Analiza rezultata posthemioterapijske retroperitonealne limfadenektomije kod pacijenata sa intermedijarnim i lošim rizikom neseminomskih tumora testisa

Argirović M. Đorđe[1], Argirović Đ. Aleksandar[2]
[1]Urološka Klinika, Klinički centar Srbije, Poliklinika Argirović, Urologija, Beograd, Srbija
[2] Kliničko bolnički centar Zemun-Beograd, Urološko odeljenje, Beograd, Srbija

Apstrakt

Cilj ove studije je procena rezultata lečenja pacijenata sa intermedijarnim i lošim rizikom po kriterijumima "International Germ Cell Cancer Collaborative Group" (IGCCCG) metastatskih neseminomskih tumora testisa (NSTT) pomoću hemioterapije i retroperitonealne limfadenektomije (RPLA). U periodu od 1982do 2005, 82 pacijenta sa metastatskim NSTT, klasificiranih kao intermedijarna (65) i loša (17) rizična grupa po IGCCCG kriterijumima, su imali posthemioterapijsku (PH)-RPLA za srednje praćenje od 95meseci. Srednji dijametar RP rezidualne mase (RM) je iznosio 3.0 cm, 15 (18.3%) pacijenata je imalo povišene vrednosti tumorskih markera u serumu (TMS) pre PH-RPLA. Dvadeset i sedam (32.9%) pacijenata je iziskivalo administraciju hemioterapije druge linije, a kod 75 (91.5%) RP RM je kompletno resecirana. Retroperitonealna histološka analiza je pokazala prisustvo fibroze kod 20 (26%), teratoma kod 36 (42%) i vitalnog karcinoma kod 26 (32%), sa preživljavanjem u 76%, 80% i 38%, respektivno. Pacijenti podvrgnuti drugoj hemioterapijskoj liniji su imali signifikantno veću učestalost vitalnog karcinoma na PH-RPLA (49% prema 24%)(P<0.001). Pacijenti sa lošim rizikom NSTT nisu imali signifikantno veću verovatnoću progresije (47% prema 55%)(P=0.5) i gori ishod (53% prema 69%)(P=0.2) nego sa intermedijarnim rizikom. Analiza pacijenata koji su primali hemioterapiju prve linije pokazuje signifikantno veću verovatnoću slobode progresije (VSP) (66% prema 41%) i bolje preživljavanje (74% prema 48%)(P<0.01) posle PH-RPLA nego oni koji su primili hemioterapiju druge linije. Konstatovano je bolje preživljavanje kod pacijenata sa prvom prema drugoj liniji hemioterapije pre PH-RPLA u pogledu nalaza na RP histologiji kod fibroze (94% prema 20%), teratoma (88% prema55%)

Outcome analysis of post-chemotherapy retroperitoneal lymphadenectomy in men with intermediate- and poor- risk nonseminomatous testicular tumors

Argirovic M. Djordje[1], Argirovic Dj. Aleksandar[2]
[1] Outpatient Clinic Argirovic, Urology, Belgrade,Serbia
[2] Clinical Hospital Center Zemun-Belgrade, Department of Urology, Belgrade, Serbia

Abstract

The aim of the present study is to evaluate the outcome in patients treated with chemotherapy and retroperitoneal lymphadenectomy (RPLA) after an diagnosis of International Germ Cell Cancer Collaborative Group (IGCCCG) intermediate- and poor- risk metastatic nonseminomatous testicular tumors (NSTT), as the integration of chemotherapy and surgery in managing advanced NSTT continue to develop. Between 1982 and 2005, 82 patients with NSTT, classified as either intermediate- 65 (79%) and poor-risk 17 (21%) by IGCCCG criteria, had post-chemotherapy (PC)-RPLA with a median follow-up of 95 months. The median RP residual mass was 3cm and 15 (18%) patients had elevated serum tumor markers (STMs) before PC-RPLA. Twenty seven (33%) patients required second-line chemotherapy, and in 75 (92%) patients RP residual masses were completely resected. Retroperitoneal histology analysis revealed the presence of fibrosis in 20 (26%), teratoma in 36 (42%) and viable germ cell tumor (GCT) in 26 (32%), with disease specific survival (DSS) in 76%, 80% and 38%, respectively. Patients submitted to second-line chemotherapy had significantly higher occurrence of viable GCT at PC-RPLA (49% vs. 24%)(P < 0.001). The patients with poor-risk NSTT were not at significantly higher risk of progression (47% vs. 55%) (P= 0.5) and worse outcome (53%vs. 69%) (P=0.2). than those with intermediate-risk NSTT. In subset analysis patients receiving first-line chemotherapy had significantly higher progression-free probability (PFP) (66% vs. 41%) and better survival (74% vs. 48%) (P<0.01) at PC-RPLA than those requiring second-line chemotherapy. There was better no evidence of disease status in patients with first- vs. second-line PC-RPLA regarding RP histology in fibrosis

