Pathologic findings and clinical outcome in patients undergoing retroperitoneal lymphadenectomy after multiple chemorherapy regimens for metastatic nonseminomatous testicular tumors

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Abstract

We reviewed our experience with retroperitoneal lymphadenectomy (RPLA) after multiple cisplatin-based chemotherapy regimens in nonseminomatous testicular tumors (NSTT) patients and specifically evaluated clinicopathologic and treatment trend in addition to potential predictors of survival. Fort-one patients with NSTT underwent their RPLA between 1982 and 2005 after ≥ 2 regimens of chemotherapy. Thirteen patients (32%) necessitate redo-RPLA, combined with nephrectomy in 6 patients. 13 extra-RP (ERP) resections were performed in 11 patients (27%), including pulmonary (7), neck (4) and liver (2) sites. Thirty patients (73%) are rendered free of disease and 26 (63%) obtained serologic remission. Nine patients who relapse, necessitated new salvage chemotherapy+surgery (3 teratoma, 6 vital carcinoma [VC]). Four of 9 relapsing patients (44%) are currently free of disease with redo-RPLA. Alive, free of disease are 19 pts (46%) at median follow-up of 131 months. Study of RP pathology demonstrated the presence of fibrosis in 15%, teratoma in 39% and VC in 46%, with survival in 67%, 56% and 32%, respectively. Different histology occurred in 38% at redo-RPLA and in 64% at ERP resection in comparison to previous RP pathology. Univariate analysis of clinicopathologic parameters associated with VC at RPLA included RP masses ≥ 5 cm ($p<0.05$), elevated AFP ($p<0.001$) or HCG ($p<0.05$) and ERP resection ($p<0.04$). On univariate analysis survival was worse in patients with RP masses ≥ 5 cm ($p<0.04$), elevated AFP ($p<0.05$) or HCG ($p<0.007$), ERP resection ($p<0.01$) and VC ($p<0.004$). On multivariable analysis, a RP masses ≥ 5 cm ($p<0.03$) and VC ($p<0.005$) predicted a worse

Patološki nalaz i klinički tok kod pacijenata sa metastazama neseminomskih testikularnih tumora kod kojih je primenjena retroperitonealna limfadenektomija posle multiplih hemoterapija

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Apstrakt

Napravljen je pregled iskustva sa retroperitonealnom limfadenektomija (RPLA), a posle brojnih hemioterapijskih ciklusa na bazi cisplatine kod pacijenata sa neseminomskim tumorima testis (NSTT) i posebno evaluirani kliničko patološki i terapeutski trendovi kao dodatak potencijalnim pokazateljima preživljavanja. 41 pacijent sa NSTT su podvrgnuti RPLA izmedju 1982.-2005. posle ≥ 2 hemioterapijskih protokola. 13 pacijenata (32%) je iziskivalo ponovnu RPLA, kombinovanu sa nefrektomijom kod 6 pacijenata. 13 ekstraretroperitonealnih resekcija je učinjeno kod 11 pacijenata (27%) uključujući pulmonalne (7), vratne (4) i jetrine (2) lokalizacije. 30 pacijenata (73%) je prevedeno u kompletnu remisiju dok je 26 (63%) imalo serološku remisiju. 9 pacijenata (32%) je imalo recidiv iziskujući novu selvage hemioterapiju i hirurgij (3 teratoma, 6 vitalni karcinom). 4 od 9 pacijenata (44%) sa recidivom je bilo bez znakova bolesti posle ponovne RPLA. Živo i bez znakova bolesti je 19 pacijenata (46%) za srednje praćenje od 131 meseca. Retroperitonealna histološka analiza je pokazala prisustvo fibroze kod 15%, teratoma kod 39% I vitalnog karcinom kod 46%, sa preživljavanjem kod 67%, 56%, 32% respektivno. Različita histopatologija je postojala kod 38% na ponovnoj RPLA i kod 64% na ekstraretroperitonealnoj resekciji u odnosu na raniju retroperitonealnu histologiju. Nivarijantna analiza kliničko patoloških parametara udruženih sa vitalnim karcinomom na RPLA je pokazala da su samostalni prediktivni faktori retroperitonealna masa preko 5 cm ($p<0.04$), povišeni AFP ($p<0.001$) ili HCG ($p<0.005$) i ekstraretroperitonealna resekcija ($p<0.04$). Na multivarijantnoj analizi, retroperitonealna masa preko 5 cm ($p<0.03$) i vitalni karcinom ($p<0.005$) su značili lošu prognozu. Naša

