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# CLINICAL IMPACT OF MDR1-EXPRESSION IN TESTICULAR GERM CELL CANCER

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***Aim:*** **The multidrug resistance protein 1 (MDR1, P-gp, p-170) is a membrane glycoprotein that acts as an energy-dependent drug efflux pump. In various malignancies its expression is associated with resistance to diverse cytostatic drugs, and therefore predicts resistance to systemic treatment. The aim of this study was to investigate the prognostic value of MDR1 expression in primary tumor tissue to predict necrosis or viable cancer in residual tumor masses after systemic chemotherapy for advanced testicular germ cell cancer.** ***Materials and Methods:*** **Out of 77 patients, histopathological characteristics of primary testicular cancer specimens and retroperitoneal lymph node dissection (RPLND) samples following chemotherapy were available from 72 and all 77 patients, respectively. Moreover, MDR1 expression was determined by immunohistochemistry in 47 primary tumors and corresponding 73 RPLND sections.** ***Results:*** **After chemotherapy and subsequent RPLND, the examination of residual tumor masses revealed that mature teratoma and active viable tumor were predominantly found in patients with non-seminoma (NSGCT; $p = 0.048$), especially in those with containing mature teratoma ($p = 0.001$). Moreover, using univariate analysis the expression of MDR1 in the primary testicular tumor predicted viable tumor/teratoma residues in RPLND sections ($p = 0.003$). However, in multivariate analysis including the tumors' histological subtype, MDR1 expression alone failed to reach statistical significance as an independent prognostic marker for residual vital tumor ($p \geqslant 0.16$).** ***Conclusions:*** **With the limited number of patients given, the correlation between MDR1 expression in primary testis cancer and active residual retroperitoneal disease after chemotherapy failed to reach statistical significance as in independent marker. Therefore, up to now routine MDR1 staining of testicular germ cell cancer samples should not be performed in clinical practice. However, as there was a clear trend, a larger number of patients suffering from metastatic non-seminomas should be studied, as MDR1 expression might have significant prognostic value in this particular subgroup of patients.**

***Key Words:*** **testis, tumor, NSGCT, seminoma, teratoma, P-gp, p170, RPLND.**

Germ cell cancer is the most frequent malignant tumor type in young men, and its incidence has continuously been increasing [1]. Fortunately, during the last 25 years it has become the "model" of a curable neoplasm. The major factor for the high cure rate is the high level of sensitivity of germ cell cancer cells to a variety of chemotherapeutic agents, in particular to cisplatin. Following orchiectomy, which should regularly be performed prior to any further treatment, today, patients suffering from a seminoma (stage ⩾ IIC) or non-seminoma (stage ⩾ IIA) should receive combined chemotherapy comprising cisplatin, etoposide, and bleomycin (BEP-regimen) [1]. For patients with good and intermediate/poor prognosis, according to IGCCCG criteria [2], standard treatment is three and four cycles of BEP, respectively [2–4]. In addition, in patients with non-seminoma who show residual masses of ⩾ 1 cm and normalisation of tumor markers after systemic therapy the residual masses have to be resected [5–7]. Histopathological examination of RPLND sections in case of residual retroperitoneal disease after first-line chemotherapy have revealed necrosis, mature teratoma and active vital cancer in about 50%, 35%, and 15% of patients, respectively [1, 8]. However, we still lack reliable markers predicting the character of the residual masses prior to surgery, even though size, the histology of the testicular tumour and, if applicable, the expression of serum tumour markers do have indicating potential.

Multidrug resistance (MDR) is a phenomenon that renders cells resistant to chemotherapeutic agents in many cancer patients. One of the mechanisms responsible for this pleiotropic effect is reduced drug accumulation inside the cells, due to the activity of a 170 kDa transmembrane protein, MDR1 (P-glycoprotein, P-gp, , P-170, or mdr1 gene product) [9, 10]. Eid et al. [11] were able to show that MDR1 is frequently overexpressed in germ cell testicular tumors of advanced stage and aggressive phenotype [12].

The aim of this study was to evaluate the significance of MDR1 expression to predict necrosis/fibrosis, teratoma or viable tumor in residual retroperitoneal tumor masses after systemic chemotherapy. Moreover, we investigated whether the MDR1 level pre/post-chemotherapy was associated with a specific histological tumour subtype and/or influenced by prior cytotoxic treatment.

