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# NON-SEMINOMATOUS TESTICULAR GERM CELL TUMOURS

## Preliminary analysis of ongoing trials in the DATECA Study

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**Abstract**

This report deals with the preliminary results of trials in the DATECA project with stage I, II and III patients with non-seminomatous germ cell tumours. Stage I patients were randomized between infradiaphragmatic irradiation and observation. No significant difference in recurrence rates has been observed as yet. Eighteen of 95 patients had recurrence with a median time to relapse of 3 months. Fifteen patients achieved complete remission after treatment by combination chemotherapy while 3 patients are still undergoing treatment.

Stage II patients received 6 series of cis-platinum, bleomycin, and vinblastine. The patients were initially randomized to receive chemotherapy alone versus chemotherapy plus irradiation. Irradiation led to increased toxicity and decreased doses of the antineoplastic drugs. Fifty-one patients were studied. The overall complete remission rate was 89 per cent including 7 patients who achieved complete remission after secondary surgery. Three patients died from testicular tumours and two toxic deaths occurred in this group.

Stage III patients were treated with 6 series of cis-platinum, bleomycin, and vinblastine. Fifty patients were studied. The complete remission rate was 72 per cent including 2 patients who achieved complete remission after secondary surgery. Sixteen patients relapsed after achieving complete remission with a median time to relapse of 4 months. Eight of these died, 4 achieved a new complete remission, while 4 patients are still under treatment. Sixty per cent of the patients are at present alive without evidence of disease, while 12 patients died from testicular tumours and 2 from toxic side effects.

The improvements in treatment and staging techniques which have taken place within the past decade have significantly changed the outlook for patients with testicular carcinoma. The improved results of treatment with combination chemotherapy have led to re-evaluation of treatment strategies, especially with regard to the combined use of different treatment modalities, i.e. surgery, irradiation, and chemotherapy.

As for non-seminomatous tumours stage I and II, the treatment strategies in the past have varied. Traditionally, patients with non-seminomatous testicular tumours in the USA and several other countries have primarily been treated by surgery, i.e. extensive retroperitoneal lymph node dissection, while in the UK and parts of Scandinavia including Denmark the primary treatment following orchiectomy has been irradiation.

In the DATECA project interest has been focused on some of the problems in this area and the present paper gives a preliminary analysis of the ongoing trials. The development in this dynamic area of oncology has been such that treatment strategies have been changed during the trials in order to

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provide at all times safe and optimal therapy to patients with a testicular tumour.

The results of treatment of patients with clinicoradiologic *stage I disease* by retroperitoneal lymph node dissection have in the hands of experienced urologists at established centres been excellent, with survival percentages ranging from 70 to 100 (12). Adverse effects have been infertility due to abolition of peristalsis of the ductus deferens and of contraction of seminal vesicles. Furthermore, extensive surgery carries a risk of surgery-related mortality and morbidity. This strategy continues to prevail in the United States and improvements in terms of limited resections to preserve fertility and postoperative treatment (with alpha adrenergic reagents) are being studied (11).

Irradiation of the retroperitoneal lymph nodes including the groin and ipsilateral pelvic lymph nodes in clinicoradiologic stage I disease, applying a dosage of 40 to 50 Gy, have shown results similar to the treatment by surgery, i.e. survival percentages ranging from 70 to 90 (10). The adverse effects of radiation therapy include the risk of secondary tumours and formation of fibrosis in the irradiated area, and the inevitable reduction in the dose of antitumour drugs should these be used for treatment of relapses later on. The fertility of patients treated by irradiation is probably not irreversibly affected by the treatment, but such claims will always be difficult to substantiate since patients with testicular tumours already at the time of diagnosis have severely reduced fertility (2). In view of the improved results of treatment for metastatic disease and because of the improved staging procedures available, it was decided to compare in a randomized fashion the standard treatment by irradiation with a control group given no treatment after orchiectomy ('wait and see' policy).

