

# Current aspects in the treatment of patients with relapsed or refractory testicular cancer

## Review Article

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**Abbreviations:** germ cell tumors, (GCT); high-dose chemotherapy, (HDCT); autologous stem cell rescue, (ASCR); cisplatin, etoposide and ifosfamide, (PEI); European Group for Blood and Marrow Transplantation, (EBMT); carboplatin, etoposide and cyclophosphamide, (PEC); carboplatin and etoposide, (CE); human chorionic gonadotropin, (HCG); alpha-fetoprotein, (AFP)

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## Summary

The optimal treatment of patients with relapsed or refractory germ cell tumors (GCT) after cisplatin-based first-line chemotherapy remains controversial. It is well known that the majority of these patients will ultimately die of their disease. Therefore, improvement of standard treatment is clearly desirable. The question of using conventional-dose or high-dose chemotherapy (HDCT) in this high-risk situation is under discussion. However, HDCT as subsequent salvage therapy in patients with relapsed or refractory GCT remains to be a relevant curative option. Prognostic factors have recently been recognized to aid in this decision. This report reviews the current treatment options and recent developments in respect to HDCT given as salvage treatment and discusses the role of prognostic factors in management of such situations.

## I. Introduction

Most patients with metastatic germ-cell tumors can be cured using multimodal treatment with standard combination chemotherapy followed by surgical resection of residual masses (Bosl and Motzer, 1997). The outcome is worse if one of poor prognostic features are present, such as extragonadal primary mediastinal nonseminoma GCT, extrapulmonary visceral metastases and high levels of tumor markers at initial diagnosis. These patients have a chance of cure of less than 50% with standard first-line chemotherapy and are being classified as "poor prognosis" patients. Most of them progress after incomplete response to first-line cisplatin-based chemotherapy or relapse from prior complete remission and will be candidates for salvage treatment (**Table 1**) (International Germ Cell Cancer Collaborative Group, 1997). Conventional-dose salvage chemotherapy in combination with resection of residual masses will result in second complete remissions in only about 30-60% of patients. In addition, at least half of these patients will suffer subsequent relapses after salvage treatment and will ultimately die of their disease.

Depending on the presence or absence of adverse prognostic factors, only about 15-30% of these relapsed patients overall will become long-term survivors after conventional-dose salvage chemotherapy (Loehrer et al, 1988; Harstrick et al, 1991).

To improve the unfavorable outcome of patients with relapse or progressive disease after conventional-dose treatment, high-dose chemotherapy (HDCT) followed by autologous stem cell rescue (ASCR) has been explored as a therapeutic option (Siegert et al, 1994; Rick et al, 2001). Due to increasing clinical experience in the management of side-effects, the use of ASCR and the availability of hematopoietic growth factors, HDCT has become a relatively safe procedure. Dose-escalations to about three to five times of the conventional-dose can be achieved for most drugs active in GCT as hematologic toxicities have become manageable with ASCR.

However, acute nonhematologic toxicities, particularly mucositis, renal impairment and peripheral neurotoxicity are increased after HDCT as compared to conventional-dose regimens.

**Table 1:** Prognostic classification for first-line treatment (International Germ Cell Cancer Collaborative Group, 1997)

<b>GOOD PROGNOSIS</b>	
<b>Non-Seminoma</b>	<b>Seminoma</b>
Testis or retroperitoneal primary <i>and</i> Non-pulmonary visceral metastases absent <i>and</i> Good markers AFP < 1000 ng/ml and HCG < 5000 U/l and LDH < 1.5 × upper limit of normal	Any primary site <i>and</i> No non-pulmonary visceral metastases absent  <i>and</i> Normal AFP, any HCG, any LDH
<b>INTERMEDIATE PROGNOSIS</b>	
<b>Non-Seminoma</b>	<b>Seminoma</b>
Testis/retroperitoneal primary <i>and</i> Non-pulmonary visceral metastases absent <i>and</i> Intermediate markers AFP 1000 and 10,000 ng/ml and HCG 5000 and 50,000 U/l or LDH 1.5 × N and 10 × N	Any primary site <i>and</i> Non-pulmonary visceral metastases present  Normal AFP, any HCG, any LDH
<b>POOR PROGNOSIS</b>	
<b>Non-Seminoma</b>	<b>Seminoma</b>
Mediastinal primary <i>or</i> Non-pulmonary visceral metastases present <i>or</i> Poor markers AFP > 10,000 ng/ml or HCG > 50,000 U/l or LDH > 10 × upper limit of normal	No patients classified as poor prognosis

