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Redo Retroperitoneal Lymphadenectomy for Germ Cell Tumor of the Testis: INCan Experience (Instituto Nacional de Cancerologia, Mexico City) and Review of Literature

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ABSTRACT

Introduction: Redo retroperitoneal lymph node dissection (redo surgery) for the treatment of germ cell tumors is an uncommonly performed procedure. We describe clinical characteristics and outcome of patients with disease requiring redo surgery for recurrence or residual retroperitoneal disease. **Material and methods**: The INCan germ cell tumor surgical database was reviewed from January 2007 to December 2012 and clinical features of patients subjected to re-operative retroperitoneal surgery (redo surgery) for germ cell tumors were individualized. Preoperative evaluation, histopathology, morbidity, and technical aspects of this procedure, which is a critical part of the management of germ cell tumors, are described. Disease-specific survival was estimated using the Kaplan-Meier method. **Results**: A total of 20 patients were identified who underwent 27 redo surgeries after post-chemotherapy retroperitoneal lymph node dissection. The most common site of disease in the redo surgery was the para-aortic region. The most frequent histologic finding at time of redo surgery was teratoma. The median interval to redo surgery was 12 moths (P_{25} 8.5-P_{75} 14.75). The overall intraoperative complication rate was 18% and median length of hospital stay was three days. The five-year disease-specific survival rate was > 55%. Disease-specific mortality for patients who underwent redo surgery was 40% (n = 8). **Conclusion:** Redo surgery is an integral component of the management of germ cell tumors in cases of retroperitoneum recurrences or failures; it is the last opportunity for cure. Clinical outcomes after repeating retroperitoneal surgery depend on re-operative histology. (J CANCEROL. 2017;4:1-9)

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RESUMEN:

Introducción: La disección ganglionar retroperitoneal (Redo) en el tratamiento de los tumores de celulas germinales (TCG) es una técnica quirúrgica poco utilizada. Nosotros describimos las características clínicas y los resultados de este procedimiento en pacientes que lo requieren por recurrencia de la enfermedad en el retroperitoneo. **Material y métodos:** Se revisó la base de datos quirúrgica de TCG del Instituto Nacional de Cancerología (INCan) entre enero de 2007 y diciembre de 2012, y las características clínicas de los pacientes sometidos a cirugía retroperitoneal (Redo) para TCG se individualizaron. Se describen la evaluación preoperatoria, la histopatología, la morbilidad y los aspectos técnicos de este procedimiento, que es una parte crítica del tratamiento de los TCG. La supervivencia específica de la enfermedad se estimó utilizando el método de Kaplan-Meier. **Resultados:** Se identificó a un total de 20 pacientes que se sometieron a la cirugía 27 Redo, después de la disección de los ganglios linfáticos retroperitoneales posquimioterapia (PC-RPLND). Los sitios más comunes de la enfermedad en la cirugía Redo fue la región paraaórtica. El hallazgo histológico más frecuente al momento de la cirugía Redo fue un teratoma. El intervalo medio para la cirugía Redo fue de 12 meses (P25 8.5- P75 14.75). La tasa global de complicaciones intraoperatorias fue del 18% y la mediana de la estancia hospitalaria fue de 3 días. La tasa de supervivencia específica a la enfermedad a 5 años fue > 55%. La mortalidad específica de la enfermedad para los pacientes sometidos a cirugía Redo fue del 40% (n = 8). **Conclusión:** La cirugía Redo es un componente integral del manejo de los TCG en casos de recurrencias o fallas retroperitoneales; es la última oportunidad para curar. Los resultados clínicos después de repetir la cirugía retroperitoneal dependen de la histología reoperativa.

Palabras clave: Redo retroperitoneal. Tumores de células germinales.

INTRODUCTION

Testicular cancer represents 1.0-1.5% of all male cancers in Western society[1] and it is considered as highly curable, even when the disease is advanced. In Mexico there are no reliable records of the true incidence; in a histopathological malignancy record of 2001 of 1,186 documented cases, representing 2.4% of malignancies in men and despite the high probability of cure, 299 deaths were reported[2].

According to the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) guidelines, the standard therapy for clinical stage II-IV germ cell tumors (GCT) is chemotherapy matched with surgery. Surgery, when combined with systemic chemotherapy, has resulted in a high long-term disease-free survival for patients with advanced GCT[3].

After chemotherapy and retroperitoneal lymph node dissection (PC-RPLND), retroperitoneal recurrence occurs in 2-3% of patients[4].

The natural history of recurrent retroperitoneal masses is poorly known; nevertheless, retrospective data prompt surgery management[5]. Indications to resect recurrent or residual retroperitoneal masses are retroperitoneal residual disease after retroperitoneal lymphadenectomy and chemotherapy, normal tumor markers, and evidence of resectable tumor[5].

Risk factors for retroperitoneal recurrence after primary RPLND and/or

PC-RPLND are inadequate initial surgery and incomplete teratoma resection; faulty primary surgery was not compensated by postoperative chemotherapy. Redo surgery is a significant component in the therapeutic algorithm of non-seminomatous germ cell tumor, resulting in overall survival rates of 55-67%[6,7].

We report the clinical presentation, sites of tumor recurrence, pre-operative and histologic findings, operative data (time and transfusion rate), adjunctive procedures required for redo surgery, and overall and disease-free survival at our institution.

MATERIALS AND METHODS

A total of 181 post-chemotherapy retroperitoneal residual mass dissections for metastatic non-seminomatous or seminomatous testis cancer were performed for GCT from January 2007 to December 2012 and entered prospectively into the Instituto Nacional de Cancerologia (INCan) of Mexico City GCT surgical database. From this database, we identified patients as having undergone 27 re-operative retroperitoneal procedures (redo surgery) for non-seminomatous GCT (NSGCT) after prior retroperitoneal surgery. The term “redo surgery” is used to describe any re-operation after a PC-RPLND or mass resection after any form of previous retroperitoneal surgery for GCT, including RPLND, node sampling, or mass resection for recurrence or failure of previous surgery.

Late recurrence was estimated as retroperitoneal relapse within two years of initial treatment. Initial surgery (PC-RPLND) was defined as complete when reported as complete excision of all residual masses with no recurrence within one month of surgery; and incomplete resection was considered as residual masses defined as unresectable or new elevation of tumor markers within one month of surgery.

Before repeating RPLND, patients received platinum-based chemotherapy. Preoperatively, all patients were evaluated by physical examination and computed tomography of the abdomen and the chest. In case the vena cava was not visible due to large tumor mass an angio-magnetic resonance imaging (MRI) was performed in order to exclude the presence of a vena cava tumor thrombus. A computed tomography (CT)-guided needle biopsy was not performed. Serum tumor markers (-fetoprotein and ß-hCG) were measured in all patients.

The procedures were performed via midline laparotomy and via thoracoabdominal. Patients were followed at regular intervals.

Detailed information was compiled, including tumor site at first resection and at redo procedure, initial clinical stage, interval to reoperation, histopathology findings of previous PC-RPLND and redo surgery, adjunctive procedures and peri-complications at time of redo. Viable tumor was considered as GCT (except teratoma) or other malignancy histology in pathological specimen. Redo surgery was performed by the same surgeon. Disease-specific mortality and disease-specific survival was calculated using the Kaplan-Meier method, starting from the date of orchiectomy (diagnosis).

RESULTS

A total of 20 patients who underwent 27 reoperations were identified from the database of 181 procedures. The 20 patients had a mean age of 24.75 (± 5.29) years. The initial operation was post-chemotherapy retroperitoneal lymph node dissection (PC-RPLND); none were primary RPLND. The initial clinical stage was Stage I in two patients (10%), Stage II in six patients (30%), and Stage III in 12 patients (60%). The primary tumor was left sided in 11 cases and right sided in nine cases. Mixed tumors were the most frequent histology of the primary tumor (18 patients), one case of mature teratoma, and one of endodermal sinus tumor. The median observation time

Table 1.

Location	PC-RPLND	Redo surgery
Para-aortic	9	13
Suprahilar	–	1
Inter-aortocaval	4	5
Renal hilum	3	1
Iliac region	1	4
Retrocrural	–	1
Intrapelvic	–	–
Paracaval	3	2

PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection.

after the initial diagnosis was 38 months (P_{25} 29.5- P_{75}66.3 months).

Twenty patients were classified based on the International Germ Cell Cancer Collaborative Group (IGCCCG) risk criteria: six with good-risk, seven with intermediate, and seven with poor-risk disease.

Four patients were subjected twice to redo surgery, and one patient three times for recurrence.

The disease-specific sites of recurrences are listed in table 1. The most common sites of masses prompting redo surgery were in the para-aortic area in 13 (48.1%), followed by the inter-aortocaval.

The median diameter of the retroperitoneal mass at the time of the first surgery was 5.5 cm (P_{25} 4-P_{75}9 cm) and for redo surgery was 4 cm (P_{25} 3-P_{75}7 cm). Serum tumor markers (α-fetoprotein and r3hrCG) were negative before redo surgery in all patients.

We found viable malignant GCT in six cases, teratoma in 10 cases, and complete necrosis in four of the PC- RPLND specimens.

Nine patients (33%) at redo surgery (27 procedures) had viable tumor,

14 patients had teratoma (51%), and four necrotic tissue (14.8%). Malignant transformation was described on re-operative pathology in two cases: one case of necrosis was found to have sarcoma in redo specimen, and one teratoma turned into adenocarcinoma. Four patients who had no nodal involvement after PC- RPLND (necrosis) were found to have one teratoma, two viable tumor, and one necrosis.

Three patients who had viable tumor in the original PC-RPLND specimen were found to have no viable tumor in the redo surgery, and two patients with teratoma in the first specimen were found with viable tumor in the repeated surgery (Table 2 and 3).

All site of mass at PC-RPLND that recurred in the same site in redo surgery represent true loco-regional failures due maybe to inadequate primary surgery (Table 4).

Prior to RPLND, patients underwent chemotherapy (Table 3): two patients had received three cycles of bleomycin/etoposide/cisplatin (PEB), 12 patients four cycles PEB, five had received three

Table 2.

PC-RPLND	Redo surgery histology (n = 27)		
Histology	**Teratoma**	**Viable tumor**	**Necrosis**
Teratoma (n = 10)	9	2	1
Viable tumor (n = 6)	2	4	1
Necrosis (n = 4)	3	3	2
Total 20	14 (51.9%)	9 (33.3%)	4 (14.8%)

PC-RPLND: post-chemotherapy retroperitoneal lymph node dissection.

Table 3.

Patient	Age	Primary histology	Prior therapy	PC-RPLND	Interval to PC-RPLND to redo surgery	Redo surgery (n)	Histology redo surgery	Follow-up (month)	Died
1	31	TM 40%, EST 30%, EC 20%, SE 10%	4 x BEP	EST 20%, TM 50%	8 years	1	TM	132	No
2	26	TM 30%, EC 40%, EST 30%	4 x BEP	TM	12 months	1	Necrosis	99	No
3	21	TM 40%, EC 50%, EST 10%	4 x BEP	TM	24 months	1	TM	99	No
4	18	SE 80%, TE 20%	BEP + VIP (second line)	TM	12 months	1	TM	84	No
5	25	TM 40%, SE 30%, EST 20%, EC 10%	4 x BEP	Necrosis	14 months	2	Sarcoma	23	Yes
6	24	EST 100%	BEP + VIP	EC	7	1	EC + EST	24	Yes
7	24	Tumor mixed	4 x BEP	EST	15	1	EST + EC	28	Yes
8	23	EC 70%, EST 30%	3 x BEP	TM	24	1	TM	65	No
9	32	Tumor mixed	BEP + VIP	TM	24	1	TM	45	No
10	21	EST 60%, TM 40%	4 x BEP	Tumor mixed	6	1	TM	56	No
11	25	TM 30%, EST 40%, EC 20%, SE 10%	BEP + VIP	TM	8	2	Necrosis	120	No
12	24	EST 60%, TM 40%	4 x BEP	Necrosis	24	3	TM/ Adenocarcinoma	60	Yes
13	36	TM	–	Tumor mixed	12	2	TM/EST	52	Yes
14	17	EST 40%, TI 30%, EC 30%	4 x BEP	TM	12	2	TM	40	No
15	20	EC 50%, EST 50%	4 x BEP	Necrosis	8	1	TM	36	No
16	20	EST 70, TM 30%	4 x BEP	TM	6	1	TM	36	Yes
17	24	TM 40%, EST 60%	3 x BEP	TM	7	1	TM	30	No
18	23	EST 40%, TM 40%, Cho 20%	BEP + VIP	EC	11	1	EST	34	Yes
19	25	EST 80%, SE 10%, EC 10%	4 x BEP	TM	11	1	EST + EC	24	Yes
20	33	Tumor mixed	4 x BEP	Necrosis	10	1	Necrosis	30	No

Cho: choriocarcinoma; EC: embryonal carcinoma; EST: endodermal sinus tumor; SE: seminoma; TM: teratoma mature; BEP + VIP: after first line with bleomycin/etoposide/cisplatin, vinblastine/ifosfamide/paclitaxel as second-line therapy.

Table 4.

Site PC-RPLND	Site redo surgery								Total
	Para-aortic	Paracaval	Inter-aortocaval	Renal hilum	Iliac region	Retrocrural	Intrapelvic	Paracaval and iliac	
Para-aortic	7 (53.8%)	–	2 (15.4%)	1 (7.7%)	1 (7.7%)	1 (7.7%)	1 (7.7%)	–	13
Paracaval	1 (25%)	–	2 (50%)	–	–	–	–	1 (25%)	4
Inter-aortocaval	3 (50%)	1 (16.7%)	2 (33.3%)	–	–	–	–	–	6
Renal hilum	2 (66.7%)	1 (33.3%)	–	–	–	–	–	–	3
Iliac region	–	–	–	–	–	–	–	–	1
Total	13 (48.1%)	2 (7.4%)	6 (22.2%)	1 (3.7%)	2 (7.4%)	1 (3.7%)	1 (3.7%)	1 (3.7%)	27

cycles PEB and additional chemotherapy regimens with vinblastine, ifosfamide, and cisplatin (VIP); one patient didn't receive chemotherapy. After PC-RPLND, additional chemotherapy was administered to nine patients for viable cancer in the resected specimen or pure solid masses with characteristic CT-features of non-seminomatous germ cell tumor elements.

The initial surgery was completed in all cases; only one was considered incomplete.

The median interval to redo surgery was 12 months (P_{25} 8.5- P_{75} 14.75). One case of redo surgery was considered unresectable.

There were intra-operative complications with adjunctive procedures in five patients (18.5 %), including nephrectomy (n = 2), ureteral injury (n = 1), injury of inferior vena cava (n = 1), and aortic injury (n = 1). Adjunctive procedures were performed by the urologic surgeon, only aortic graft by vascular surgeon. There were no early or late complications.

The perioperative transfusion rate was 22.2% (6/27). Median operative time for redo surgery was 135 minutes (P_{25} 80- P_{75} 240), and median hospitalization time was three days (P_{25} 2- P_{75} 4).

At mean follow-up of 4.31 years (range 1.92-11.0), the disease specific mortality rate for the entire group was 40% (eight patients).

The disease-specific mortality rate for patients with necrosis/fibrosis was 0%, with mature teratoma 10%, and 100% for patients and vital cancer in the resected specimens, respectively. At the last follow-up, 60% of our patients were alive, including nine patients with teratoma and three with necrosis in redo surgery. The disease-specific survival for the entire group of patients was significantly dependent on the histologic findings at time of repeat RPLND. Disease-specific overall survival at follow-up of five years was > 55% (Fig. 1 and 2).

DISCUSSION

There are few series reported of redo surgery, and this is the reason why our experience of this procedure is described. Indications for redo RPLND include: residual or recurrent retroperitoneal mass after initial RPLND or PC-RPLND, normal tumor markers (α-fetoprotein and β-hCG), otherwise negative metastatic workup, and evidence that the mass is resectable.

Patients who undergo primary or post-chemotherapy retroperitoneal surgery may develop recurrence in retroperitoneum and unresectable disease[5]. Retroperitoneal recurrence is infrequent after RPLND and it seems to be an underreported occurrence[8]. The majority of relapses in patients with GCTs occur within two years of initial treatment; only 2-4% of cases may present later[9]. In the present study, only one patient with intermediate-risk non-

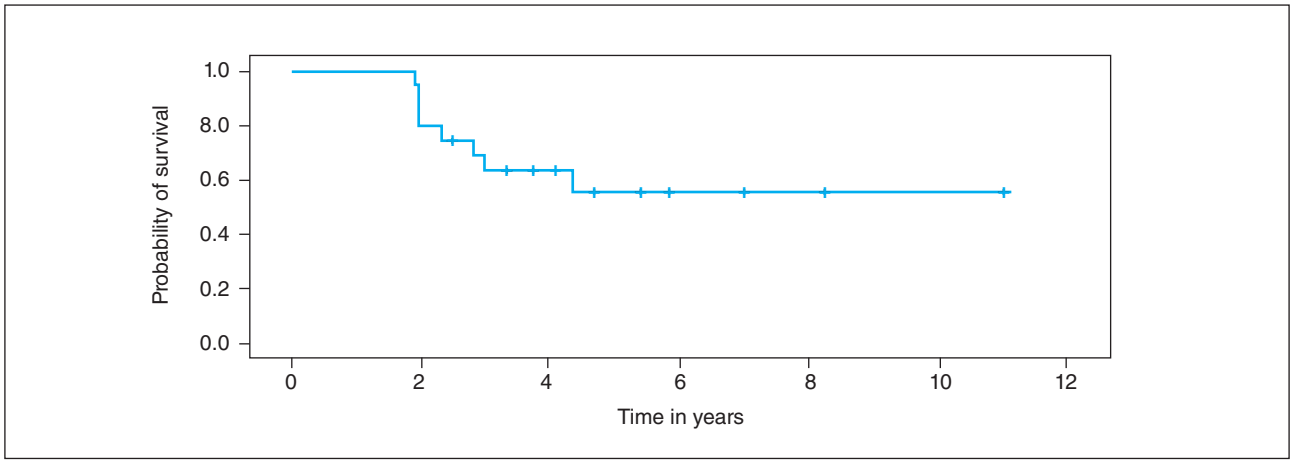

Figure 1.

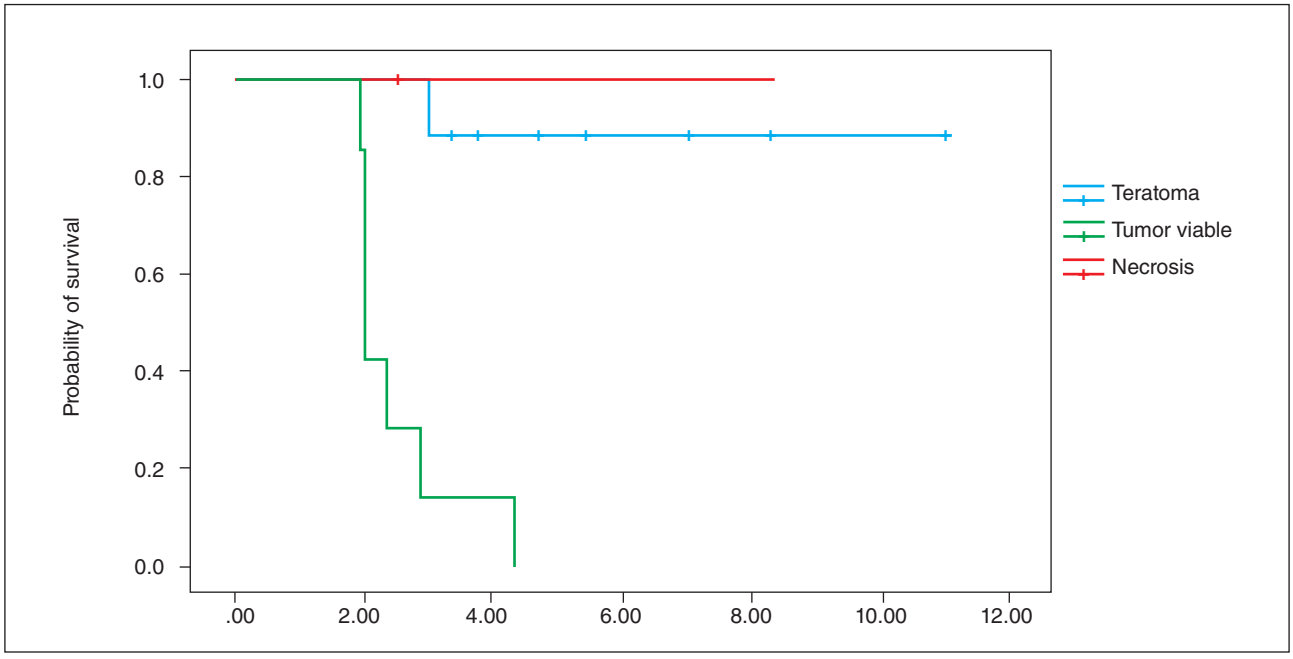

Figure 2.

seminomatous GCT, who had stage IIA disease (para-aortic), developed late relapse, in region retrocrural, eight years after complete response of the initial tumor. Pathologic analysis of the redo resected specimens in this patient revealed elements of mature teratoma. Only one case of our series had no relapse, but was residual tumor because it was considered unresectable by primary surgery.

One case is described of malignant transformation of teratoma in adenocarcinoma after 12 months to the first redo surgery; the patient died of liver and lung progression 13 months after the last redo surgery. Late recurrences with teratoma malignant transformation have been reported and it has been associated with poor prognosis[10,11]. Notwithstanding, there no reports that describe malignancy his-

tology in repeat surgery with fibrosis/ necrosis in primary or post-chemotherapy RPLND, as our case of sarcoma that presented necrosis at first surgery. McKiernan, et al. reported that only one patient with fibrosis on initial PC-RPLND was found with malignant teratoma on re-operative pathology[7].

As noted for the first time by Comisarow in 1976, recurrent retroperitoneal disease requires re-operative surgery or salvage chemotherapy[12]. However, the chemotherapy had limitations because relapses tend to be chemoresistant[5]. Results of published series demonstrate that insufficient initial surgery cannot compensate by chemotherapy[7,13,17], so it is evident that repeat surgery is the last chance of cure for the patients. Completeness and adequacy of retroperitoneal resection is an independent predictor of clinical outcome. As well-demonstrated, complete primary resection of retroperitoneum is important to attain relapse-free survival[15]. Also the two factors associated with local recurrence at lymph node dissection were incomplete lumbar vessel division and teratoma histology after initial RPLND[16]. In our study the most common histologic finding at both PC-RPLND and redo surgery was teratoma and this may explain the number of re-operations of our series, which is equivalent with the data from McKiernan, et al. and Willis, et al.[7,14]. In contrast, the series published by Heidenreich, et al.[13] reported teratoma in only six of 18 patients (39%) and necrosis/fibrosis (47%) as most common histology at repeat surgery.

The conclusions of present series in combination with data described by previous groups[7,13] show that disease-specific survival was dependent on tumor histology. Re-operative histology was a significant predictor of disease-specific survival. The disease-specific survival reported for teratoma histology is 80-85% and for viable tumor is 44-50%[7,13]; our survival results are similar to the 56% survival rate of the Memorial Sloan Kettering Cancer Center experience at a median follow-up of 29.5 months[7]. Overall survival rates in redo surgery are lower than initial PC-RPLND[8]. In our series, nine patients had viable malignant cells in the redo surgery and eight of these nine patients died secondary to widespread metastases.

The most common primary site was the left testis; this predominance confirms the most frequent para-aortic location of retroperitoneal masses requiring redo surgery. These trends are given in the literature, and the prevalence of left para-aortal, left region hilar area in retroperitoneal recurrence is widely described. The high incidence of retroperitoneal failures in these regions can be attributed, according to the authors, to inadequate surgical technique[13,14,17].

Post-chemotherapy retroperitoneal surgery and redo surgery are technically challenging procedures with great risk of complications due to peritumoral desmoplastic reaction, adhesions related to previous surgery and chemotherapy, and no clear dissection plane remains between the vascular wall and the tumor. These factors' risk increases the possibility of adjunctive procedures, such as nephrectomy, resection of visceral structures, and vascular surgery. Involvement of vascular structures can occur requiring performing an *en bloc* resection of the retroperitoneal tumor with the involved vascular structure. Also the patients' status, with compromised pulmonary, renal, and nutritional reserves, enhances the risk of intraoperative and perioperative complications. In our series, adjunctive procedures for complications was necessary in 18.5% of all patients, which is similar to data reported by Sexton, et al.[17] who described adjunctive procedures in 2/21 patients; but in others series this was 59-71% of patients[4,7]. Nephrectomy is the most common adjunctive procedure in repeat surgery[5].

Retrospective studies reported that the transfusion rate ranged between 18 and 71%[7,17], and perioperative complications were 9-57%. Common postoperative complications described were chylous ascites, prolonged ileus, lymphocele, deep vein thrombosis, ureteral injury, and vascular injury requiring graft reconstruction[7,13,17].

Although we are aware that redo surgery is a complicated procedure, our series argue that repeat retroperitoneal surgery can be carried out safely without perioperative morbidity. The literature described that re-operative retroperitoneal surgery can be performed with acceptable morbidity.

CONCLUSION

On the basis of our findings, it is necessary to prolong the follow-up for detection of late relapses or failures in patients who underwent initial suboptimal retroperitoneal surgery.

Recurrence of residual retroperitoneal of GCT disease must be treated with redo surgery, when chemotherapy or previous surgery fails, thinking that tumor or teratoma growth can be viable.

In this scenario, it is the last chance of cure for patients with advanced disease, although the overall survival rate is lower than initial RPLND. Clinical outcomes after repeat retroperitoneal surgery depend on re-operative histology.

Redo surgery is not a routine procedure. It is complex and it should be carried out in a specialized center in order to manage possible intraoperative complications.

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