Results of treatment by surgery and/or irradiation without systemic treatment have been unsatisfactory for patients with clinicoradiologic *stage II disease* (10). The DATECA group decided at an early stage to supplement the irradiation of infra- and supradiaphragmatic lymph nodes by chemotherapy. Before the era of platinum-based combination chemotherapy the treatment results were still not satisfactory (13). With the advent of efficient chemotherapy with high curative potential it was decided to base the treatment strategy on the PVB (cis-platinum+ vinblastine + bleomycin) treatment in all cases of stage II irrespective of the size of the tumour burden. In order to define the possible role of irradiation as an adjuvant to chemotherapy a randomized trial comparing chemotherapy with chemotherapy plus irradiation was undertaken in 1979. During the trial it became evident, that the overall results were so good that it would not be possible to detect any advantage from adjuvant irradiation, and that the combined radiation and chemotherapy schedule was accompanied by a considerable toxicity necessitating postponement and reduction of dose in the last series of chemotherapy. Randomization was thus discontinued in 1981. A preliminary analysis of the trial is discussed in the present paper.

Patients with *disseminated testicular carcinoma* (*stage III*) had a dismal prognosis with few long-term survivors 10 to 15 years ago. Combination chemotherapy was introduced by LI et coll. (12), who used actinomycin-D, chlorambucil, and methotrexate. Considerable improvement was achieved by SAMUELS et coll. (20) when combination chemotherapy with bleomycin plus vinblastine was introduced. The discovery of the activity of cis-diaminodichloroplatinum (DDP) in germ cell neoplasms further improved the possibility of designing curative combination chemotherapy regimens for patients with this disease. The pioneer work by EINHORN & DONOHUE (7) revealed that more than 60 per cent of patients with disseminated testicular tumours could achieve complete remission when treated with cis-platinum, vinblastine, and bleomycin (PVB). Most of these patients are probably cured. Several other groups have confirmed these results (19, 23) and several other combination regimens including these drugs have been applied with success (5). Since relapses after achieving complete remission in this disease nearly always occur within 12 to 18 months after the initial treatment the prediction of long-term survival is fairly safe. In Denmark, cis-platinum became available in 1977 to 1978 and PVB treatment was piloted shortly thereafter. In 1979 the DATECA group decided to use PVB treatment as a basic treatment for stage II as well as stage III patients, and randomized trials were initiated. The purpose of the investigation of patients with stage III disease was to evaluate the possible beneficial effect of maintenance therapy with vinblastine and actinomycin-D. During 1981 it became clear, however, firstly, that the number of relapses after initial treatment was so low that it precluded any conclusion with regard to the possible difference between two different maintenance schedules, secondly, that compli-

**Table 1**

*Site of recurrence, stage I patients*

| | No. of cases | Inguinal iliac nodes | Para-aortic nodes | Mediastinal nodes | Pulmonary nodes | Markers only | Total (%) |
|---|---|---|---|---|---|---|---|
| Observation | 51 | 1 | 5 | 1 | 3 | 2 | 12 (24%) |
| Irradiation | 43 | | | | 5 | 1 | 6 (14%) |

ance of patients in complete remission to the treatment schedule in this multi-centre study was unsatisfactory from a scientific point of view, and thirdly several trials were reported to show that maintenance therapy was unnecessary (9, 24). On the basis of this information maintenance therapy was stopped in the treatment of stage II and stage III patients in the DATECA project in 1981. The present report thus does not discuss the value of maintenance therapy, and the report is based on the status of the project's stage III protocol and concerns the group as a whole.

## Material and Methods

All patients were staged according to previously described procedures, which included CT, lymphangiography, urography, chest radiography, and measurements of tumour markers in serum. The classification used was a modification of the WHO staging system (21). Some of the stage III patients with obvious lung metastases were not extensively staged before the start of treatment.

*Stage I patients.* These patients were stratified according to whether or not the levels of the tumour markers in serum were increased prior to orchiectomy. After orchiectomy the patients were randomized to receive infradiaphragmatic irradiation given as 40 Gy in 23 fractions in 4 ½ weeks or 37.44 Gy in 18 fractions in 4½ weeks. The target volume was identical with the fields described for patients with seminoma in stage I (22).

*Stage II and III patients.* For the chemotherapy six series of PVB were given in all cases. Each series consisted of cis-platinum 20 mg/m$^2$ on days 1 to 5, vinblastine 6 mg/m$^2$ on days 1 and 2, and bleomycin 15 mg/m$^2$ on days 2, 9 and 16. The bleomycin dose was reduced to 5 mg/m$^2$ after a cumulative dose of 150 mg/m$^2$. The vinblastine doses were reduced according to hematologic toxicity, bleomycin was discontinued if clinical or radiologic signs of pulmonary toxicity were found, and the cis-platinum dose was reduced if the kidney function decreased by more than 35 per cent. Kidney functions were evaluated by serum creatinine and clearance measurements (CrEDTA or creatinine). Lung function was evaluated only clinically in some patients. while other patients were examined repeatedly by lung function tests during the trial.

