoneal nodes is to administer two courses of BEP postoperatively as an adjuvant.[13] This lowers the chance of recurrence after RPLND to less than 1%. This approach was developed in the late 1970s and 1980s to avoid administering the third and fourth courses of chemotherapy. During that era, the morbidity of chemotherapy was significantly greater, with many patients experiencing severe problems with nausea, vomiting, and granulocytopenia. Therefore, avoiding the third and fourth course of chemotherapy was desirable to reduce the morbidity of therapy. Currently, however, with the availability of better antiemetics and growth factors, the current three courses of chemotherapy are not associated with as high a morbidity as in former times. Therefore, the rationale for adjuvant chemotherapy in patients found to have retroperitoneal metastasis is not as strong. Currently, patients who are found to have retroperitoneal metastasis are given the choice of close follow-up or two courses of adjuvant BEP. The choice is dependent on the patient's opinion about receiving or avoiding chemotherapy. A discussion of the possible acute and long-term side effects of chemotherapy with the patient is imperative in this situation. Psychological issues are also important in this process.

Patients with clinical stage I nonseminoma who choose nerve-sparing RPLND as a method of management usually cite fertility issues as one reason for their choice. Systemic chemotherapy can affect spermatogenesis in the contralateral testis, and since nerve-sparing preserves emission and ejaculation, some patients will opt for surgical therapy in an effort to avoid chemotherapy.[14] Also, testis cancer chemotherapy has been associated with long-term side effects, and patients may want to avoid chemotherapy for these reasons also.[15] Psychological issues are important as some patients find it difficult to have a good quality of life on a surveillance scheme while worrying about disease recurrence. Finally, the follow-up after nerve-sparing RPLND does not involve CT scans, and some patients will choose surgical therapy in an effort to avoid such intense and prolonged follow-up.

Clinical Stage II

Patients who have nonseminomatous testis cancer and have evidence of retroperitoneal metastasis on CT scanning are classified as having clinical stage II disease. Similar to clinical stage I disease, two methods of management are available, each yielding a chance for cure of greater than 95%. The first approach is to administer systemic cisplatin-based chemotherapy, with approximately one third of such patients requiring RPLND after chemotherapy. The second approach is to perform a primary RPLND to remove metastatic nodes in the retroperitoneum, with approximately one third of patients requiring chemotherapy after primary RPLND due to systemic recurrence.[11]

The advantage of treating clinical stage II patients with primary chemotherapy is that some will experience a clinical complete remission and thereby avoid any surgical therapy. All such patients, however, receive three or four courses of chemotherapy and are exposed

to the potential side effects of the therapy. In testis cancer, there is the potential for clinical overstaging; 15% to 23% of patients who are believed to have retroperitoneal tumor on CT scanning in fact have no metastatic tumor to the retroperitoneum if managed by RPLND.[11] If all such patients are managed with primary chemotherapy, some will receive chemotherapy that they do not require. Another disadvantage of managing patients with primary chemotherapy is that one third of such patients will require postchemotherapy RPLND, usually for teratomatous elements in the retroperitoneum. Teratoma is not sensitive to chemotherapy and requires surgical removal. As mentioned previously, postchemotherapy RPLND has higher acute morbidity than does primary RPLND. Similarly, nerve-sparing is not as appropriate or technically possible in postchemotherapy RPLND compared to primary RPLND. Therefore, postchemotherapy RPLND is associated with a higher probability of loss of emission and ejaculation.

Patients with clinical stage II nonseminoma who are managed with primary RPLND usually undergo full bilateral RPLND instead of a template-type dissection. The rationale for this is that previous studies have shown that with increasing volumes of retroperitoneal metastasis, the probability of having disease bilaterally in the retroperitoneum is higher. The chance for a surgical cure in these patients ranges from 50% to 75%, depending on the amount of retroperitoneal spread.[4,11] In most clinical stage II patients, nerve-sparing is possible and thus preservation of emission and ejaculation is possible (Fig 3). After RPLND for stage II disease, patients are followed with physical examination, chest radiograph, and determination of serum tumor markers in order to diagnose recurrence. As noted, approximately one third of patients who are treated with RPLND for clinical stage II nonseminoma will experience a recurrence. These recurrences are usually pulmonary or detected by rising serum AFP or beta hCG. Virtually all of these patients with recurrence are curable with three courses of BEP.

