Outcome of Resection and Chemotherapy *versus* Chemotherapy Alone for Retroperitoneal Recurrence of Testicular Cancer Involving the Inferior Vena Cava: A Retrospective Cohort Study of 22 Consecutive Patients

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Abstract. *Background/Aim: Optimal treatment strategy for retroperitoneal recurrence of testicular cancer involving the inferior vena cava (IVC) is uncertain. The purpose of this study was to validate the hypothesis that surgical resection, en-bloc with the involved segment of IVC and its subsequent reconstruction followed by chemotherapy, would yield better oncologic results than chemotherapy alone. Patients and Methods: Two consecutive series of patients with retroperitoneal recurrence of testicular cancer involving the IVC, treated with surgical resection plus chemotherapy (group A, n=14) or chemotherapy alone (group B, n=8) were retrospectively reviewed. The mean duration of follow-up was was 65 months (range=8-184). Operative mortality and morbidity in group A, response to chemotherapy in group B, disease-specific survival and quality adjusted life-years (QALY) for both groups, were primary end-points of the study. Results: Postoperative mortality and morbidity (group A) were, respectively, nil and 14%. In group B, two patients (25%) fully responded to chemotherapy and remained free from disease progression. Disease-specific survival at 3 and 5 years was 81% and 54% in group A and 36% in group B both at 3 and 5 years, respectively (p=0.02). QALY was 3.92 in group A and 0.77 for both 3 and 5 years in group B, respectively, (p=0.031). Conclusion: En bloc resection of retroperitoneal recurrence of testicular tumors invading the IVC, followed by chemotherapy, allows a better survival rate compared to chemotherapy alone.*

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Chemotherapy has a definite role in the treatment of retroperitoneal recurrence of seminomatous and non-seminomatous cancer of the testis, due to their sensitivity to this treatment (1). However, persistence of viable tumor cells and persistent, enlarging retroperitoneal disease after chemotherapy alone reaches 30% of cases (2). Aggressive surgical resection of such recurrence, especially when inferior vena cava (IVC) involvement by the tumor mass exists, is controversial, given the magnitude of the operation and the fact that up to 35 % of the patients already present extra-retroperitoneal disease at the time retroperitoneal mass is detected (3-6). Nonetheless, surgery of retroperitoneal recurrence after chemotherapy, provided that R0 margins and low postoperative mortality/morbidity can be obtained, is reasonably supposed to allow a better local control of the disease, as well as an overall better survival compared to chemotherapy alone (2, 7). The purpose of the present study was to retrospectively review and compare two groups of patients with retroperitoneal recurrence of testicular tumor invading the IVC, respectively, undergoing resection of the tumor *en bloc* with the involved caval segment followed by caval reconstruction and chemotherapy or receiving iterative cycles of chemotherapy alone, in order to evaluate the eventual benefit of aggressive surgical resection on control of disease progression and survival.

Patients and Methods

Twenty-two consecutive patients undergoing treatment for retroperitoneal recurrence of testicular cancer involving the inferior vena cava (IVC) from January 1st, 1990, to December 31st, 2014, were retrospectively reviewed and divided into two groups. Patients in group A (n=14) underwent en bloc resection of the metastatic cancer and the involved segment of the IVC, followed by adjuvant chemotherapy, whereas patients in group B (n=8) received chemotherapy only due to their refusal of surgical resection. The study was conducted at one academic, tertiary care hospital and an