Stage II patients were allocated to receive irradiation in a randomized fashion (before late 1981) using a closed envelope system. The therapy was given as a split course of (2.5 Gy ×8) ×2 following the third and fourth series of PVB. The target volume was defined on the basis of CT with a margin of at least 2 centimetres.

All patients receiving chemotherapy were evaluated after every treatment series and the treatment results were categorized according to standard rules: complete remission (CR) = no sign of residual tumour, partial remission (PR) = >50 per cent reduction of measurable disease, no change (NC) =<50 per cent reduction or <25 per cent growth of measurable disease, and progressive disease (PD) = >25 per cent increase in measurable disease or occurrence of new metastatic lesions.

After conclusion of treatment all patients were followed monthly for at least one year with measurements of serum tumour markers, chest radiography, and liver biochemical parameters. After one year, the intervals between controls were extended to 3 months.

## Results

*Stage I.* From December 1980 to October 1982, 94 patients participated in the trial. Forty-three patients received infradiaphragmatic irradiation and 51 patients were placed in an observation group. Six patients in the treatment group and 12 in the control group relapsed. The site of recurrences is seen in Table 1. The median time to relapse was 3 months

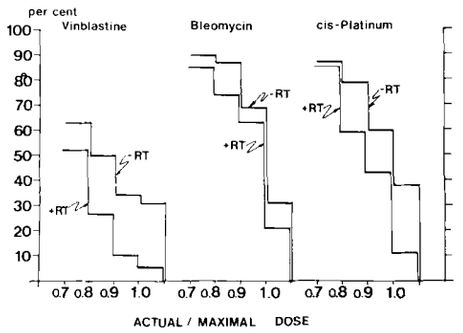



Fig. 1. Effect of radiation therapy in patients with stage II disease. Cumulative doses of chemotherapy given in 6 series of PVB. The percentages indicate the fraction of patients who received the indicated fraction of the calculated maximum dose.

**Table 2**

*Recurrence by stratification group*

| Preoperative markers | No. of cases | Recurrence |
|---|---|---|
| AFP/HCG and/or elevated | 46 | 12 (26.1%) |
| AFP and HCG both negative | 34 | 4 (11.8%) |
| AFP and HCG not assessed | 14 | 2 (14.3%) |
| Total | 94 | 18 |

**Table 3**

*DATECA, stage II*

| | Per cent |
|---|---|
| Retroperitoneal metastases | |
| No | 14 |
| Single | 24 |
| Multiple | 59 |
| Uncertain | 4 |
| Iliac/inguinal metastases | |
| No | 78 |
| Present | 22 |

**Table 4**

*DATECA, stage II*

| | Per cent |
|---|---|
| Histology | |
| Pure | 29 |
| Mixed | 69 |
| Uncertain | 2 |
| Components | |
| Embryonal carcinoma | 82 |
| Choriocarcinoma | 14 |
| Teratoma | 45 |
| Yolk sac | 25 |
| Seminoma | 31 |

(range 0–9 months). Tumour markers were elevated in 13 of 18 patients at the time of recurrence, while radiologic signs of recurrence were present in 10 patients, including one patient with an abnormal CT as the initial sign of recurrence. All 18 relapsing patients were treated with PVB according to the principles of treatment for stage III patients. Fifteen patients achieved complete remission and are continuously free of disease, while 3 patients were still receiving chemotherapy at the time of analysis. No patients died from testicular malignancy in this group.

Recurrence by stratification group is indicated in Table 2. The differences in recurrence rates were not significant. With regard to the influence of histology in the primary tumour all histologic subtypes were represented in the group of patients who had recurrence. The frequency of recurrence varied from 15 per cent (seminoma and endodermal sinus tumour) to 33 per cent (choriocarcinoma) when evaluated according to the presence of the individual histologic subtypes. The recurrence rates were based on small numbers and the variations were not significant.