## MATERIALS AND METHODS

***Patients and histology***. All patients (n = 77) included in this retrospective study had been treated at the Philipps-University Medical School, Marburg (n = 64) and the Bundeswehrzentralkrankenhaus, Koblenz, (n = 13) between 1987 and 2002. Study was agreed with local ethical committee and informed consents from patients were received. Testicular specimens were obtained from 72 patients who had undergone orchiectomy for testis cancer. The tumors' histology was classified due to the World Health Organisation (WHO) [13]. Median age at

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*Abbreviations used:* MDR1 – multidrug resistance protein 1; NSGCT – nonseminomatous germ cell tumor; RPLND – retroperitoneal lymph node dissection.
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surgery was 29 years (range, 14–67). The majority of patients suffered from retroperitoneal metastases at diagnosis: clinical stage I, II and III were diagnosed in 5, 37, and 35 patients, respectively. Following initial orchiectomy, all patients received platin based chemotherapy including combinations with bleomycin (B), cisplatin (C), etoposide (E), ifosfamide (I), and/or carboplatin. Subsequently retroperitoneal lymph node dissection (RPLND) was performed in all patients; histological specimens were obtained and classified into complete necrosis, mature teratoma, and active viable tumor. Moreover, tissue samples to evaluate MDR1 expression were available from primary testicular tumors and RPLND specimens from 47 and 73 patients, respectively.

***Antibodies.*** The monoclonal mouse $IgG_{2b}$ antibody Mdr (G-1): sc-13131 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), diluted 1 : 250 and 1 : 500, was used for the detection of MDR1 expression [14]. The optimal dilution for immunostaining was obtained using testicular tumor-tissue as control; the optimal titer was defined as the dilution that gave clearly identifiable membrane or granular cytoplasmatic staining. Normal testicular tissue served as negative control.

***Immunohistochemistry.*** Immunohistochemical staining was performed with the 3,3'-diaminobenzidine (DAB) chromogen — detection method (DAKO Cytomation, Hamburg, Germany) employing an enzyme linked antibody technique. Briefly, paraffin serial sections were prepared in xylol and hydrated in ethanol. The peroxidase was inactivated with phosphate-buffered saline (PBS) and 3% $H_2O_2$. Subsequently, the sections were dampened with target retrieval solution (pH 6.1; TAKO Cytomation, Hamburg, Germany) and incubated in water vapour at 94 °C for 30 min. After rehydration with phosphate-buffered saline (PBS), the sections were incubated in PBS containing 2% skim mild powder solution (Fluka BioChemika, Buchs, Switzerland). Subsequently, these sections were exposed to the primary antibody sc-13131 for 60 min followed by an incubation with anti-mouse EnVision® labelled polymer immunoglobulin (DAKO Cytomation, Hamburg, Germany) for 30 min at 20 °C. Each step was followed by washing in PBS. Finally, they were immersed in DAB (Liquid DAB+ substrate solution, DAKO, Hamburg, Germany) for 15 min to visualise the reaction products. After washing in aqua dest, specimens were counterstained with Mayer's haemalaun solution (Merck, Darmstadt, Germany).

***Scoring of immunostaining results.*** The evaluation of immunostaining results was scored by two investigators without knowledge of the clinical data of the patients. Sections were scored as follows: –, no staining; +, positive staining (weak/moderate); ++, strong staining in most tumor cells.

***Statistics.*** Data analysis was performed using the SPSS statistical software package (SPSS, Inc., Chicago, USA). Relations between clinicopathological characteristics and staining of MDR1 were determined using $\chi^2$ analysis and the Fisher-exact-test with $p < 0.05$ considered significant. MDR1 expressions pre- and post-chemotherapy were compared with the Wilcoxon test.

## RESULTS

***Histology of the testicular tumor and residual retroperitoneal tumor mass after chemotherapy.*** The histological subtype of the primary testicular tumor was available from 72 patients; 17 (23.6%) and 55 (76.4%) suffered from a seminoma and NSGCT (nonseminomatous germ cell tumor), respectively. Out of those with NSGCT, 30 patients presented with primary tumor containing teratoma. After orchiectomy and chemotherapy with various regimens (BEP, PEI, Carboplatin) and dosage (2–6 cycles), RPLND was performed in all 77 patients, and the residual retroperitoneal tumor masses were examined histologically. Entirely necrotic tumor tissue, mature teratoma, and active viable tumor were found in 44 (57.1%), 18 (23.4%), and 15 (19.5%) patients, respectively.

Moreover, we examined whether the tumor subtype of the primary testicular tumor predicts the histological findings after RPLND. Out of 17 patients with seminoma, only 2 (11.8%) and 1 (5.9%) patients presented with pure teratoma and viable cancer in the residual retroperitoneal tumor masses. In contrast, in 15 (27.3%) and 14 (25.5%) patients with NSGCT (n = 55), teratoma and viable tumor tissue were found in RPLND sections, respectively ($p = 0.048$; Fisher's exact test; the Table). Looking at the subgroup of NSGCT patients with teratoma-constituents in their primary testicular tumor tissue (n = 30) in comparison to all patients with teratoma-free primary tumors (n = 42), the correlation was even more significant: teratoma and viable germ cell tumor in RPLND sections were found in 40% versus 11.9% and 30% versus 14.3% of patients ($p = 0.001$; Fisher's exact test). All results are summarized in the Table.

**Table.** Histopathology and MDR1 expression in primary testicular tumours and the respective retroperitoneal RPLND sections after chemotherapy

| Primary tumor | RPLND histology | | | |
|---|---|---|---|---|
| | Viable tumor | Mature teratoma | Necrosis | Total |
| Histology Testicular Tumor | | | | |
| Seminoma (%) | 1 (5.9%) | 2 (11.8%) | 14 (82.4%) | 17 (100%) |
| NSGCT (%) | 14 (25.5%) | 15 (27.3%) | 26 (47.3%) | 55 (100%) |
| Total (%) | 15 (20.8%) | 17 (23.6%) | 40 (55.6%) | 72 (100%) |
| Teratoma-free (%) | 6 (14.3%) | 5 (11.9%) | 31 (73.8%) | 42 (100%) |
| Teratoma-components (%) | 9 (30%) | 12 (40%) | 9 (30%) | 30 (100%) |
| Total (%) | 15 (20.8%) | 17 (23.6%) | 40 (55.6%) | 72 (100%) |
| MDR1 Expression Testicular Tumor | | | | |
| Negative (%) | 3 (12.5%) | 2 (8.3%) | 19 (79.2%) | 24 (100%) |
| Low/moderate (%) | 2 (40%) | 2 (40%) | 1 (20%) | 5 (100%) |
| High (%) | 5 (27.8%) | 8 (44.4%) | 5 (27.8%) | 18 (100%) |
| Total (%) | 10 (21.3%) | 12 (25.5%) | 25 (53.2%) | 47 (100%) |

In total, the histological differentiation of the primary testicular tumor (NSGCT/seminoma and teratoma/non-teratoma) allowed prediction of the composition of residual retroperitoneal tumor masses following chemotherapy.

***MDR1 expression in the primary testicular tumor and the residual retroperitoneal tumor mass after chemotherapy.*** MDR1 expression was determined by immunohistochemistry in 47 primary tumor samples and 77 RPLND sections following chemotherapy. Perfoming semiquatitative analysis 24 (51.1%) patients presented with testicular germ cell tumors lacking MDR1 protein whereas weak/modera-

te and strong staining were found in 5 (10.6%) and 18 (38.3%) patients, respectively (the Table). No seminomatous tumor expressed MDR1. In contrast, 5 (16.7) and 18 (60.0%) out of 30 NSGCT expressed weak/moderate and high levels of MDR1 protein, respectively ($p < 0.001$, Fisher's exact test). Moreover, in testicular tumors containing teratoma-constituents MDR1 was detected in a significantly higher frequency (15/18, 83.3%) compared to teratoma-free tumors (8/29, 27.6%; $p < 0.001$, Fisher's exact test).