i vitalnog karcinoma (54% prema 23%)(P<0.001). Ukupno, 5-godišnja VSP i preživljavanja su iznosili 57%(95% IP, 50%-62%) i 69%(95% IP, 61%-77%). Multivarijantna analiza je pokazala da nepotpuna resekcija (P<0.001), veličina PH RM (P=0.01) i nalaz teratoma i vitalnog karcinoma (p<0.01) na PH-RPLA predstavljaju nezavisne prediktivne faktore za recidiv bolesti. Pacijenti sa uznapredovalim NSTT imaju dug vremenski interval do progresije kada se hemioterapija kombinuje sa resekcijom RM. Naši nalazi ukazuju da odgovor tumora na hemioterapiju u kombinaciji sa kompletnom resekcijom svih RM, predstavlja garanciju za dugotrajno preživljavanje bez progresije bolesti.

Ključne reči: tumori testisa, neseminomski, hemioterapija, hirurgija, retroperitonealna limfadenektomija.

(94% vs. 20%9, teratoma (88% vs. 55%9 and viable GCT 854% vs. 23%9 (P<0.001). Overall, the 5-year PFP and DSS were 57% (95% CI, 50-65%) and 69% (95% CI, 61-77%). In multivariate analysis incomplete resection (P<0.001), size of PC RM (P=0.01) and the finding of teratoma and viable GCT (P<0.01) at PC-RPLA independently predicted disease relapse. Patients with advanced NSTT have long-term freedom from disease progression when chemotherapy is combined with resection of residual masses. Our data suggest that the tumor response to chemotherapy, coupled with complete resection of all RM, predicts long-term freedom from disease progression.

Key words: testicular tumors, nonseminomatous, chemotherapy, surgery, retroperitoneal lymphadenectomy.

Introduction

In patients with advanced germ cell tumors (GCTs), the introduction of cisplatin (CDDP)-based combination chemotherapy has resulted in cure rate approaching 80% [1].A better understanding and use of STMs and integration of adjunctive surgical resection of residual masses has contribute significantly to the comprehensive care of these patients. Nonetheless, approximately 80%of patients presenting with metastatic disease eventually died from GCT. Currently therapeutic goals are directed at obtaining maximum treatment efficacy in those destined to fail, while at same time reducing treatment-related toxicity in those considered most likely to have a complete response.

Several published reports have assessed the use of clinical prognostic variables that might predict the outcome of patients with metastatic GCT [2-4]. In general, the level of STMs and the extent and sites of metastatic disease have been found to predict the response to chemotherapy, and ultimately the probability of survival. In an effort to achieve a uniform and standardized predictive model, the IGCCCG published prognostic factor-based system [5]. Among patients with advanced NSTT, three prognostic groups are indentified on the basis of STMs level and sites of metastatic involvement. Of these patients, approximately 40% fall within the intermediate- or poor-risk categories, achieving overall 5-year survival rates of 79% and 48%, respectively. We think that the integration of risk-based chemotherapy and aggressive surgery is essential in the overall care of patients with advanced NSTT. Currently, standard therapy in patients with intermediate- and poor-risk metastatic NSTT at the authors institutions consist of four cycles of conventional doses of CDDP, bleomycin and etoposide followed by RPLA of residual masses. In selected cases surgery is used in those with elevated STMs. In addition, all extra-retroperitoneal residual masses are resected regardless of histological findings at RPLA. In the current study, we analyzed our contemporary results in patient with intermediate- and poor-risk NSTT managed with chemotherapy and RPLA.