Abbreviations: AFP, alpha-fetoprotein; HCG, -subunit human chorionic gonadotropin; LDH, lactat dehydrogenase

Also long-term non-hematologic organ toxicities and hematologic complications such as the incidence of secondary myelodysplasias or leukemias may be a concern years after successful HDCT.

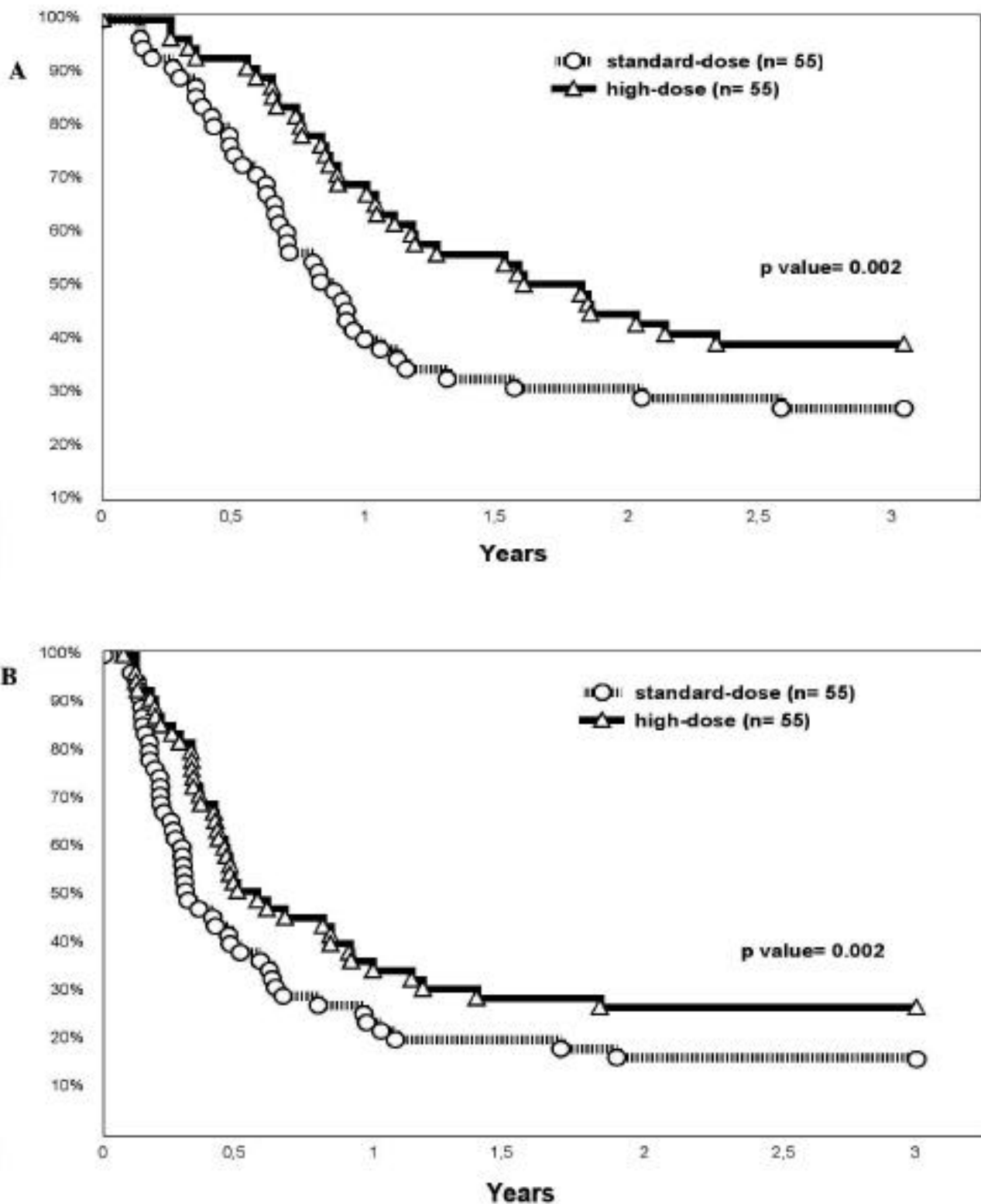
## II. Salvage HDCT in patients with relapsed or refractory GCT

Standard treatment for patients with relapsed or refractory GCT after cisplatin-based first-line chemotherapy includes a combination of cisplatin, etoposide and ifosfamide (PEI) or cisplatin, vinblastine and ifosfamide (VeIP) (Rick et al, 1999). With regard to the worse long-term prognosis of patients with relapsing or progressing GCT after conventional-dose chemotherapy, however, the concept of HDCT with ASCR was investigated in numerous studies. Overall, event-free survival rates of 40-60% have been reported after such

treatment which seems to be superior to survival rates obtained with conventional chemotherapy schedules. In patients receiving second or subsequent salvage treatment investigators in the US and Europe still reported long-term remission rates of 15-25% using high-dose carboplatin and etoposide with or without the addition of an alkylating agent (Rick et al, 1999). More recently, three study groups have modified this initial schedule. Rick et al, and the GTCSG explored a treatment strategy that combined intensive conventional-dose salvage with paclitaxel, ifosfamide and cisplatin followed by a single HDCT cycle with carboplatin, etoposide and thiotepa. The rationale for the trial was to optimize conventional-dose salvage treatment by using paclitaxel as well as intensifying HDCT with thiotepa (Rick et al, 2001). Motzer et al. (2000) investigated sequential dose-intensive paclitaxel and ifosfamide followed by three sequential cycles of high-dose carboplatin and etoposide. Rodenhuis et al, (1999) explored sequential dose-intensive treatment with

etoposide and ifosfamide, followed by one cycle of high-dose carboplatin and etoposide and two cycles of high-dose carboplatin, cyclophosphamide and thiotepa supported by ASCR. Recently, Bhatia and co-workers (2000) reported data from 65 patients with relapsed or

refractory GCT treated with high-dose carboplatin and etoposide followed by PBPC rescue as initial salvage chemotherapy.



**Figure 1:** Overall-(A) and event-free (B) survival of patients after salvage treatment either with high-dose or standard-dose chemotherapy in 55 pairs of patients (Beyer et al, 2002)

However, the majority of the patients included in the latter study showed "good-risk" factors for relapse prior to salvage HDCT. This fact may explain the very good outcome of these patients. In a retrospective matched-pair analysis Beyer et al, (2002) compared HDCT with conventional-dose chemotherapy as first-salvage treatment in patients with relapsed or refractory non-seminomas. The analysis suggests a benefit from HDCT with an estimated absolute improvement in event-free survival of 12% and in overall survival of 11% at 2 years (**Figure 1**).

At the ASCO meeting Rosti et al, (2002) presented the data from a preliminary analysis of a prospective randomized multicenter study initiated by the European Group for Blood and Marrow Transplantation (EBMT), the "IT94 study". 280 patients with relapse from first-line cisplatin-based chemotherapy were randomized to receive either three cycles of conventional-dose PEI/VeIP plus HDCT included carboplatin, etoposide and cyclophosphamide (PEC) or four courses of standard PEI/VeIP.

Calculation of the sample size was based on a 15% difference in the event-free survival rate at one year. The recruitment of the study stopped in September 2001 and 128/140 patients (91%) for the conventional treatment and 135/140 patients (96%) for the HDCT could be analyzed. In terms of event-free and overall survival no statistically significant differences were observed between both treatment groups (Rosti et al, 2002). However, only patients without any prior salvage chemotherapy who relapsed from complete remission or progressed from incomplete remission were included. Therefore the results of the study can only allow interpretation for patients with these "good prognosis

factors". Until now the minimal range of the follow-up period is short and only 104/280 (37%) patients were analyzed for disease-free survival. Considering the interpretation of the results these facts must be mentioned.