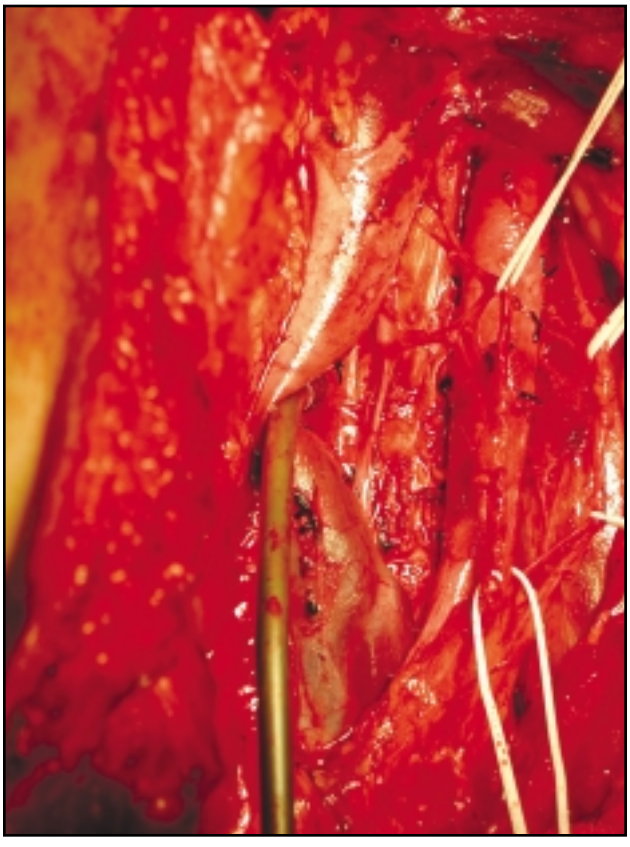

Fig 3. — Intraoperative photo of full bilateral RPLND with bilateral preservation of sympathetic fibers.

Similar to clinical stage I patients who are found to be pathologic stage II, clinical stage II patients may be offered two adjuvant courses of BEP after RPLND. Again, this approach virtually eliminates the probability of recurrence and therefore is reasonable in selected patients. However, there is no *requirement* for administering two courses of BEP after RPLND for stage II disease since, as noted above, 50% to 75% of patients are cured by surgical therapy alone.

Laparoscopic RPLND

With increasing use of laparoscopic techniques, several centers from around the world have begun to investigate the feasibility of laparoscopic RPLND.[16,17] As in other indications, these series have shown that there is a learning curve but that laparoscopic RPLND appears to be technically feasible. In these published series, sometimes variations on the open technique are employed. For instance, some investigators believe that dividing the lumbar arteries and veins is not necessary, and some feel that nerve-sparing techniques are similarly not mandatory. The presumed advantage of laparoscopic RPLND is a quicker return to full physical activity.

What is consistent in these varied series, however, is that when metastatic disease is found in the retroperitoneum adjuvant chemotherapy is universally given. Therefore, these laparoscopic series have not really tested the therapeutic capability of removing involved nodes. Instead, laparoscopy is used as a staging technique, with all patients found to have metastatic disease receiving either two or three courses of BEP. Predictably, the oncologic outcome is excellent since all patients with metastatic disease are given chemotherapy.

The rationale for such an approach is unclear. As noted, the morbidity of chemotherapy to a large degree relates to effects on spermatogenesis in the contralat-

eral testis. If a patient is willing to accept this potential morbidity and treat metastatic disease with chemotherapy (as opposed to surgical removal), it is unclear why a patient would elect laparoscopic RPLND as a staging procedure and then receive two or three courses of chemotherapy. Since the results of surveillance are excellent, why would a patient who has no disincentive to receive chemotherapy simply elect surveillance and thereby avoid any sort of surgical procedure? Currently, patients at our institute who elect to treat any metastatic tumor with chemotherapy are followed on a surveillance regimen. Similarly, patients who want to avoid chemotherapy will be advised to undergo nerve-sparing RPLND followed by observation if metastatic disease is present.

If laparoscopic RPLND could be shown to have an equivalent therapeutic value as a conventional curative surgical procedure and if it had lower morbidity and a quicker return to full physical activity, there would be little reason to continue with open RPLND. However, since the "bar is set relatively high" for open RPLND in terms of its oncologic efficiency and long-term outcome, the standard in terms of therapeutic capability should be set at a similar height for a laparoscopic RPLND. Laparoscopic surgeons who wish to employ RPLND can test its therapeutic capability if, after a patient is found to be pathologic stage II at RPLND, no postoperative chemotherapy is given. Thereby, the therapeutic capability as a curative surgical procedure of laparoscopic RPLND would be tested. Whether this will be done remains unclear.