*Stage II.* Fifty-one patients participated in the study from late 1979 to January 1982. Evaluation took place in October 1982. The median age was 29 years (range 16–58), and the median observation time 20 months (range 9–42). The metastatic pattern is shown in Table 3. Sixty per cent of the patients had multiple or large retroperitoneal metastases. Fourteen per cent had metastases only in the iliac or inguinal area. Fifty-five per cent had elevated alpha-fetoprotein, 49 per cent had elevated HCG, and at least one of the tumour markers was elevated before chemotherapy in 75 per cent of the patients. The histology of the primary tumours is shown in Table 4. One patient had a primary tumour that was too necrotic to allow histologic classification, but since the patient had an increased level of AFP in serum he was regarded as having a non-seminomatous testicular tumour stage II.

Nineteen patients were randomized to receive radiation therapy. The effect of irradiation on the dose of antineoplastic drugs given is shown in Fig. 1. The

**Table 5**

*DATECA, stage II. Response to treatment*

| | No. of cases | Per cent |
|---|---|---|
| 1. Complete remission | 38/51 | 75 |
| 2. Partial remission | 10/51 | 20 |
| 3. No change | 1/51 | 2 |
| 4. Progressive disease | 2/51 | 4 |
| 5. Partial remission → complete remission (surgery) | 7/51 | 14 |

1+5= 'Complete remision': 89 per cent.

**Table 6**

*DATECA, stage II. Overall results*

| | No. of cases | Per cent |
|---|---|---|
| No evidence of disease | 44 | 86 |
| *Alive with disease* | 2 | 5 |
| Deaths (disease) | 3 | 6 |
| Deaths (toxicity)* | 2 | 5 |
| Total | 51 | |

* One postoperative sepsis, one renal toxicity (cis-platinum + gentamycin).

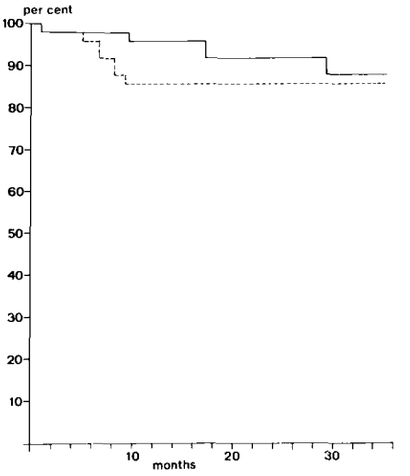



Fig. 2. Life table estimate of crude survival (——) percentages and relapse-free survival (- - -) in stage II patient (n=51).

reduction in the given dose was most pronounced for vinblastine, where 25 per cent of the patients treated by irradiation, in contrast to more than 50 per cent of the non-irradiated patients, received more than 80 per cent of the scheduled dose. Irradiation also led to reduction of the actually given cis-platinum doses, as less than 60 per cent of the irradiated patients and more than 80 per cent of the non-irradiated patients received more than 80 per cent of the scheduled dose. Since treament results did not differ for the two groups the following results are given for the total group of patients with stage II.

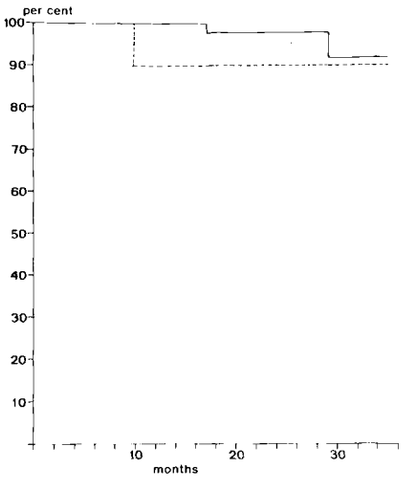
The results of treatment evaluated at the end of the last series of chemotherapy are shown in Table 5. Thirteen patients underwent surgery during or immediately after the scheduled therapy. Three had residual malignant disease, one of these died from progressive disease after a non-radical surgical procedure, while the other two patients, after subsequent treatment, remained disease-free. Five patients had retroperitoneal teratomas that could be removed radically; one of these died postoperatively from sepsis and the other four remained free of disease. Finally, in five patients, only fibrous tissue was found in the area where CT had indicated residual tumour. These five patients are all alive without evidence of disease. Accordingly, seven patients categorized as having partial remissions achieved complete remission after surgery, leading to a complete response rate of 89 per cent.