affiliated surgical center. It was approved by the local ethics committee and informed consent was obtained from all the patients. The patients' mean age was 40 years in group A (range=26-58) and 43 in group B (range=29-56) ($p=1$). In group A, the presenting symptoms and signs were abdominal discomfort and palpable abdominal mass in 8 patients (57%), whereas in the remaining 6 (43%) the retroperitoneal mass was detected at control abdominal ultrasound (US), computed tomography (CT)-scan or magnetic resonance imaging (MRI), performed as part of post-orchiectomy and chemotherapy regular, oncologic follow-up (Figure 1). In group B, 7 patients (87%) had abdominal recurrence detected at follow-up control imaging and one patient (23%) presented with abdominal discomfort and palpable abdominal mass in the interval between imaging controls. Nine patients in group A (64%) had undergone previous orchiectomy and chemotherapy for a known testicular cancer, whereas in the remaining 5 patients (36%) the testis was identified as the primary site of the tumor after detection of the retroperitoneal mass. All patients in group B had undergone previous treatment of testicular disease with orchiectomy and chemotherapy. Histology of the primary tumor in 9 of group's A patients in whom it was previously detected and treated was seminoma in 5 cases (55%) and non-seminomatous cancer in 4 (45%). After primary surgery, all these patients received two cycles of chemotherapy with etoposide and cisplatin. Beside retroperitoneal recurrence, none of the patients in both groups presented any other metastasis evident at CT-scan. The surgical treatment of the retroperitoneal mass consisted of *en-bloc* resection of the mass itself together with the involved portion of the IVC and lombo-aortic lymphadenectomy. Caval reconstruction depended on the extent of tumor involvement. Partial caval resection/polytetrafluoroethylene (PTFE) patch closure (W.L. Gore and Associates, Flagstaff, AZ, USA) was performed whenever the tumor involved no more than 1/3 of caval circumference, without complete encasement of the vein wall and over less than 2 cm length. In case of more extensive caval involvement, resection followed by PTFE grafting was performed. According to this principle, a patch closure was performed in 8 cases (57%), whereas a cavo-caval grafting with a graft diameter ranging from 14 to 18 mm was performed in the remaining 6 patients (43%). Intraoperative frozen section examination was not performed; however, pathology confirmed that an R0 resection had been carried on in all but one patient. Histological sections confirmed invasion of the caval wall by the tumor in 11 patients (75%), which was a seminoma in 8 patients (57%) and non-seminoma in 6 (43%). Postoperatively, the patients received a regimen of low molecular-weight heparin for 6 weeks and were then prescribed 100 mg/day of oral aspirin; oral anticoagulation was prescribed only when thrombosis of the graft and consequent edema of the lower limbs occurred. Before discharge from the hospital, patency of IVC reconstruction was assessed with duplex ultrasonography (8). Five patients underwent subsequent orchiectomy within one month from retroperitoneal surgery. All patients received 4 cycles of adjuvant therapy with etoposide and cisplatin. In group B, all patients received chemotherapy alone, also consisting of 4 cycles of etoposide and cisplatin. All patients were followed-up with regular clinical and imaging controls according to standard oncologic protocols. The mean length of follow-up was 65 months (range=8-184) in group A and 45 months (range=28-64) in group B. For patients in group A, the primary end-points of the study were operative mortality and morbidity, as well as patency of venous reconstruction. For patients in group B, the primary end-point was response to chemotherapy. For patients in both groups, disease-specific survival and quality of life were also evaluated as primary end-points. Secondary end-points for patients of group A were intraoperative blood loss and postoperative length of stay. Operative mortality and morbidity were defined as any death or complication occurring within 30 days of the operation or the whole length of postoperative stay in the hospital. Patency of the venous reconstruction was defined as the absence of thrombosis of the graft and IVC at CT scan. Response to chemotherapy was defined as a stable local regression or cure of the retroperitoneal disease without evidence of recurrent disease at other sites at imaging during follow-up. Disease-specific survival was defined as patients' survival minus any death due to neoplastic disease. Life-table analysis according to the Kaplan-Meier method was used to calculate survival. Quality of life was assessed according to the quality-adjusted life-year (QALY) EQ-5D-5L methodology (9-10). The Chi2 test for categorical variables and the Student's *t*-test for independent samples were employed. Statistical significance was defined as $p<0.05$.

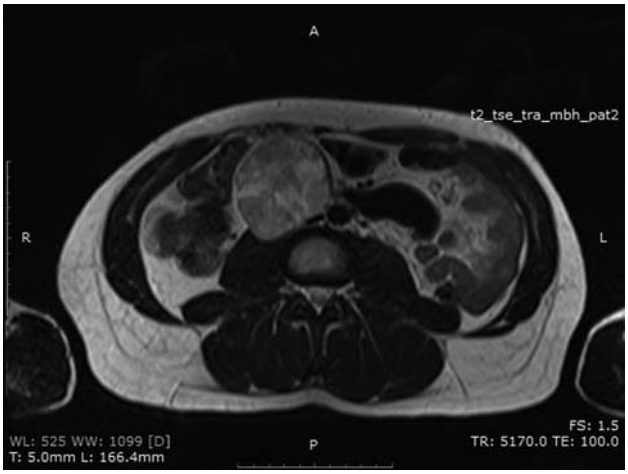

Figure 1. *Preoperative magnetic resonance imaging (MRI) of the abdomen showing a retroperitoneal mass involving the inferior vena cava, nine months after orchiectomy and adjuvant chemotherapy for non-seminomatous cancer of the testis.*

Results

In group A, no patient died in the postoperative period. Two patients (14%) presented non-fatal complications consisting of 1 case of dehiscence of the abdominal wound and 1 case of clostridium enteritis, both successfully managed with appropriate, local and medical treatment. The mean estimated blood loss was 600 ml (range=300-1,100 ml). The mean postoperative length of stay was 11 days (range=6-19 days). Overall, 2 caval reconstructions (14%), consisting of 2 cavo-caval grafts thrombosed during follow-up at 9 and 10 months, respectively. The consequent edema of the lower limbs was treated with elastic stockings and oral anticoagulation. These 2 grafts represented 33% of the 6 cavo-caval graft

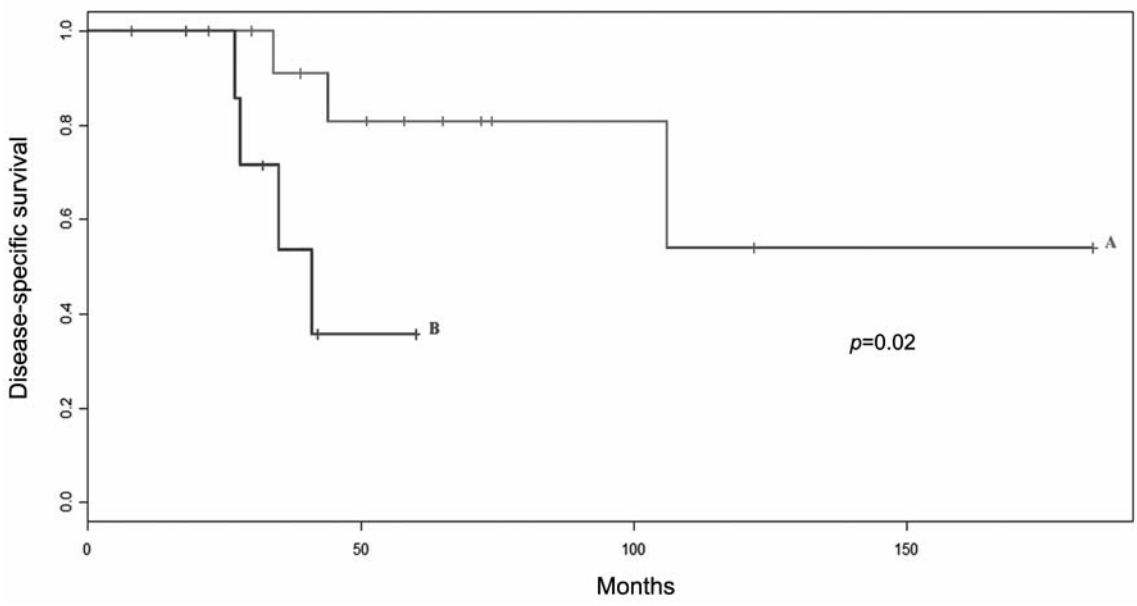

Figure 2. *Kaplan-Meier estimate of disease-specific survival in patients undergoing resection plus chemotherapy (A) vs. chemotherapy alone (B) for retroperitoneal recurrence of testicular cancer involving the inferior vena cava.*

reconstructions performed. In group B, two patients (25%) fully responded to chemotherapy and remained free of disease progression for the whole length of follow-up.

Two patients in group A (14%) and 4 in group B (50%) died of metastatic disease (p=0.02). Overall, disease-specific survival at 3 and 5 years was 81% and 54% in group A, respectively, while it was 36% both at 3 and and 5 years in group B (p=0.02) (Figure 2). Overall QALYs were 3.6 with a significant difference between patients in group A (n=14, QALYs=3.92) and group B (n=8, QALYs=0.77) (p=0.031) (Table I). The essential clinical data of patients in both groups are summarized in Tables II and III.

Table I. *QUALY estimate for patients undergoing resection plus chemotherapy (A) vs. chemotherapy alone (B) for retroperitoneal recurrence of testicular cancer involving the inferior vena cava.*

Patients	QALYs	*p*-Value
A (n=14)	3.92	0.031
B (n=8)	0.77	

Discussion

The results of this study show that *en-bloc* resection with caval reconstruction followed by adjuvant chemotherapy yields better results, in terms of disease-specific survival and quality of life, compared to chemotherapy alone. These results could be obtained in the absence of operative mortality and any major or significant morbidity. As a consequence, reluctance to perform what is thought to be an operation of excessive magnitude, hardly justified in a hopeless oncologic setting, should be overcome (9-11). However, obtaining an R0 resection is of paramount importance to avoid rapid and massive local recurrence (9, 11), as shown in patient #1 in group A, experiencing an early local recurrence after an R1 resection. If the possibility of performing an R0 resection cannot be soundly anticipated at preoperative imaging, surgery would better not be attempted and chemotherapy alone should be considered (9, 11). In order to reduce the extent of the operation, the blood loss and the risks of pulmonary embolism case of graft thrombosis, en-bloc resection, followed by simple caval resection has been proposed (12). However, this technical choice exposes to the risk of an invalidating edema of the lower limbs. This risk is enhanced by the need of interrupting a significant amount of collateral outflow when resecting a quite long segment of IVC involved by the tumor (8). In the present report, as well as in previous ones dealing with IVC reconstruction after resection for cancer, no pulmonary embolism related to graft thrombosis has been observed (8, 13-15), whereas lower limbs edema of new onset was systematic after graft thrombosis, thus supporting the value of caval reconstruction for its prevention and for providing a good quality of life to the patients (8, 13, 15). A further support to systematic caval reconstruction is the observation that it does not enhance operatively the blood loss, which is overall largely

Table II. *Essential clinical data of patients undergoing resection plus chemotherapy for retroperitoneal recurrence of testicular cancer involving the inferior vena cava (Group A).*

Pt	Age	Symptoms	Previous orchiectomy (interval)	Histology	Previous chemotherapy	Postoperative chemotherapy	IVC reconstruction	Post-op complication	Graft patency	Blood loss (ml)	Subsequent surgery	FU (months)	Resection margins	Outcome
1	31	Abdominal discomfort	No	NS	No	Yes	Patch	None	Patent	300	Orchiectomy	8	R_1	Local recurrence
2	47	Abdominal discomfort	Yes (8 months)	S	Yes	Yes	Patch	None	Patent	400	None	30	R_0	Free from disease
3	54	None. Fu-US, CT/MRI	Yes (11 months)	NS	Yes	Yes	Patch	None	Patent	350	Pulmonary lobectomy	10,22	R_0	Free from disease
4	28	Abdominal discomfort	Yes (19 months)	NS	Yes	Yes	Patch	None	Patent	300	None	72	R_0	Free from disease
5	36	Abdominal discomfort Limb edema	No	S	No	Yes	IVC resection, PTFE graft	Dehiscence of abdominal wound	Patent	900	Orchiectomy	13,34	R_0	Dead pulmonary metastases
6	49	Abdominal discomfort	Yes (10 months)	NS	Yes	Yes	IVC resection, PTFE graft	Respiratory distress	Patent	1000	None	106	R_0	Dead, MI
7	35	None. Limb edema	Yes (16 months)	S	Yes	Yes	IVC resection, PTFE graft	None	Thrombosed 9 mths	850	None	184	R_0	Free from disease
8	37	None. Fu-US, CT/MRI	No	S	Yes	Yes	Patch	None	Patent	900	None	122	R_0	Free from disease
9	26	Abdominal discomfort	No	S	No	Yes	Patch	None	Patent	300	Orchiectomy	37,44	R_0	Dead pulmonary/ bone metastases
10	44	Abdominal discomfort	No	NS	No	Yes	Patch	None	Patent	400	Orchiectomy	39	R_0	Free from disease
11	58	None. Fu-US, CT/MRI	Yes (22 months)	NS	Yes	Yes	IVC resection, PTFE graft	None	Patent	800	None	65	R_0	Free from disease
12	42	None. Fu-US, CT/MRI	Yes (13 months)	S	Yes	Yes	IVC resection, PTFE graft	None	Thrombosed 10 mths	1100	None	58	R_0	Free from disease
13	29	None. Fu-US, CT/MRI	Yes (15 months)	S	Yes	Yes	IVC resection, PTFE graft	None	Patent	700	None	51	R_0	Free from disease
14	52	Abdominal discomfort	No	S	No	Yes	Patch	None	Patent	300	None	74	R_0	Free from disease

IVC, Inferior vena cava; S, seminoma; NS, non-seminomatous tumor; PTFE, polytetrafluoroethylene; Fu, follow-up; US, ultrasound; CT, CT-scan; MRI, magnetic resonance imaging; pt, patient.

Table III. *Essential clinical data of patients undergoing chemotherapy alone for retroperitoneal recurrence of testicular cancer involving the inferior vena cava (Group B).*

Pt	Age	Previous orchiectomy (months)	Symptoms	Histology	Freedom from disease progression, total Fu (months)	Outcome
1	42	7	None. Fu-US, CT/MRI	NS	29, † 35	Mediastinal N, pulmonary metastases, died 6 months after recurrence
2	56	12	None. Fu-US, CT/MRI	S	42	Freedom from disease progression
3	36	9	Abdominal discomfort	S	22, † 41	Bone metastases, died 19 months after recurrence
4	29	11	None. Fu-US, CT/MRI	NS	16, 32	Local recurrence plus mediastinal N, alive
5	47	19	None. Fu-US, CT/MRI	NS	20, † 27	Local recurrence, caval thrombosis plus leg swelling, died 7 months after recurrence
6	53	14	None. Fu-US, CT/MRI	NS	14, 18	Mediastinal N, pulmonary/bone metastases, alive
7	30	13	None. Fu-US, CT/MRI	S	60	Freedom from disease progression
8	49	20	None. Fu-US, CT/MRI	NS	17, † 28	Local recurrence plus pulmonary metastases. Died 11 months after recurrence

Fu, Follow-up; US, ultrasound; CT, CT-scan; MRI, magnetic resonance imaging; S, seminoma; NS, non-seminomatous tumor; Pt, patient; †, death; N, node metastases.

acceptable, as shown in the present and other studies (8, 13, 15-17). Reconstruction of IVC is done preferably with PTFE, that is readily available, resistant to infections and allows a good long-term patency, also in the absence of an associated arterio-venous fistula, as in the present study (8, 13, 15-17). IVC reconstruction with autologous vein is to be avoided as it is cumbersome to perform, does not always allow a good anastomotic match and is prone to occlusion by abdominal pressure (11, 17-19). Patients receiving chemotherapy alone presented a significantly low survival and quality of life compared to patients undergoing surgical resection with caval reconstruction. Poor quality of life in the former group of patiens can be directly related to progression of the disease, persistence of lower extremity edema and psychological awareness of failure to obtain freedom from the disease. Nonetheless, IVC involvement must be considered as a marker of particular aggressiveness of the disease and a condition limiting the possibilities of obtaining R0 resection margins. As incomplete surgical resection margins expose the patient to a rapid local expansion of the disease, with consequent abdominal discomfort, shorter survival and poorer quality of life, compared to chemotherapy alone, this latter choice is to be preferred whenever some doubt of difficulty in obtaining R0 resection margin exists at preoperative imaging. This study has the limitations of being retrospective over a long time span and of a limited number of effectives. However, its results are validated by those of other previous reports and it is unlikely that a prospective study based on larger and homogeneous patients' cohort could be performed in a timely fashion. It would also be questionable whether the benefits of a feasible surgical resection with R0 margins should be denied to some patients simply on the basis of entering them into a randomized study. In conclusion, the results of this study show that aggressive, en bloc resection of retroperitoneal recurrence of testicular tumors invading the IVC followed by chemotherapy allows a better survival rate compared to chemotherapy alone, provided that R0 resection margins can be obtained.

Conflicts of Interest

The Authors declare no potential conflicts of interest.

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