RPLND After Chemotherapy

Standard Postchemotherapy RPLND

Patients who are clinically staged and found to have higher volume metastatic disease are managed with systemic chemotherapy. The rationale for this approach is that in patients who have retroperitoneal tumors greater than 10 cm in diameter, the chance for cure with surgical removal alone is less than 50%, and therefore systemic chemotherapy is reasonable.[3] Patients who have metastasis to the lungs or mediastinum in addition to retroperitoneal tumor are not cured with surgical therapy only, and systemic chemotherapy is appropriate in these circumstances as well.

Chemotherapy for so-called good-risk disease includes either three courses of BEP or four courses of etoposide and cisplatin.[3] In nonseminoma, good risk disease generally includes those patients with pulmonary visceral metastasis or nonmediastinal primaries, and those who do not have excessively high levels of serum AFP and beta hCG. Patients who are managed in this fashion will normalize serum tumor markers and experience the disappearance of all radiographic tumor approximately 70% of the time. The other 30% will experience normalization of serum markers but have persistent retroperitoneal, mediastinal, or pulmonary tumor (Fig 4).

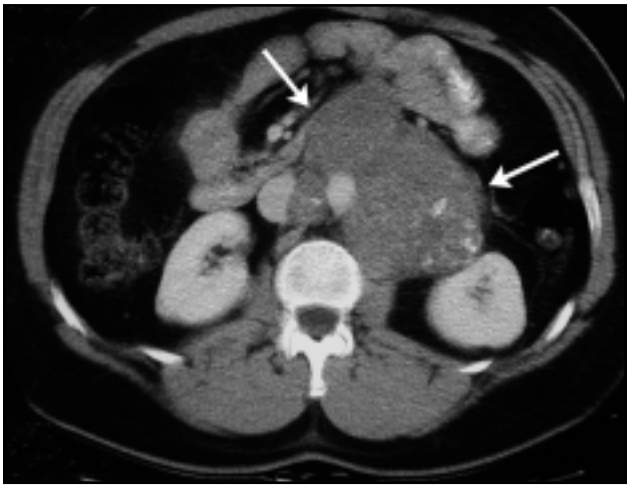

Fig 4. — CT scan showing residual retroperitoneal tumor after chemotherapy at the level of the lower pole of the kidneys.

Patients who normalize serum markers but have persistent radiographic tumor undergo postchemotherapy surgery. This is usually a postchemotherapy RPLND since, in most cases, these patients have persistent tumor only in the retroperitoneum. The rationale for removing this residual tumor is threefold. First, an accurate determination of the histologic makeup of the tumor is quickly obtained, which in the case of persistent cancer allows the more expeditious administration of additional chemotherapy. Second, the surgical removal of residual teratoma is therapeutic. Removing residual teratoma is important since if not removed, teratoma can degenerate into other types of cancer that are generally chemoresistant. Residual unresected teratoma can grow and merely by its bulk can lead to intraperitoneal organ dysfunction. Third, in some cases, residual germ cell cancer remains, and the surgical removal of this cancer may be therapeutic.

After primary chemotherapy, if postchemotherapy RPLND is performed, the histologic findings of the mass generally will consist of necrosis 45% of the time, teratoma 45% of the time, and persistent germ cell cancer approximately 10% of the time.[18] The removal of teratoma or cancer may be therapeutic, while the removal of necrosis confers no therapeutic benefit to the patient. Many studies from around the world have attempted to accurately predict those patients who have only fibrosis and necrosis based on generally available clinical parameters.[19] Unfortunately, this pre-

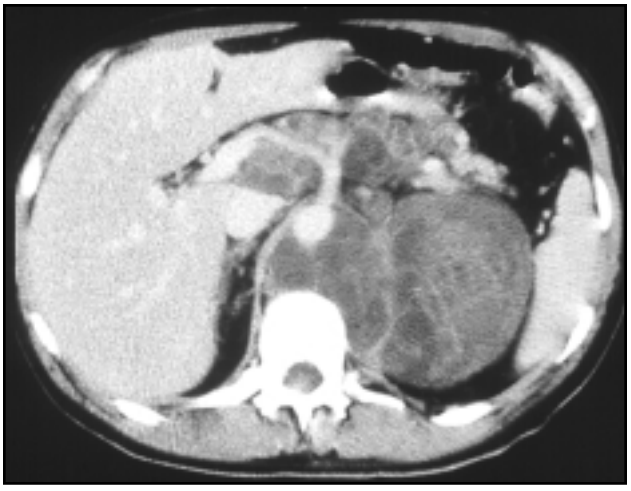

Fig 5. — Residual teratoma after chemotherapy in the upper left periaortic, retrocrural, and precaval.

dictability is not high enough to reliably exclude patients from postchemotherapy RPLND. Therefore, postchemotherapy RPLND is indicated in any patient who has residual radiographic tumor with normalization of serum markers after chemotherapy.

As noted previously, the morbidity of postchemotherapy RPLND is higher than the morbidity of primary RPLND. Acute postoperative problems include ileus, a higher probability of requiring concomitant nephrectomy or vena cavectomy, bleomycin-induced pulmonary problems, and a lower probability of maintaining emission and ejaculation. Some of these postchemotherapy procedures are technically demanding due to tumor bulk, the position of tumor relative to the great vessels, and the acknowledged desmoplastic reaction that may occur after metastatic tumor is treated with chemotherapy (Fig 5). The long-term survival after postchemotherapy RPLND is dependent on the pathology. Patients with only teratoma or necrosis and fibrosis do well long-term, while patients found to have persistent cancer are usually treated with two further courses of postoperative chemotherapy and experience a long-term disease-free status approximately 66% of the time.[3]

Complicated Postchemotherapy RPLND

As previously discussed, the term "standard RPLND" applies to patients who have postchemotherapy RPLND after induction chemotherapy alone. The term "complicated postchemotherapy RPLND" applies to patients who have received more than induction chemotherapy only, have experienced retroperitoneal recurrence after primary RPLND, have failed all chemotherapy as indicated by elevated tumor markers but persistent retroperitoneal-only tumor, and have late relapse. Postchemotherapy surgery in this group of patients is technically demanding and is associated with a higher probability of requiring nephrectomy, colon resection, vena cavectomy, and/or aortic resection and replacement. However, even in these complicated patients, the morbidity is acceptable since some patients are cured with postchemotherapy surgery. Even in the two groups of patients with the most ominous pathologic findings (late relapse with yolk sac tumor and so-called desperation RPLND for chemoresistant cancer), the chance for cure with surgery alone is between 30% and 40%.[20] It is remarkable that these patients with documented chemoresistant metastatic cancer can be cured at this rate with the addition of surgical therapy alone.

Postchemotherapy Seminoma

Patients with higher volume retroperitoneal seminoma or widely metastatic seminoma are treated with cisplatin-based chemotherapy similar to patients with nonseminoma. Unlike patients with nonseminoma, however, teratoma is never associated with pure seminoma. Therefore, the issue of whether to resect postchemotherapy masses after chemotherapeutic treatment for pure seminoma is controversial. Generally, patients with residual masses after chemotherapeutic treatment of seminoma are managed expectantly, with only a small percentage of patients recurring in the area of the mass. Also, standard second-line chemotherapy in seminoma is curative at the 50% level, and most patients who experience growth of a postchemotherapy mass after induction chemotherapy are usually given second-line chemotherapy. Therefore, surgical resection is reserved for patients who fail second-line chemotherapy and have a localized mass. Alternatively, some centers advocate surgical resection of postchemotherapy masses in pure seminoma if the mass is greater than 3 cm in diameter.[21] This issue of whether to resect postchemotherapy masses in seminoma remains controversial, and management should be individualized. The use of positron emission tomography scanning in this situation is also controversial.

Conclusions

In low-stage disease, the surgical removal of involved retroperitoneal lymph nodes has a solid rationale. The morbidity of nerve-sparing RPLND is low, and many patients who undergo removal of retroperitoneal metastatic disease are cured with surgical therapy alone, thereby avoiding chemotherapy. In postchemotherapy disease, the rationale for removing these retroperitoneal masses is strong. Approximately 60% to 70% of the time, the mass will be composed of either teratoma or persistent cancer, and surgical removal may

be therapeutic. In more complicated postchemotherapy disease such as late relapse or the removal of chemoresistant retroperitoneal cancer (desperation RPLND), 30% to 40% of these patients with chemoresistant metastatic cancer can be cured with surgical therapy alone. These postchemotherapy procedures, however, can be technically challenging and require specialized vascular capabilities. Similarly, the appearance of the tumor on CT scans may not be a valid indication of the technical requirements for surgical removal. These difficult surgical procedures require diverse technical capabilities and a commitment to a sometimes lengthy and arduous procedure.

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