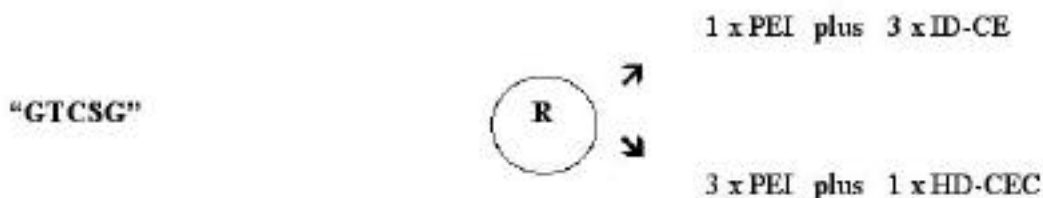
In 1986 Indiana University initiated a phase I/II trial using tandem HDCT with carboplatin and etoposide (CE) followed by ASCR in patients with multiple relapses, since then several investigators have examined the concept of repetitive HDCT cycles. Employing tandem cycles of HDCT with CE might be a method to overcome cisplatin resistance and to eradicate residual cancer cells rather than a single application or multiple applications with long term intervals between the cycles. Therefore, to maximize the dose-intensity of chemotherapy multiple large doses may be administered in short intervals (Nichols et al, 1989; Broun et al, 1997; Bhatia et al, 2000; Motzer et al, 2000).

However, all current trials are encouraging that some of the patients with second or subsequent relapses can successfully be salvaged by HDCT. In addition, patients with poor prognostic features at the time of relapse or progression also seem to profit from early intensification of first salvage treatment. Whereas side-effects differ between schedules, the results of these most recent trials indicate, that prognostic factors for treatment outcome after HDCT could be more important than the use of a particular HDCT strategy or combination.

### III. Ongoing trials

Since September 2001 the "IT94"-study was stopped, in the salvage situation only one trial in Europe is actively recruiting.

#### The randomized HDCT study



#### Oral etoposide after complete resection of vital cancer cells in the salvage situation

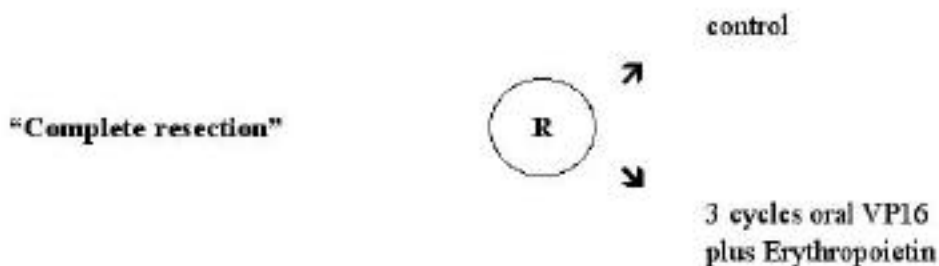


Figure 2: Ongoing GTCSG trials for salvage treatment.

Colleagues from Berlin, Marburg and Tübingen in cooperation with the GTCSSG initiated a prospective randomized multicenter trial to compare three cycles of standard PEI plus single HDCT with carboplatin, etoposide and cyclophosphamide versus one cycle of PEI followed by sequential cycles of dose-intensified carboplatin and etoposide (**Figure 2**).

Patients with good or intermediate prognosis according to the criteria from Beyer et al, (1996) who require salvage treatment are included into the study and in January 2003 two thirds of the planned number of 230 patients were recruited. This trial continues to include patients with first relapse after a minimum of three cycles of a cisplatin-based chemotherapy despite the preliminary data from the "IT94-study".

The randomized GTCSSG-study includes patients with insufficient response to primary treatment and patients who relapsed after first- or subsequent salvage treatment. The results of this trial should help to determine the optimal HDCT regimen in terms of clinical outcome, long-term survival and toxicities when given as intensification of salvage treatment.

#### IV. Prognostic factors

Several retrospective analyses have tried to identify prognostic factors for conventional-dose as well as for high-dose salvage chemotherapy. Primary mediastinal nonseminomatous tumors seem to be incurable if first-line treatment fails. At least two large series did not find long-term survivors, neither with conventional-dose treatment nor with HDCT (Saxman et al, 1994; Beyer et al, 1996).

In a multivariate analysis Beyer et al, (1996) tried to identify prognostic variables in 383 patients treated with HDCT given as first or subsequent salvage treatment. Progressive disease at the time of HDCT, nonseminomatous mediastinal primary tumor, refractory disease to conventional-dose cisplatin and human chorionic gonadotropin (HCG) levels greater than 1,000 U/L prior HDCT were identified as independent adverse prognostic factors for long-term survival after HDCT (Beyer et al, 1996). Overall survival rates for each prognostic group are shown in **Figure 3**. One of the relevant conclusions of the study was that all patients of the poor prognosis category progressed immediately after HDCT, had no benefit from the dose intensive strategy and should not be treated with HDCT.

Fossa et al, (1999) analyzed the results of 164 nonseminoma patients who relapsed or progressed after cisplatin-based first-line chemotherapy and who received different conventional-dose regimens as first-salvage treatment. In a multivariate analysis response to first-line treatment, response duration as defined by the progression-free interval as well as serum levels of HCG and alpha-fetoprotein (AFP) prior to salvage treatment were identified as independent prognostic variables (**Table 2**). Unfortunately, the impact of histology on prognosis could not be assessed as seminoma patients were not included. Limited by its retrospective approach and the lack of a control group, this analysis cannot exclude the possibility that the results of salvage chemotherapy might

have been more favorable, if HDCT had been used early in these patients.

#### V. Treatment related toxicities

Early as well as the late toxicities after salvage chemotherapy are substantial. Although the treatment-related mortality was considerably lower compared to reports that pioneered HDCT, it remained constantly around 3% in consecutive protocols. Apart from the expected hematologic toxicity that resulted in transfusion requirements in all patients, the majority of patients also experienced severe mucositis that necessitated hospitalization, total parenteral nutrition and intravenous analgesia (Siegert et al, 1994; Rick et al, 1998; Rick et al 2001). Other non-hematologic toxicities that eventually became dose-limiting were renal impairment. Overall, 8% of the patients required hemodialysis, of whom most patients recovered with their renal function until discharge. The use of ifosfamide as a third drug in addition to high-dose carboplatin and etoposide might have precipitated these toxicities. Despite activity of ifosfamide in germ cell tumors at conventional-doses, only modest dose increments were possible in high-dose combinations (Siegert et al, 1994; Beyer et al, 1997; Rick et al, 1998). Another relevant side effect after conventional-dose chemotherapy and HDCT is the peripheral nervous toxicity. After salvage treatment with three cycles of conventional-dose paclitaxel, ifosfamide and cisplatin followed by high-dose carboplatin, etoposide and thiotepa sensorymotor toxicity grade II developed in 29% of the patients among 8% suffered from grade IV sensorymotor toxicity. Furthermore, paresthesias grade II developed in 24% of the patients. Peripheral nervous toxicity after HDCT persisted during the 12 week re-evaluation period and improved only gradually thereafter. Ototoxicity with tinnitus and hearing loss greater or equal grade II occurred in 32% of the patients after HDCT. Hearing began to improve in most patients shortly after HDCT and therefore, hearing aids were required in only few patients (Rick et al, 2001).

Whereas most of the acute toxicities were reversible, about one third of the patients reported persisting side-effects, mainly paresthesias and/or tinnitus, that interfered with their daily activities (Rick et al, 1998). Long-term toxicities have also been reported after conventional-dose cisplatin-based treatment, but persisting side-effects as well as more severe late toxicities such as renal impairment, transfusion-related hepatitis and etoposide-induced secondary leukemia clearly represent a reminder to use HDCT judiciously, preferably only within clinical trials and at experienced centers (Beyer et al, 1997; Rick et al, 1998).

#### VI. Residual tumor resection and adjuvant chemotherapy

After primary cisplatin-based chemotherapy surgical resection of residual tumor masses is currently the standard treatment if the metastases have not completely disappeared (Donohue et al, 1992; Fox et al, 1993). The histological status of the operated specimen may reveal

necrosis, mature teratoma or viable cancer cells. Whereas the resection of necrosis has no therapeutic benefit, the resection of mature teratoma or undifferentiated cancer is relevant. Therefore, attempts have been made to distinguish between patients with necrosis from patients with viable cancer (De Santis et al, 2001).

Only few data exist of the histological status of tumor residuals and the probability of viable cancer after first or subsequent salvage chemotherapy (Hartmann et al,

1997; Donohue et al, 1994). Furthermore, the relevance of residual tumor resection and the incidence of cancer cells after HDCT has not yet been determined. Hartmann et al, (1997) found undifferentiated tumor in 20/25 patients (80%), Donohue et al, (1994) reported from viable carcinoma only in 53/164 patients (32%). Furthermore, two other analyses confirmed these results and demonstrated a high rate of patients with viable cancer after second-line chemotherapy (Peckham et al, 1988; Fox

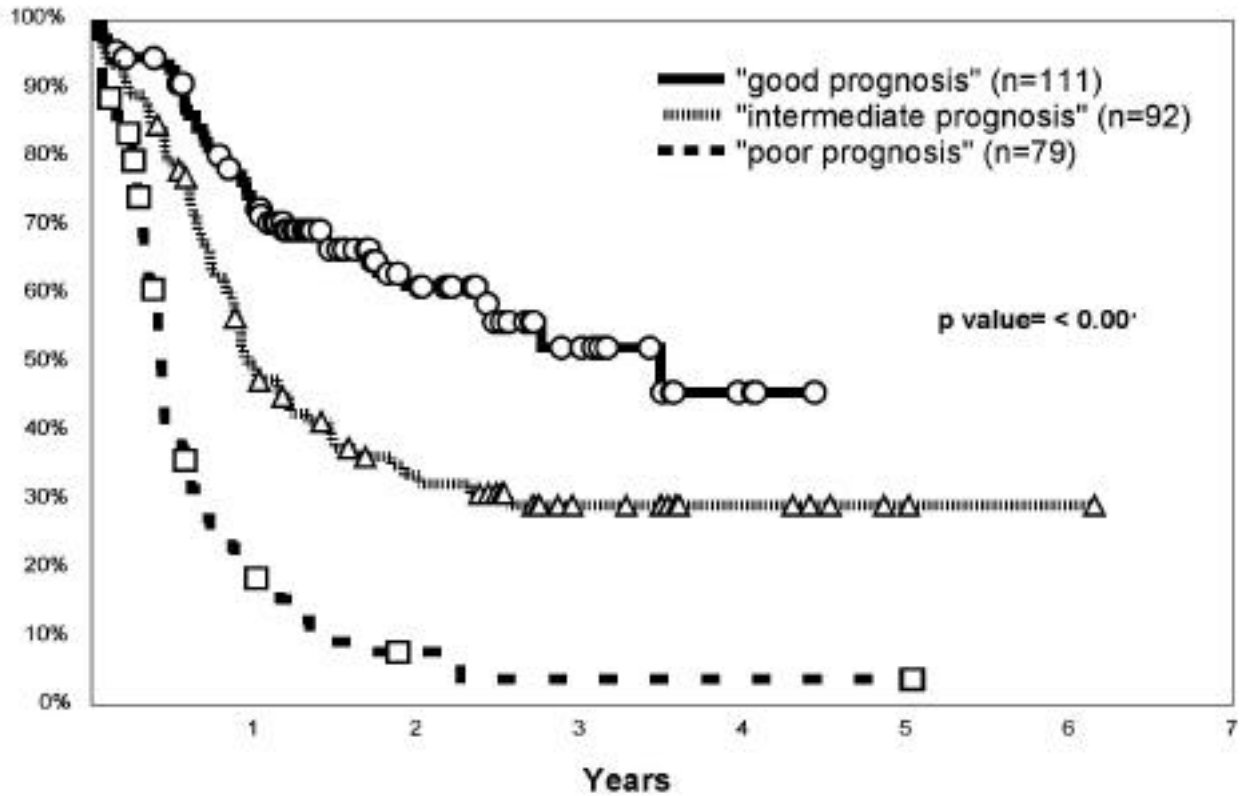


Figure 3: Survival according to prognostic categories in 282 patients treated with high-dose salvage chemotherapy (Beyer et al, 1996)

Table 2: Prognostic model for conventional-dose salvage according to Fossa et al, (1999)

- no complete remission to first-line treatment
- progression-free interval < 2 years
- AFP > 100 kU/L or HCG > 100 U/L at initiation of salvage

Prognostic groups	survival at 2 years (95% confidence intervals)
“good prognosis” one risk factor present #	74% (60% - 88%)
“intermediate prognosis” any two risk factors present	45% (32% - 58%)
“poor prognosis” all three risk factors present	7% (0% - 15%)

et al, 1993). These data after salvage treatment showed a much higher frequency of viable cancer in comparison with histological findings after primary chemotherapy. Residual tumor resection following first-line cisplatin-based chemotherapy showed viable cancer in 10% of the patients (Fossa et al, 1989; Fizazi et al, 2001). One explanation may be the development of resistance against chemotherapy in patients received salvage treatment. Viable cancer and mature teratoma may be the origin of localized and/or late relapse (Loehrer et al, 1986). Thus, the complete removal of mature teratoma or residual cancer is indicated, particularly due to the lack of reliable non-invasive examinations to detect viable cancer cells.

After resection of necrosis or mature teratoma, no further treatment is required. In the case of resection of viable cancer cells after primary cisplatin-based chemotherapy the application of an adjuvant chemotherapy remains disputable. Whereas several investigations have confirmed that the use of additive chemotherapy may improve the outcome of these patients (Tait et al, 1984; Fox et al, 1993; Donohue et al, 1994; Gerl et al, 1995; Stenning et al, 1998), other trials could not detect any benefit from an adjuvant treatment (Pizzocaro et al, 1998). Furthermore, Fizazi et al (2001) performed a multivariate analysis of prognostic factors for overall and event-free survival after resection of viable tumor cells in patients with disseminated GCT. They identified an incomplete resection, 10% viable malignant cells in the residual tumor manifestation and an "intermediate or poor prognosis" in according to the IGCCCG classification as unfavourable features. Only patients with one adverse prognostic factor showed a statistically significant advantage from the adjuvant chemotherapy.

In the salvage situation there is also no clear recommendation because only few data are available (Hartmann et al, 1997; Donohue et al, 1994) Whereas some authors did not find any benefit from adjuvant chemotherapy after resection of residual viable cancer, other investigators recommended the maintenance chemotherapy with daily oral etoposide following salvage therapy (Donohue et al, 1994; Cooper and Einhorn, 1995; Hartmann et al, 1997; Pizzocaro et al, 1998). Therefore, to answer this question the GTCSG have investigated a prospective randomized multicenter study to evaluate the efficacy of three cycles of oral etoposide in patients with viable cancer cells in the resected residual tumor masses (Figure 2).

## VII. Conclusion

In patients with relapsed/refractory disease HDCT has been demonstrated as a feasible and safe treatment concept which will be curative for a substantial proportion of these patients. Therefore, all of these patients should be included in ongoing studies. Considering the complication rate and the not yet finally clarified role of HDCT this treatment is not acceptable outside clinical trials. Prognostic factors in patients with relapsed or progressive disease are clearly necessary and therefore known risk factors should be included in future prospective randomized trials. These results, if confirmed by

subsequent retrospective multivariate analyses, may lead to individualized risk-adapted treatment strategies in relapsed patients. Considering these evaluated prognostic subcategories the addition of a new drug, such as paclitaxel, to the conventional-dose salvage chemotherapy in patients with good prognosis features could be a new option. In patients with poor prognosis factors the use of HDCT may be helpful to optimize the treatment efficacy. This risk-adapted strategy can avoid HDCT-induced toxicities in good prognosis patients and maintain a curative option in patients of the intermediate/poor prognosis category. Nevertheless, the use of a sequential HDCT concept in patients with unfavorable prognostic features could enhance the clinical outcome of these patients and should be investigated in future trials. Therefore, the results of the randomized GTCSG study are necessary to answer this open question and the data must constantly be seen and evaluated.

The results of salvage chemotherapy may be further improved if combined with residual tumor resection in selected patients. Patients with viable cancer cells in the resected tumor masses should be included in ongoing studies. In order to find rational approaches for rare clinical situations, cooperative multiinstitutional efforts are needed.

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