Looking at the sections of residual retroperitoneal masses obtained during RPLND after chemotherapy, weak/moderate and high MDR1 protein levels were identified in 18 (24.7%) and 8 (11%) out of 73 evaluable patients, respectively. Regarding the MDR1 expression level there was no difference between RPLND sections containing viable tumor (12/14) or mature teratoma (14/15; $p = 0.75$, Fisher's exact test), neither within the expression level of each group ($p > 0.15$; binominal analysis). No specific MDR1 staining was detected in necrotic tissue samples (n = 47).

Evaluating whether the MDR1 expression level detected in the primary testicular germ cell tumor might predict the histological outcome after RPLND, we were able to reveal a significant correlation. In patients whose testicular tumour stained positive for MDR1 protein expression (n = 23) the likelihood of persisting residual retroperitoneal disease (mature teratoma or active viable tumor) was significantly higher than in patients with MDR1-negative primary tumors (n = 24; 73.9% vs 20.8%; $p = 0.003$, Fisher's exact test).

However, MDR1 expression was significantly associated with the tumors histological characteristics (vide supra). Therefore, we evaluated whether MDR1 might serve as an independent marker of residual retroperitoneal tumor after chemotherapy. We found that the MDR1 expression alone did not reach statistical significance as an independent marker for residual vital tumor ($p \geqslant 0.16$, Fisher's exact test) as its expression was highly associated with the histological subtype of the primary testicular tumor (NSGCT/seminoma and teratoma-containing/free disease).

Interesting, looking at those 47 patients whose testicular and retroperitoneal tumor tissue was available for MDR1 staining, we were able to show that the mean MDR1 expression level was rather lower in the retroperitoneal lymph node tissue following chemotherapy compared to the primary testicular tumor (increased, stable, and decreased in 8.5%, 59.6%, and 31.9%, respectively; $p = 0.018$, Wilcoxon test).

## DISCUSSION

The multidrug resistance gene product MDR1 (P-glycoprotein) belongs to the super family of ATP-binding cassette (ABC) transporters whose functions include the efflux of ions, nutrients, lipids, amino acids, peptides, proteins and — in particular — cytotoxic drugs [15–17]. In many human cancers, the level of MDR1-expression is an important independent prognostic factor that determines response to combination chemotherapy [18, 19]. Recent clinical trials in haematological and solid malignancies have shown promise for a prolonged remission and improved overall survival by combining MDR1 inhibitors with chemotherapy [18, 20]. Germ cell testicular tumors in general are very sensitive to systemic anti-cancer treatment. However, especially patients with stage $\geqslant$ IIC nonseminoma, particularly with teratoma-components in their primary testicular tumor, frequently present with residual retroperitoneal disease following chemotherapy which has to be dissected after initial chemotherapy to ensure therapeutic success [1, 4]. Therefore, this study was performed to investigate whether MDR1 expression in testicular tumor tissue could serve as an independent marker for residual vital tumor growth, and potentially chemoresistance. Moreover, we intended to prove an association between MDR1 expression and different malignant tumor subtypes.

In our patient cohort high expression of MDR1 was particularly observed in NSGCT containing teratoma-components whereas pure seminoma did not express any detectable MDR1 protein. This is in well accordance with earlier studies published by Katagiri, Eid et al. [11, 12, 21]. The latter group identified MDR1 protein expression in two (8%) of 25 seminomatous and 23 (46%) out of 50 non-seminomatous testicular tumors. Unlike Katagiri et al. [21], they further indicated that there might exist a positive correlation between MDR1 expression and tumor stage [11] as well as a progressive malignant phenotype [12].

Evaluating the potential predictive value of MDR1 expression in testicular tumor tissue for active malignant residues after chemotherapy we were able to show that at least using univariate analysis MDR1 expression was significantly correlated with positive RPLND sections: for patients with MDR1 negative and positive primary cancer 5/24 (20.8%) and 17/23 (73.9%) RPLND specimens tested positive for vital residual disease, respectively. However, in our study the MDR1 expression level was significantly associated with the non-seminomatous tumor subtype. Therefore, we evaluated whether MDR1 might also have the capacity to serve as a tumor-type independent marker for residual retroperitoneal disease after chemotherapy. Conversely, we revealed that its expression alone failed to reach statistical significance as an independent marker for residual vital tumor, even though there was a positive statistical trend.

A large number of authors investigate MDR1 expression in hematologic (AML, CLL, multiple myeloma) as well as solid malignancies including breast cancer, ovarian cancer, cervical cancer, CNS cancer, and osteosarcoma. They indicated that MDR1 expression levels are frequently up-regulated by systemic chemotherapy as compared to those prior to therapy (for review see [20, 22]). However, our results suggest a different regulation in germ cell cancer: Out of 47 patients whose testicular and retroperitoneal tissue were available for MDR1 staining, we found out that MDR1 was upregulated by platinum based treatment

in a minority of patients (4/47, 8.5%), only. In contrast, no significant change and a decrease in MDR1 expression were seen in 28/47 (59.6%) and 15/47 (31.9%) samples. However, unlike most of those tumors with upregulated MDR1 levels after chemotherapy the majority of testicular germ cell tumors is highly chemosensitive which might account for the dissimilar regulation revealed here.

Taken together, MDR1 was frequently, at times highly expressed in NSGCT, only. Both, MDR1 expression and the non-seminomatous histological subtype correlated with viable residual disease found in retroperitoneal lymph nodes after chemotherapy. On the other hand, in our rather small cohort of patients MDR1 expression alone failed to reach statistical significance as a histology-independent marker for residual vital tumor. Therefore, up to now routine MDR1 staining of testicular germ cell cancer samples should not be performed in clinical practice. However, as there was a statistical trend towards significance, our study should and will be continued with a larger number of patients suffering from metastatic NSGCT, only, as it appears that MDR1 expression could have prognostic value in this subgroup of testicular germ cell cancer patients.

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# КЛИНИЧЕСКАЯ ЗНАЧИМОСТЬ ЭКСПРЕССИИ MDR1 ПРИ ГЕРМИНАТИВНОМ РАКЕ ЯИЧКА

**Белок 1 множественной лекарственной устойчивости (MDR1, P-gp, p-170) – это мембранный гликопротеин, функционирующий как энергозависимый насос. При различных формах опухолей его экспрессия связана с устойчивостью опухоли к различным цитостатикам, что может быть использовано для выбора типа терапии.** ***Цель работы*** **— исследование прогностической значимости экспрессии MDR1 в ткани первичной опухоли для оценки возможности развития некроза или сохранения живых клеток в остаточной ткани опухоли после применения системной химиотерапии на поздних стадиях герминативных опухолей яичка.** ***Материалы и методы:*** **проанализированы гистопатологические характеристики первичной тестикулярной опухоли и образцов, полученных при иссечении ретроперитонеальных лимфатических узлов (RPLND) после химиотерапии у 72 и 77 больных соответственно. Экспрессию MDR1 определяли иммуногистохимическим методом в 47 образцах первичной опухоли и соответствующих 73 срезах RPLND.** ***Результаты:*** **после химиотерапии и последующей RPLND исследование остаточных опухолевых тканей показало, что зрелая тератома и жизнеспособные опухолевые клетки выявляют преимущественно у больных, у которых не была обнаружена семинома (NSGCT; $p = 0{,}048$), особенно у таковых, у которых была тератома ($p = 0{,}001$). Более того, данные однофакторного анализа показали, что экспрессия MDR1 в ткани первичной тестикулярной опухоли может служить прогностическим фактором сохранения живых опухолевых клеток в срезах RPLND ($p = 0{,}003$). Однако применение мультифакторного анализа, в том числе с учетом гистологического подтипа опухоли, показало, что экспрессия MDR1 не имеет самостоятельной прогностической значимости для выявления живых остаточных опухолевых клеток ($p \geqslant 0{,}16$).** ***Выводы:*** **ввиду небольшой выборки больных не выявлено статистически значимой корреляции между экспрессией MDR1 в первичной опухоли яичка и наличием активных резидуальных очагов поражения в ретроперитонеальном пространстве. В то же время, учитывая выявленную тенденцию, экспрессию MDR1, в качестве возможного прогностического маркера, имеет смысл исследовать именно у больных с метастатическими опухолями, не являющимися семиномой.**

***Ключевые слова:*** **яичко, опухоль, семинома, тератома, P-gp, p170, иссечение ретроперитонеальных лимфатических узлов.**

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