Material and methods

Between 1982 and 2005, 82 patients with NSTT, classified as either intermediate- or poor-risk by IGCCCG criteria, had RPLA after first- or second-line chemotherapy. Patients with primary extragonadal NSTT were excluded from the study.

All patients were staged before induction chemotherapy with STMs, ultrasound and/or CT of the abdomen and pelvis, and either CT or chest X-ray. Nadir STM level after orchiectomy and before chemotherapy

were used in the assignment of IGCCCG risk groups. After first-line chemotherapy, patients were re-staged with STMs and imaging as above. Patients were considered to have elevated STMs if the level of alpha-fetoprotein (AFP) or hCG were above the upper limit of normal (6.2 ng/mL and 2.2 mIU/mL, respectively). Patients with persistently elevated STMs or progression of disease went on to receive second-line chemotherapy before RPLA/ All patients had RPLA after chemotherapy, and with rare exceptions all men treated for advanced NSTT at our institution are recommended to undergo RPLA after chemotherapy and normalization of STMs, irrespective of residual mass size, and in selected cases where STMs remained persistently elevated. The size of the retroperitoneal mass before and after chemotherapy was assessed by maximum transverse diameter on ultrasound and/or CT imaging. Complete resection was defined as complete excision of all residual retroperitoneal masses.

Progression-free probability (PFP) and disease-specific survival (DSS) were estimated using the Kaplan-Meier method. For survival analysis, the follow-up was started at the time of RPLA. Factors associated with progression after RPLA were evaluated in univariate and multivariate analyses using the Cox proportional hazards regression, with P\0.05 considered to indicate statistical significance, and hazard ratios with 95% CIs reported for the Cox regression model.

Results

The patients clinical features are listed in Table 1.The median (range) AFP and HCG levels before chemotherapy were 624 (0-92.000) ng/mL and 708 (0-860.000) mIU/mL, respectively, and the retroperitoneal mass was 7.5 (0-18) cm. After first-line chemotherapy 55 patients had RPLA and 27 required second-line chemotherapy before RPLA. After chemotherapy the median AFP level declined to 3.6 (0-1820) ng/mL, and the median HCG declined to null (0-101) mIU/mL. In all, 15 (18%) patients had persistently elevated STMs before RPLA. The median residual retroperitoneal mass was 3.0 (0-15) cm. Residual extra-retroperitoneal masses were present in 20 (17%) patients. The sites of extra-retroperitoneal metastases included lung (16), neck lymph nodes (2), mediastinal and neck lymph nodes (1), brain (2) and liver (3).

VARIABLE	NO. OF PATIENTS (%)
Mean age, ± SD (range)	28.4 ± 3.8 (16-57)
Histology at initial diagnosis	
With teratoma compound	53 (65)
Initial clinical stage	
A (I /IS)	5 (6)
B1/B2 (IIA/IIB)	14 (17)
B3 (IIC)	31 (38)
C (III)	32 (39)
IGCCCG classification	
Intermediate risk	65 (79)
Poor risk	17 (21)
Chemotherapy regimen	
1st line	82 (100)
PVB	21 (25)
PEB	45 (56)
HDPVBE	15 (18)
2nd line	27 (33)

Residual retroperitoneal mass, cm	
None	1 (1)
<2	4 (4)
2-5	10 (12)
5-10	43 (53)
>10	25 (30)

Table 1. The clinical and patient characteristics before RPLA

All 82 patients had RPLA and histological findings are also outlined in Table 2. Among these, all retroperitoneal masses were completely resected in 75 (92%) patients. Twenty seven (33%) patients requiring second-line chemotherapy had a significantly higher occurrence of viable GCT et RPLA (49% vs. 24%)(P<0.001). In 5 (5%) patients with residual masses of < 20 mm, 3 (60%) had teratoma and 2 (40%) fibrosis. Overall, retroperitoneal pathology revealed fibrosis in 24%, teratoma in 44% and viable GCT in 32%, with DSS in 76%, 80% and 38%, respectively. Redo-RPLA due to relapse were performed in 16 (19%) patients, 2 after initial previous attempt elsewhere combined with nephrectomy in 4 patients (discordant redo- histology vs primary surgery occurred in 5 patients).

VARIABLE (n)	NO. OF PATIENTS (%)
All patients (82)	
Fibrosis	20 (24)
Teratoma alone	36 (44)
Mature	25 (30)
Immature	9 (11)
With malignant transformation	2 (22)
Viable GCT	26 (32)
1st line chemotherapy alone (55)	
Fibrosis	16 (29)
Teratoma	26 (47)
Viable GCT	13 (24)
2nd line chemotherapy alone (27)	
Fibrosis	5 (18)
Teratoma	9 (33)
Viable GCT	13 (49)

Table 2. The pathological characteristics in resected retroperitoneal masses

In all, 20 patients had evidence of residual disease outside the retroperitoneum. Overall histological finding in extra-retroperitoneal residual masses were fibrosis in 6 (30%), teratoma in 6 (30%) and viable GCT in eight (40%) patients. Fourteen (70%) of 20 patients had extra-retroperitoneal specimen with the same histological findings as retroperitoneal specimen. Four patients underwent repeat extra-retroperitoneal resection due to relapse with discordant histology vs. primary surgery (Table 3.).

		ERP HISTOLOGY, No. Pts (%)		
RP HISTOLOGY	**No. Pts (%)**	**FIBROSIS**	**TERATOMA**	**VIABLE GCT**
Fibrosis	5 (25)	4 (80)*	-	1 (20)
Teratoma	9 (45)	-	6 (67)*	3 (33)
Viable GCT	6 (30)	2 (33)	-	4 (67)*
Total	20 (100)	6 (30)	6 (30)	8 (40)

* CONCORDANT HISTOLOGY

Table 3. Concordance of RP and ERP histology in 20 patients

The median (interquartile range) follow-up for survivors was 95 (39-273) months. Thirty eight (46%; 29 in the intermediate- and 9 in the poor-risk group) relapsed at a median of 5 months. Figure 1. summarizes the clinical outcome of the patients according to treatment algorithm.

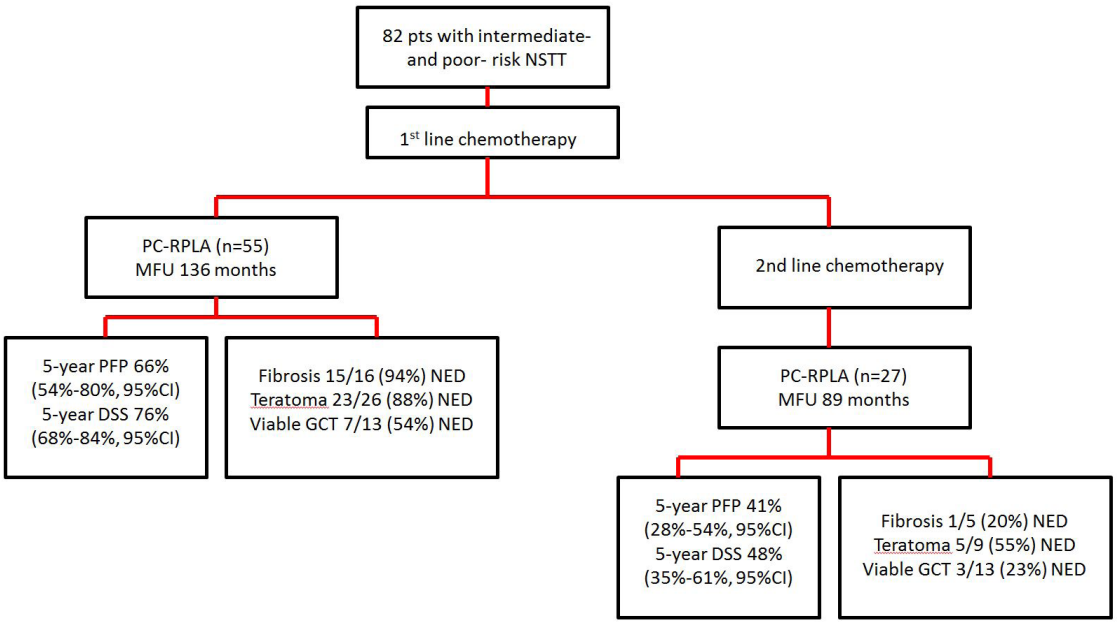

Figure 1. The clinical outcome for pts metastatic NSTT

Overall, the 5-year PFP (95% CI) for all patients was 57 (50-65)%, and the 5-year probability of DSS was 69(62-76)%. The patients with poor-risk were not at significantly higher risk of progression 847% vs. 55%((P=0.5) and worse outcome (53% vs. 69%)(P=0.2).Twenty eight (34%, 20 in the intermediate- and 8 in the poor-risk group) died from progressive disease at median follow-up of 44 months. In a subset analysis, patients receiving only first-line chemotherapy differ significantly in their probability of disease progression after RPLA from those requiring second-line chemotherapy (5-year PFP 66% and 41%, respectively, P < 0.01). There was significantly better no evidence of disease status in patients with first- vs. second-line PC-RPLA regarding histology in fibrosis (94% vs. 20%), teratoma (88% vs. 55%) and viable GCT (54% vs. 23%) (P<0.001). there was no difference in outcome between the patients with extra-retroperitoneal and those with disease limited to the retroperitoneum (50% vs. 66%)(P=0.2).

In a univariate analysis of clinical and pathological variables, residual RP mass size (P<0.001), incomplete surgical resection (P<0.01), and histologic finding of teratoma and viable GCT (P<0.01) were significant predictors of disease progression and relapse. IGCCCG risk classification, the need for second-line chemotherapy,

and elevated STMs at the time of RPLA were not significant predictors of disease recurrence. In a multivariate analysis, incomplete resection (P<0.001), size of post-chemotherapy residual masses (P=0.01) and the finding of T or viable GCT (P<0.01) at RPLA independently predicted ds relapse (Table 4.).

VARIABLES	HAZARD RATIO (95% CI)	p
Univariate analysis		
Clinical		
Size of mass		
Before chemotherapy	1.05 (0.97-1.13)	0.2
After chemotherapy	1.15 (1.05-1.25)	0.002
Elevated STMs at RPLA	1.30 (0.63-2.73)	0.5
Poor vs. Intermediate IGCCCG risk group	0.80 (0.44-1.47)	0.5
2^{nd} line chemotherapy	1.40 (0.75-2.62)	0.3
Pathological		
Incomplete vs. complete resection	7.85 (3.51-17.55)	<0.001
RP histology		
Teratoma vs. Fibrosis	2.49 (1.16-5.32)	0.02
Viable GCT vs. Fibrosis	6.61 (2.84-15.43)	<0.001
Multivariate analysis		
RP histology		
Teratoma vs. Fibrosis	3.34 (1.43-7.79)	0.005
Viable GCT vs. Fibrosis	7.26 (2.81-18.80)	<0.001
Incomplete vs. complete resection	10.42 (3.89-27.91)	<0.001
Size of mass after chemotherapy, cm	1.14 (1.03-1.25)	0.01

Table 4. Univariate and multivariate analysis of clinical and pathological variables associated with relapse and ds progression

Discussion

Overall cure rates for patients with advanced NSTT have approach 80% over the last two decades. While effective CDDP-based chemotherapy has been held largely responsive for these trends, the role of RPLA after chemotherapy remains essential. It is well recognized that the prognosis after surgery is primarily predicted on histological features of resected residual masses. Initial reports of post-chemotherapy residual mass histology indicated the presence of fibrosis, teratoma or viable GCT in about a third of cases each [6]. Current series reports necrotic debris or fibrosis in 40-50%, teratoma in 35-40% and viable malignant cells in 10-15% [7]. Such a decrease in the proportion of viable malignant cells is generally attributed to stage migration and the use of more effective chemotherapy regimens. In the present study of patients with intermediate- and poor-risk NSTT, the distribution of retroperitoneal histology at RPLA is not consistent with other contemporary series.

In an attempt to obviate adjunctive surgery, many criteria and statistical models have been proposed to predict the presence of fibrosis, nonetheless, there is a false-negative prediction of approximately 20% [8]. Oldenburg et al. [9] showed that after chemotherapy a third of retroperitoneal masses of <20 mm had teratoma (60%) and fibrosis (40%).

While many advocate a policy of surveillance for such small masses, the consequence of residual viable GCT is disease progression [10,11]. Furthermore, the histological potential of unresected teratoma remains unpredictable. Despite a benign histological appearance, teratoma can grow, obstruct and invade local structures or became entirely unresectable. It might also undergo malignant transformation into chemo-resistant sarcoma or carcinoma [12]. Lastly, late relapses (> 2 years) is associated with unresected teratoma and is also highly chemo-resistant [13,14,15].

Given the uncertainty in predicting the histology of residual masses after chemotherapy, we routinely use RPLA on normalization of STMs. However, in a few selected patients with persistently elevated STMs, residual masses are also resected [16]. Moreover, as the reported rate of discordant histology between retroperitoneum and extra-retroperitoneal masses is 29-46%, all sites of disease are resected [17, 18].

The present study underscore the essential role of surgery after chemotherapy in the comprehensive management of patients with metastatic NSTT. We report an overall 5-year PFP and DSS of 57% and 69%, respectively, when all sites of residual disease are resected. In the multivariate analysis the only preoperative indicator of disease relapse was the size of residual retroperitoneal masses after chemotherapy.

Contrary to reports by Fizazi et al. [19], the IGCCG risk category did not affect the overall prognosis after RPLA, but it is possible that a higher proportion of men initially with IGCCCG poor-risk disease had rapid disease progression and never had RPLA, and therefore were not included in this study [10]. The use of second-line chemotherapy predict higher probability of relapse and lower DSS after surgery. Such a finding suggests that patients who receive second-line chemotherapy before RPLA are less likely to be salvageable at subsequent relapse. Nevertheless, the overall outcome strongly support RPLA in patients who received second-line chemotherapy [20].

Several investigators emphasized the importance of complete resection of residual masses after chemotherapy [19, 21, 22]. We showed similarly, in a multivariate analysis, that complete resection of residual retroperitoneal masses independently predicted progression-free survival. As outlined previously, while the consequence of incompletely resected viable GCT is certain disease progression, residual teratoma behaves less predictable [23]. In the present series, among 36 patients with retroperitoneal teratoma, 2 (5.5%) had evidence of malignant transformation. Unlike GCTs, teratoma with malignant transformation is un responsive to conventional cisplatin-based chemotherapy regimens and complete surgical resection remains the mainstay of therapy [24]. Finally, in multivariate analysis the finding of residual retroperitoneal teratoma, viable GCT, and the size of the retroperitoneal mass after chemotherapy independently predicted disease relapse.

Conclusions

In patient with advanced NSTT, long-term cancer control is achieved by instituting cisplatin-based chemotherapy coupled with aggressive resection of all sites of residual masses. Our data suggest that there is no significant difference in outcome between patients with IGCCG intermediate- and poor-risk disease undergoing RPLA. However, PFP and DSS differs significantly after RPLA for men receiving first- and second-line chemotherapy. In the multivariate analysis, the size of residual retroperitoneal mass after chemotherapy, incomplete surgical resection, and the histological finding of retroperitoneal teratoma and viable GCT, independently predicted disease relapse after RPLA for men with IGCCG intermediate- and poor-risk NSTT.

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Corresponding author:
Đorđe Argirović
Outpatient Clinic Argirović, Urology
11.120 Belgrade
Serbia
Tel.: ++381 11 2788 498, 2788900
Fax.: ++ 381 11 32 90 324
Mob.: ++ 381 63 23 66 59
E-mail: cvijiceva@yubc.net