prognosis. Our data support the continued use of salvage RPLA in three separated groups of patients: 1. Patients who achieved a complete response (CR) to 2nd -line chemotherapy and have no radiologic evidence of disease should undergo RPLA; 2. Patients who achieved a partial response (PR) to chemotherapy should undergo RPLA with ERP surgery, as indicated; 3. Highly selected group of patients with residual masses and elevated serum tumor markers (STM), particularly AFP, after chemotherapy may be candidate for surgery.

Key words: retroperitoneal lymphadenectomy, salvage therapy, chemotherapy, nonseminomatous testicular tumors, metastatic.

studija podržava kontinuiranu primenu primenu salvage RPLA kod 3 separatne grupe pacijenata : (1) pacijenti koji postignu kompletnu remisiju na drugu liniju hemioterapije I nemaju radiološke znake za prisustvo rezidualne bolesti moraju biti podvrgnuti RPLA; (2) pacijenti koji postignu parcijalnu remisiju posle hemioterapije moraju imati RPLA, sa ekstraretroperitonealnom hirurgijom ukoliko je indikovano; (3) Strogo selekcioniran grupa pacijanata sa rezidualnom masom i povišenim vrednostima tumorskih markera, posebno AFP, posle hemioterapije mogu biti kandidati za hirurgiju.

Ključne reči: Retroperitonealna limfadenektomija, salvage terapije, hemioterapija, neseminomski tumori testis, metastatski.

Introduction

Induction chemotherapy is the initial treatment for men with clinical stage IIA/B or C NSTT or patients with elevated STM. Approximately 20% to 30% of patients experience disease progression or recurrence and that require salvage chemotherapy[1]. Depending on their risk profile, from 35% to 70% of these patients will achieve a CR to ifosfamide and cisplatin -based regimens[2,3,4]. Patients with disease amenable to surgery are candidates for RPLA in addition to resection of any ERP disease. Disease progression during 2nd- line therapy or subsequent recurrence portends very poor prognosis.

Relatively few contemporary data exist on RPLA after multiple regimens of chemotherapy. When RPLA is performed in this setting, it has been reported that VC occurs in approximately 50% of patients[5,6,7]. Because of the high proportion of men with VC or teratoma after salvage chemotherapy, surgical resection of all disease sites is attempted when feasible. The objectives of the current study were to review our experience with RPLA after multiple cisplatin-based chemotherapy regimens and specifically evaluate the clinicopathologic and treatment trends in addition to potential predictors of survival.

Material and methods

Forty-one patients with metastatic NSTT underwent their RPLA after > 2 regimens of chemotherapy between 1982 and 2005. At initial diagnosis, patients were classified as good, intermediate, or poor risk according to the International Germ Cell Consensus Classification Group (IGCCCG)[8]. In majority of patients 1st -line chemotherapy included PVB (platinum, vinblastine, bleomycin)/PEB (platinum, etoposide, bleomycin) regimen and 2nd -line according to PVI (platinum,vinblastine, ifosfamide)/PVE (platinum, vinblastine, etoposide) regimen. After each chemotherapy regimen, STM levels were obtained, x-ray of the lung, ultrasound and computed tomography (CT) of the abdomen and minor pelvis were performed to assess tumor response. STM elevation was defined as an AFP level > 6.65 ng/ml or a HCG level > 2.25 mIU/ml that did not decline according to its serum half-life. Lymph node size before and after chemotherapy was determined by measuring the greatest transverse dimension of the largest mass on CT imaging. In patients with normalized STM levels, an RPLA and surgical resection of all ERP residual masses were recommended when feasible. The patients with finding of fibrosis and teratoma are only strictly followed-up without further therapy, whereas the patients with VC received 3rd -line chemotherapy. Preoperatively, it was believed that all 41 patients had disease that was amenable to complete surgical resection.

The chi-square test for independence, with Yates correction when necessary, was used to compare time-specific trends and histological findings at RPLA. Univariate predictors of VC or disease-specific survival (DSS) from the time of RPLA were analyzed by using the Kaplan-Meier method and log-rank test. A Cox proportional hazards regression model that included all variables with a P values < 0.05 on univariate analysis was built to predict DSS. All statistical analysis where performed using SPSS (version 17.0; SPSS Inc., Chicago, Il., JUSA).

Results

Patients characteristics prior to RPLA are summarized in Table 1. and 2.The initial histopathological diagnosis of the primary testicular tumor was obtained after radical orchiectomy. Prior to 2nd -line chemotherapy, 32 patients (78%) failed to achieve CR to 1st -line treatment and 9 (22%) had achieved CR followed by disease recurrence. All patients underwent postchemotherapy-RPLA (incomplete in 7 patients), whereas 13 patients (32%) necessitate redo-RPLA (accompained with nephrectomy in 6 patients). Initially, 13 ERP resections were performed in 11 patients (27%) including pulmonary (7), neck (4) and liver (2) sites.

Mean age at diagnosis was 28.8 years. Initially, 72% patients had far advanced metastatic disease, 68% had teratoma compound in the primary testicular tumor, indication for 2nd -line chemotherapy was mainly residual disease (57%), 90% patients received previously at least 2 chemotherapeutical regimens, 73% have bulky abdominal disease ≥ 5 cm in diameter and 68% patients were classified to be intermediate/poor IGCCCG risk group. At RPLA, 32% had elevated AFP and 15% had elevated HCG. RP mass pre-induction chemotherapy and pre-RPLA were 5.9+/-4.2 and 4.9+/-5.1 cm in diameter, respectively.

Characteristics	No. of patients (%)
Age, years	
Mean ± SD	28.8±3.6
Range	16-52
Initial clinical stage	
I	7(18)
IIA/IIB	4(10)
IIC	9(20)
III	21(52)
Histology and initial diagnosis	
With teratoma compound	28(68)
Without teratoma compound	13(32)
Indication for 2nd line chemotherapy	
Disease progression	8(19)
Disease recurrence	10(24)
Residual disease	23(57)
No. of chemotherapy regimens before RPLA	
2	37(90)
>2	4(10)
Retroperitoneal mass pre-RPLA	
< 5 cm	11(27)
≥ 5 cm	30(73)

Table 1. Characteristics of patinetnts before salvage RPLA

CHARACTERISTICS/REGIMENS	No. of patients (%)
IGCCCG at iduction chemotherapy	
Good	13(32)
Intermediate/poor	28(68)
First chemotherapy regimen (n=41)	
PVB	15(42)
PEB	18(34)
PE	1(3)
HD PVBE	6(18)
HDPEB	1(3)
Second chemotherapy regimen (n=48)	
PVI	32(68)
PVE	9(18)
PE	1(2)
VAB – 6	3(6)
CARBOPEC	3(6)
RP mass preinducation chemotherapy (mean±SD) cm	5.9±4.2
RP mass pre-RPLA(mean±SD) cm	4.9±5.1
Elevated serum tumor markers at RPLA	
AFP	13(32)
HCG	6(15)

Table 2. Trends in clinical characteristics and chemotherapy regimens

RPLA histology

Studies of RP pathology demonstrated the presence of fibrosis in 15%, teratoma in 39% and VC in 46%, with survival in 67%, 56% and 32%, respectively. Worse (VC) vs. favorable (fibrosis/teratoma) histology occurred in relation of 54% vs. 46% ($p<0.05$). RPLA histology was not associated with the size of the RP mass. Different histology occurred in 5 of 13 patients (38%) on redo-RPLA in comparison to previous RP histology, whereas 6 patients (46%) are alive and free of disease (Table 3.).

Histology	No. of patients	Died	Alive free of disease
Fibrosis	**5(15%)**	**2(33%)**	**4(67%)**
Teratoma	**16(39%)**	**7(44%)**	**9(56%)**
Vital carcinoma	**19(46%)**	**13(68%)**	**6(32%)**
Total	**41(100%)**	**22(54%)**	**19(46%)**

Table 3. Clinical outcam in relation to histological analysis on salvage RPLA

ERP sites of resection

VC was indentified in 6 patients (55%), teratoma in 2 patients (18%) and fibrosis in 3 patients (27%). Overall, 4 of 11 patients (36%) had ERP specimen with the histologic finding as at the RPLA specimen, and 7 patients (64%) had discordant histology (Table 4.)

EXTRA-RETROPERITONEAL HISTOLOGY, NO: OF PATINENTS(%)

RPLA HISTOLOGY	FIBROSIS	TERATOMA	VC
FIBROSIS (n=1)	1(100)*	-	-
TERATOMA (n=4)	1(25)	-	3(75)
VC(n=6)	1(17)	2(68)	3(49)*
TOTAL(n=11)	**3(27)**	**2(18)**	**6(55)**

*concordinant histology

Table 4. Concordance of retroperitoneal and extra-retroperitoneal histology in 11 patinets

Clinical outcome

Thirty patients (73%) are rendered grossly free of disease and 26 (63%) obtained serologic remission. Nine patients (32%) who relapse within median free interval of 28 months

(8 in RP lymph nodes, 1 in RP lymph nodes and lung) necessitate new salvage chemotherapy followed by surgery (3 teratoma, 6 VC). Twenty two patients (54%) died: 19 of primary disease, 2 of chemotherapy related toxicity and 1 of metachronous germ cell testicular tumor. Alive and free of disease are 19 patients (46%) at median follow-up of 121 months (Table 5.).

Univariate analysis of clinicopathologic parameters associated with VC included RP mass ≥ 5 cm in diameter, elevated level of AFP ($p<0.001$) or HCG ($p<0.05$) and ERP resection ($p<0.04$) (Table 6.).

RPLA

CHARACTERISTICS	NO: OF PATIENTS (%)
	41
Rendered grossly free of disease	30(73)
Serologic remission	26(63)
Continously free of disease	15(34)
Relapse	9(32)
MFI to relapse, months (range)	28(5-120)
Localisation of relapse	RPLN(8), RPLN + lung (1)
CR following surgery in relapse	4(44)
Died	22(54)
Alive free of disease	19(46)
MFU, months (range)	131(49-225)

Table 5. Fate and survival following salvage

VARIABLE	VC, NO. OF PATIENTS (%)	P
Clinical stage		
IIC	10(50)	0.4
III	9(43)	
IGCCCG category		
Good (n=13)	7(54)	0.9
Intermediate/poor(n=28)	12(43)	
Indication for 2nd line chemotherapy		
Disease progression (n=8)	4(50)	0.8
Disease recurrence (n=10)	3(30)	
Residual disease (n=23)	12(52)	
RP mass before salvage RPLA, cm		
≥ 5 (n=30)	15(50)	<0.05
< 5 (n=11)	4(37)	
AFP elevated		
Yes (n=6)	9(69)	<0.001
No (n=28)	10(36)	
HCG elevated		
Yes (n=6)	4(67)	<0.05
No (n=35)	14(43)	
Extraretroperitoneal resection		
Yes (n=11)	6(54)	<0.04
No (n=30)	13(43)	

Table 6. Univariante analysis of clinical pathological parameters and VC at the time of salvage RPLA

On univariate analysis, survival was worse in patients who had RP mass ≥ 5 cm in diameters (p<0.04), elevated level of AFP (p<0.05) or HCG (p<0.007), ERP resection (p<0.001) and VC (p<0.04).

On multivariable analysis, a RP mass ≥ 5 cm in diameter (p<0.005) and VC (p<0.03) predicted worse prognosis. For a sensitivity of analysis, we excluded the patients who had elevated STM at the time of RPLA. VC either in RP or in ERP sites predicted worse prognosis (p=0.001). Although it was not statistically significant, there was trend toward improved survival in patients who had RP mass < 5 cm (p=0.14) and in patients who had teratoma or fibrosis in the RP (p=0.07) (Table 7.).

VARIABLE	HR	95% CI	p
Worst histology of RP or extra-RP resection (VC vs teratoma or fibrosis)	4.42	1.6-12.4	0.005
Size of RP mass pre RPLA (≥5 vs < 5cm)	3.02	1.1-8.1	0.03
Elevated HCG	2.89	0.9-10	0.08

Table 7. Cox proportional hazards regression analysis for survival

Discussion

Resection of residual masses after multiple chemotherapy regimens is an integral component of the successful treatment of patients with advance NSTT[9].The histologic findings after multiple chemotherapy regimens differ substantially from those generally reported for RPLA after induction chemotherapy, in which approximately 40% to 45% of patients have fibrosis, 40% to 45% of patients have teratoma, and 10% to 20% have VC[9,10]. For RPLA after multiple chemotherapy regimens, the largest series of patients, which was reported by Fox et al[5], had 55% with VC, constant with 2 subsequent studies by Hendry et al[6] and Rick et al[7], which showed rates of 42% and 49%, respectively.

In the current study, there were three important findings for patients undergoing RPLA after multiple chemotherapy regimens. First, nearly 85% patients have either VC or teratoma.

Second, ERP disease frequently harbors VC or teratoma (73%). Third, DSS is unfavorable (46%).

Eggener et al in 2007 reported that the patients who received taxane-containing salvage regimens had a higher rate of fibrosis (51%) and lower rate of VC (28%) with CR in 70% patients who received TIP (taxanes,ifosfamide,platinum) and in 57% of patients who received TICE (taxanes,ifosfamide, carbolatin, etoposide)[11]. The 10-year DSS rate was 70%. Although it was lower, the frequency of VC confirm the important therapeutic role of salvage surgery while predicting the need for additional chemotherapy. The TIP regimen is administrated to patients who developed recurrent disease after achieving a CR to induction chemotherapy[2], whereas TICE is administrated after incomplete response to induction chemotherapy[4].

In addition, nearly 39% of all patients in our study had elements of teratoma at RPLA. Considerable evidence highlights the importance of complete resection of teratoma. Residual teratoma has the potential for local growth, leading to local invasion and the growing syndrome[12]. Malignant transformation to sarcoma and various other histology has been reported[13,14]. Finally, patients with teratoma are at risk for late recurrence, which carries an increased probability of being refractory to treatment[15,16,17,18].

Elements of VC or teratoma were indentified in 73% of patients who underwent ERP resection in comparison to only 31% in series of patients managed with taxane-containing regimens[11]. This study highlights the importance of resection of all sites of disease after chemotherapy, including ERP masses, to optimize outcome. Although there is an inherent appeal to determine the need for ERP resection on RP histology we observed an overall of 64% discordance rate between RP and ERP histology, in comparison of 25% in previously mentioned study[11]. Although patients with fibrosis in the RP had a high likelihood of fibrosis at ERP sites, the number of patients is small, and RP histology is not know when ERP resection are performed during the same surgery. Hence, without complete certainly regarding fibrosis at ERP sites, we continue to advocate resection of all ERP sites[16].

We also found a trend toward worse survival when the HCG level was increased prior to surgery, whereas the AFP level was not associated with worse outcome. These findings are consistent with previous reports

that an elevated AFP level at time of salvage surgery is associated with a more favorable outcome compared with patients who have an elevated HCG[19,20].

Conclusions

In a series of 41 patients who underwent RPLA after multiple chemotherapy regimens DSS can reach only 46%, with finding of fibrosis in 15%, teratoma in 39% and VC in 46% patients following conventional salvage chemotherapeutical regimens. During the latter years, taxanes-containing regimens resulted in significantly lower incidence of VC and higher incidence of fibrosis within resected specimen at RPLA, with 10-year DSS rate of 70%. Therefore, TIP and TICE are salvage regimens of choice following relapse or incomplete response to 1st -line chemotherapy. On the other hand, our data support the continued use of salvage surgery in three separate groups of patients. First, patients who achieve a CR to 2nd -line chemotherapy and have no radiologic evidence of disease should undergo RPLA. Second, patients who achieve a PR to chemotherapy with resectable residual masses should undergo RPLA with ERP resection, as indicated. Finally, highly selected patients with residual masses and elevated STM levels, particularly AFP, after chemotherapy may be candidates for surgery.

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