Aside from the above mentioned postoperative death one patient died during induction treatment from hepatorenal insufficiency following sepsis and treatment with gentamycin. One patient relapsed 5 months after chemotherapy. By treatment with cis-platinum, VP-16, and bleomycin complete remission was induced. The patient was still alive without evidence of disease more than a year later. Altogether 3 patients died from testicular malignancy; 2 of these were irradiated infradiaphragmatically according to the protocol.

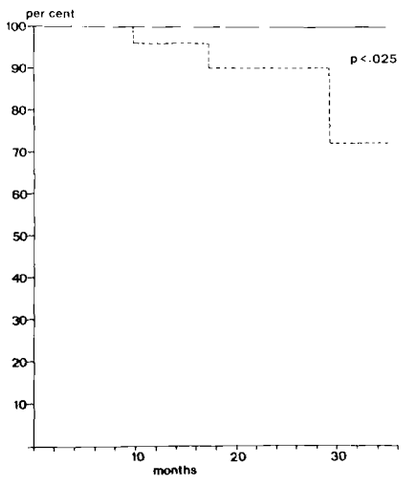
The overall results are given in Table 6. Survival curves calculated by means of a life table analysis are shown in Fig. 2.

In order to define prognostic factors the patients were categorized according to histologic subtypes in the primary tumour, extent of metastatic disease, and level of serum concentrations of AFP and HCG (Fig. 3). All but one of these calculations gave negative results. The only identifiable prognostic factor was an AFP value in serum greater than 90 ng/ml (Fig. 3b).

With regard to chronic toxicity none of the patients experienced any clinically significant impairment of lung function. Details of lung function in-




a




b

Fig. 3. Life table estimate of survival percentages in patients with a) HCG<1 000 IU/l (n=40 ——) and >1 000 IU/l (n=9 - - -) and b) AFP<90 ng/ml (n=28 ——) and >90 ng/ml (n=21 - - -).

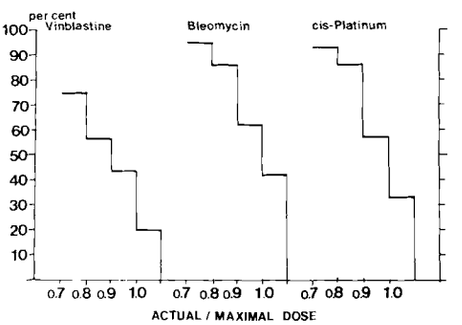



Fig. 4. Cumulative doses of vinblastine, bleomycin and cis-platinum in patients with stage III disease. The percentages indicate the fraction of patients who received the indicated ratio of the maximum dose.

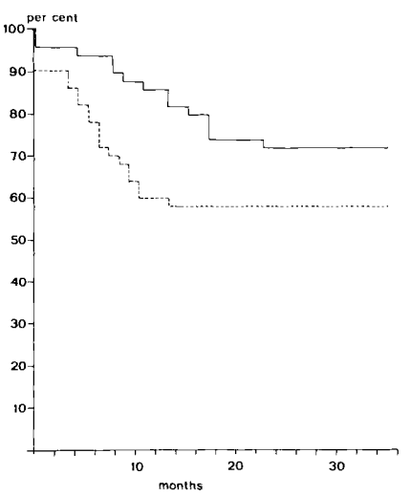



Fig. 5. Life table estimate of crude survival (——) and relapse-free survival (- - -) percentages in stage III disease (n=50).

vestigations will be published elsewhere. Kidney function was systematically evaluated in 30 patients by CrEDTA clearance. Twenty-three of these experienced a reduction in clearance (median 15% with a range of 6–41%), while in 7 patients an improvement of the kidney function was found (1–31%), presumably indicating an improved post-renal function due to shrinkage of a retroperitoneal tumour.

*Stage III.* Fifty patients participated in the study from 1979 to January 1982. All patients were evaluated. The median age was 27 years (range 15–59), and the median observation time 27 months (range 9–40). Twenty-nine patients had extensive lung metastases (bilateral and multiple), and 11 had minimal lung disease. Eighteen patients had extensive retroperitoneal metastases and 5 had multiple liver metastases. