ORIGINAL ARTICLE

Oncological outcomes of retroperitoneal node dissection for residual masses after chemotherapy in germ cell tumor. Retrospective analysis of 15 years

Resultado oncológico de linfadenectomía retroperitoneal por tumor residual posquimioterapia en cáncer germinal. Análisis retrospectivo de 15 años

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Abstract

Objective: *To report experience in a hospital in Mexico regarding oncological results in overall survival (OS) and specific cancer survival (SCS), the presence of recurrence in the management of residual masses after chemotherapy with lymphadenectomy retroperitoneal for 15 years.* **Method:** *Between 2004 and 2019, a retrospective study was carried out in a single centre with patients with a germ cell tumor diagnosis who have received first or second line of chemotherapy and who present retroperitoneal residual mass were included have performed RPLND. Sociodemographic characteristics were analyzed, overall and histological survival.* **Results:** *346 patients had inclusion criteria, mean age was 27.6 years, the most affected testis was the left, the most frequent testicular histology was mixed germline. The most frequent retroperitoneal location was paraortic, the most frequent type of RPLND was standard, the most frequent histology was necrosis. Recurrence occurred in 24.2%, mean of 17.1 months, when analyzing individual factors, the most significant was the type of RPLND. The clinical stage, histology of the retroperitoneal tumor and type of RPLND influence mortality. Global follow up of 141 months, OS was 85.5% and SCS was 86.1%, mean of 139.9 months and 141 months respectively.* **Conclusions:** *RPLND is effective in survival and recurrence in advanced disease in patients who present postchemotherapy retroperitoneal tumor and although there is a clear benefit in the resection of retroperitoneal tumors in teratoma, there are conditioning factors that must be analyzed individually.*

Keywords: *Germ tumor. Retroperitoneal lymphadenectomy. Overall survival. Retroperitoneal masses.*

Resumen

Objetivo: *Reportar nuestra experiencia en supervivencia y recurrencia en el manejo de masas residuales posquimioterapia con linfadenectomía retroperitoneal durante 15 años.* **Método:** *Estudio retrospectivo de 2004 a 2019. Se incluyeron pacientes con diagnóstico de tumor de células germinales que habían recibido quimioterapia y presentaron una masa residual retroperitoneal en un solo centro y se les realizó linfadenectomía retroperitoneal. Se analizaron las características sociodemográficas, de supervivencia global e histológicas.* **Resultados:** *Cumplían los criterios de inclusión 346 pacientes, con una media de edad de 27.6 años. El testículo más afectado fue el izquierdo, y la histología testicular más frecuente fue germinal mixto. La localización retroperitoneal más frecuente fue paraaórtica, el tipo de linfadenectomía más frecuente fue la estándar y la histología más frecuente fue la necrosis. Se presentó recurrencia en el 24.2% de los pacientes, en una media de 17.1 meses; al analizar los factores*

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individuales, el más significativo fue el tipo de linfadenectomía. El estadio clínico, la histología del tumor retroperitoneal y el tipo de linfadenectomía influyen en la mortalidad. El seguimiento global fue de 141 meses, la supervivencia global fue del 85.5% y la supervivencia específica del cáncer fue del 86.1%, con media de 139.9 y 141 meses, respectivamente. **Conclusiones:** *La linfadenectomía retroperitoneal es efectiva en cuanto a supervivencia y recurrencia en la enfermedad avanzada en pacientes que presentan tumor retroperitoneal posquimioterapia, y aunque existe un claro beneficio en la resección de los tumores retroperitoneales en teratoma, existen factores condicionantes que deben ser analizados de manera individual.*

Palabras clave: *Tumor germinal. Linfadenectomía retroperitoneal. Supervivencia global. Tumor retroperitoneal.*

Introduction

Testicular cancer represents 1% of neoplasms in men and 5% of urological tumors; 3-10 new cases occur per 100,000 men per year in Western societies[1]. Its incidence has increased in recent decades[2].

The incidence of testicular cancer varies significantly by geographic region: rates are highest in Scandinavian regions, Germany, Switzerland, and New Zealand; intermediates in the United States and Great Britain; and minimum in Asia and Africa[3]. In Mexico, testicular cancer is the second leading cause of death from malignant tumors between 18 and 29 years of age, with a mortality rate of 2.19 in 2016 and a higher diagnosis between 20 and 34 years of age[2]. According to the results of Globocan, in 2018, in Mexico, 4,603 new cases were registered per year, with a mortality of 571 cases, a mortality rate of 0.88, and an incidence of 6.5 cases per 100,000 inhabitants[4]. The incidence has been increasing, especially in industrialized countries[5,6].

Retroperitoneal lymphadenectomy is one of the treatment options after radical orchiectomy. These patients should be referred to high-volume hospitals for resection of residual masses in non-seminoma and advanced clinical stages after first- and second-line chemotherapy, as well as in selected cases of patients who have undergone prior retroperitoneal lymphadenectomy (Redo)[7,8].

Approximately 70% of patients with retroperitoneal metastases respond to chemotherapy (defined as normalization of radiographic and tumor markers); the remaining 30% can be treated with surgery on the grounds that these residual tumors harbor viable tumor or teratoma which in turn can cause somatic malignant transformation or teratoma. Despite having a complete radiological response to chemotherapy, 20-30% will present residual teratoma and 9% viable tumor[9-11].

In postchemotherapy residual disease in nonseminoma after first line treatment, 6-10% will have viable cancer, 50% teratoma, and 40% necrotic tissue; this percentage should be reserved for tumors larger than 1 cm. Late recurrences (> 2 years) present viable neoplasia in 54-88%, teratoma in 12-28%, and malignant transformation mainly to adenocarcinoma in 10-20%[3,11].

Patients with a complete serologic response to second-line chemotherapy but with residual tumor should undergo surgery after salvage chemotherapy. Patients with viable malignancy following salvage chemotherapy have a poor prognosis, but in a highly selected group with positive tumor markers surgery may be indicated in despair[3]. After salvage chemotherapy, survival after surgery after first-line chemotherapy is 70% at 10 years; when resectable, a significant proportion of these patients can be disease-free for a long time[12].

In the study by Miller et al.[13] in retroperitoneal masses after second-line chemotherapy with etoposide, ifosfamide, and cisplatin, between 1994 and 2001, a specific survival of 74% at 5 years was found in 131 patients who underwent retroperitoneal lymphadenectomy, and it is concluded that patients with resistance to platinums who underwent a second line of chemotherapy have a larger viable tumor or teratoma, therefore surgery is suggested as an optimal approach in advanced disease.

Overall 5-year survival is 45-77%. It is important to recognize teratoma surgery mainly due to proliferative teratoma syndrome, in malignant transformation and late recurrences; in this case, complete surgery provides a long-term survival of 75-90%[3].

Long-term oncological results vary depending on histology, since at 10 years of follow-up 80% of patients with teratoma remained free of recurrence, which demonstrates the durability of surgery in the control of retroperitoneal disease[10]. In the study by Mano et al.[14], a history of primary carcinoma was associated with less recurrence, and recurrence in patients with fibrosis after retroperitoneal lymphadenectomy remains a rare event.

In pure seminoma, 58-80% of patients present residual tumor in the retroperitoneum and 15% present it early. Histological examination reveals necrosis and viable neoplasia in 90% and 10%, respectively. Surgery after chemotherapy in seminoma represents a

significant technical difficulty, with desmoplastic reaction and perioperative morbidity[3,15].

Regarding complications, the probability of vascular injury is 20% in tumors larger than 5 cm[16,17], perioperative mortality is 0.8-6%[18], the reduction in local recurrence is 16% to 3%[18], and nearly one third of patients with retroperitoneal lymphadenectomy require resection of an organ affected by the disease (kidney, psoas, intestine, and great vessels), and sometimes the placement of vena cava and aortic prostheses will be required[15]. At Indiana University[19] reported complications in 3.7% and per year in 0-7.3%. Mosharafa found an incidence of complications of 6.7%, that the size of the mass and the presence of positive tumor markers were the most significant, and that necrosis and large tumors were more likely to present a surgical complication[20].

The objective of this work is to report our experience in terms of oncological results in terms of survival and recurrence in the management of first- or second-line post-chemotherapy residual masses with retroperitoneal lymphadenectomy for 15 years.

Method

A retrospective, analytical study, supported by descriptive statistics, was carried out after its approval by the hospital's ethics committee, which included patients diagnosed with germ cell tumors who received first or second line chemotherapy and who presented residual retroperitoneal mass, and who underwent retroperitoneal lymphadenectomy at the National Institute of Cancerology of Mexico between January 1, 2004 and January 1, 2019, who met the following inclusion criteria: diagnosis of germinal cancer and presence of residual masses post-chemotherapy in first or second line, who have undergone retroperitoneal lymphadenectomy surgery, seminomatous and non-seminomatous germ cell tumors. Those who had extragonadal primary germ cell tumors, who underwent retroperitoneal lymphadenectomy surgery without prior chemotherapy, who underwent other types of visceral or pulmonary resections without retroperitoneal resection, with non-germ testicular tumors, and who were lost to follow-up were excluded.

Sociodemographic and histological characteristics, overall survival, and recurrence were analyzed. Data were analyzed in SPSS Statistics 23.0 (IBM). Kaplan-Meyer curves were used for survival and recurrence, the chi-square test to determine the most significant factors, and descriptive statistics for frequencies.

Results

A total of 559 retroperitoneal surgeries for germ cell tumor performed at the National Institute of Cancerology were analyzed; 346 patients met the inclusion criteria. The mean age was 27.6 years (range: 15-58). The most frequently affected testicle was the left (53.5%) and bilaterality corresponded to 2%. Regarding histology, the most frequent tumor was mixed germ cell (74.3%). Among the testicular histological recurrence factors, the most frequent was lymphovascular permeation for non-seminomatous germ cell tumors, and for seminomas it was size > 4 cm (1.4%). 55.5% did not present histological factors of recurrence.

Regarding the prognostic group, the most frequent was good (38.4%) and the most frequent clinical stage was III C; up to 6.6% were clinical stage I, which corresponds to patients who presented recurrence to the retroperitoneum and who were previously treated with chemotherapy.

The most frequent retroperitoneal location of the residual tumor was the para-aortic (44.2%). The most common type of lymphadenectomy was standard surgery (74.6%) by Indiana classification. 75.7% were R0 (free of residual disease) and 24.3% were R2 (residual disease). Regarding tumor histology in the retroperitoneum, the most frequent was necrosis (46%), followed by teratoma (39.6%) and 9% viable tumor. 2.3% presented somatic transformation of the primary tumor.

14.5% of the patients presented some type of complication; the most frequent were vascular complications (8.7%) (Table 1).

The mean overall follow-up was 141 months (range: 1-166). Recurrence occurred in 84 patients (24.2%), in a mean of 17.1 months (range: 11.8-22.5). According to the histology of the retroperitoneal tumor, teratomas recurred more (n = 42), mixed germ cells in the testicular piece (n = 64), R0 (n = 59) and those who underwent standard surgery (n = 59); this has more to do with the frequency of procedures (Table 2 and Fig. 1).

When analyzing the individual factors that may influence recurrence and the time to recurrence, it was observed that in terms of retroperitoneal tumor histology, teratoma had the longest time to recurrence, while the shortest corresponded to necrosis. Regarding the histology of the primary tumor, those with the shortest time until recurrence were those with endodermal sinuses and those with the longest time were those subjected to deferred orchiectomy.

Table 1. Frequencies

Testicular side	Left	53.5%
Histology of the testicular tumor	Mixed germinal	74.3%
Prognostic group	Good	38.4%
Clinical stage	III C	61%
Location of the tumor in the retroperitoneum	Para-aortic	44.2%
Type of retroperitoneal lymphadenectomy	Standard	74.6%
R0-R2 resection	R0	75.7%
Histology of the retroperitoneal tumor	Necrosis	46%
Complications	Vascular	8.7%
Overall mortality	Yes	14.5%
Cancer specific mortality	Yes	13.9%

The most frequent result corresponding to each variable is shown.

Table 2. Means and minimum and maximum values of the quantitative variables

	Mean	Min–Max
Age	27.6 years	15-58
Retroperitoneal tumor size	66.4 mm	10-350
Follow-up	141 months	1-166
Mean recurrence	17.1 months	11.8-22.5
Mean overall survival	139.9 months	133.2-146.6
Mean of cancer-specific survival	141 months	134.4-147.6
Overall survival	85.5%	
Cancer-specific survival	86.1%	
Time to recurrence	43 months	

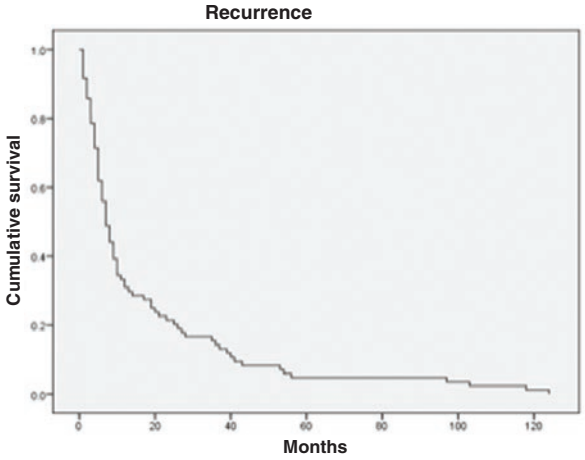

Figure 1. *Recurrence (Kaplan-Meyer curve).*

Table 3. Factors influencing time to recurrence

Histology of the tumor in the retroperitoneum (p = 0.45)
Histology of the testicular tumor (p = 0.24)
Resection R0 and R2 (p = 0.37)
Type of lymphadenectomy (p = 001)

Table 4. Factors influencing mortality

Clinical stage (p = 0.3)
Histology of the tumor in the retroperitoneum (p = 0.01)
Type of retroperitoneal lymphadenectomy (p = 0.02)
Recurrence (p = 0.06)
R0-R2 resection (p = 0.29)

The longest time until recurrence was presented by patients who had complete resection of the retroperitoneal tumor (R0) (18.7 vs. 13.48 months). Standard lymphadenectomy presented more time until recurrence, and the one with the shortest time was despair (20.5 vs. 4.6 months) (Table 3).

Overall mortality was 50 patients. Analyzing the individual factors for mortality, this was more frequent in clinical stage IIIC (78%), with a time to death of 11 months, and the least frequent was in clinical stages I and IIB (4%) (17.5 and 71.5 months, respectively). Regarding the histology of the retroperitoneal tumor, the most frequent was teratoma and fibrosis (32%), but the shortest survival time was presented by patients with somatic transformation (5 months). Standard retroperitoneal lymphadenectomy had more cases of deaths, but the shortest survival time was for despair lymphadenectomy (7.5 months). Mortality was higher in R0 patients than in R2, but survival time was observed to be shorter in R2 (12.5 vs. 18.9 months); this has to do with the fact that operated patients who remain R0 are more frequent than R2, which may be proportional to mortality.

70% of the patients who died presented recurrence with an average survival of 19 months, with the histology of the retroperitoneal tumor and the type of retroperitoneal lymphadenectomy being the most statistically significant factors ($p < 0.05$) (Table 4).

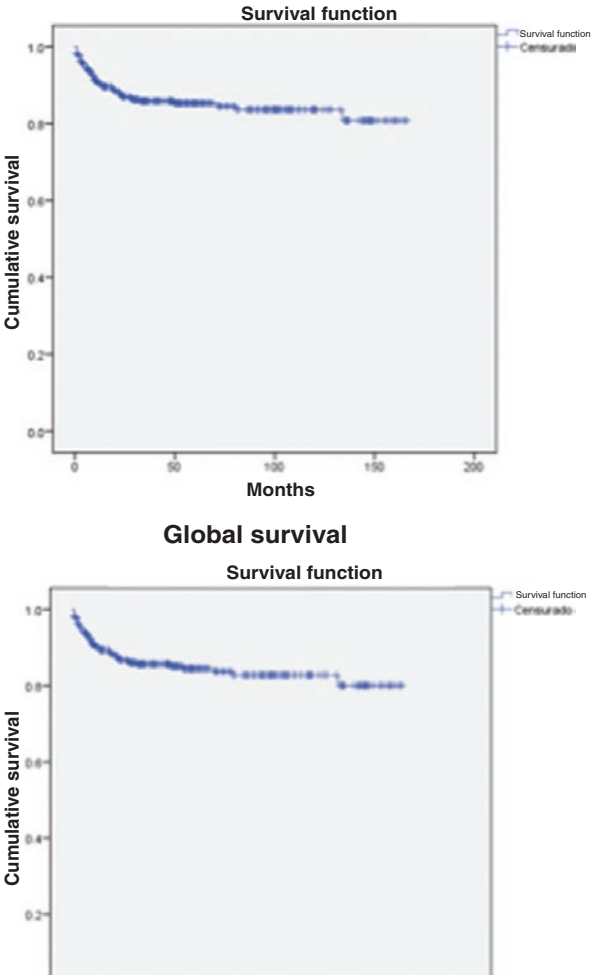

Figure 2. *Overall and cancer-specific survival.*

The 5-year overall survival was 85.5% and the cancer-specific survival was 86.1%. Median overall survival was 139.9 months (95% confidence interval [95% CI]: 133.2-146.6 months) and the mean cancer-specific survival was 141.0 months (95% CI: 134.4-147.6 months). Overall survival according to the type of lymphadenectomy was lower for despair (43.7 months) than for standard (150.3 months), lower with R2 resection (113 vs. 147.9 months), higher in the group with a good prognosis (154 months) than in the intermediate group (128.9 months) and poor prognosis (110.2 months), higher in patients with necrosis (148 months) and lower in those with transformation somatic (68.1 months) (Table 2 and Fig. 2).

Discussion

6-10% of post-chemotherapy residual masses will present viable cancer, 50% teratoma and 40% necrotic tissue. In this study, necrosis was found to be the most frequent. These percentages vary between the first and second lines of chemotherapy (necrosis in 40%, teratoma in 45% and viable neoplasia in 15%). We did not consider subgroups, but included all patients who received one or two lines of chemotherapy treatment.

Patients with viable malignancy in the retroperitoneal tumor have a poor prognosis. In our results, it was observed that despair surgery has an unfavorable prognosis and the viable tumor is the one with the shortest time until recurrence and the shortest overall survival time. Regarding the type of retroperitoneal surgery, whether standard or salvage, an average overall survival of more than 120 months was achieved.

Cancer-specific survival of patients with salvage lymphadenectomy is similar to that of world series[13], with reports of 74% at 5 years; in our series it was 76.7%.

The results of the world literature in terms of overall survival can be heterogeneous in their percentages, ranging from 45% to 77%[3]. In this study, an overall survival of 85.5% was reported. There have been predictors of retroperitoneal disease since 1987 (Donohue 1987). Size as a predictor of recurrence has been studied in the experience of the Memorial Sloan Kettering Cancer Center and the Indiana University, and the prognostic risk group has not been considered a common predictor of recurrence, but it is with respect to overall survival[10]. Our study evaluated the impact on overall survival.

An important situation is the patients who had teratoma in the primary tumor and who in certain cases were sent to chemotherapy and subsequent resection, as well as the patients who presented somatic transformation, who had a worse prognosis of the disease and high mortality, as well as shorter time to recurrence.

The histology of the retroperitoneal tumor influences the disease free of recurrence, especially in teratoma, which demonstrates the durability of surgery with complete resections in disease control in the retroperitoneum. In our study, it was observed that teratoma is the histology with the longest recurrence-free time (mean: 20.2 months)[10], and although the study by Mano et al.[14] mentions that recurrence in patients with fibrosis after retroperitoneal lymphadenectomy is a rare event, we observed that fibrosis in the retroperitoneum corresponds to 28% of recurrences and that it is the histology with the shortest time to recurrence.

Regarding complications, it has been shown that a retroperitoneal tumor size > 5 cm implies a 20%

probability of vascular injury[15,17]. In our study, although the mean number of tumors exceeded 5 cm, subgroups of patients were not considered according to the size of the retroperitoneal tumor, but they presented a frequency of 8.7% and vascular complication was the most frequent.

Perioperative mortality was 0%. Regarding intraoperative organic conditions, they were presented by 7.4% of the patients; in the Indiana University series[19] the percentage was 3.7%.

Conclusions

In our study we analyzed the survival of patients with retroperitoneal surgery for testicular germ cell cancer. Overall survival, cancer-specific survival, and recurrence rate are similar to those of hospital centers around the world. We conclude that retroperitoneal lymphadenectomy is effective in advanced disease in patients with post-chemotherapy retroperitoneal tumor, and although there is a clear benefit in resection of retroperitoneal tumors, especially teratoma, and in standard surgeries, and it is of great help in tumors with persistent tumor markers or in salvage surgeries, there are conditioning factors that must be subsequently analyzed individually.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments were carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed the protocols of their work center regarding the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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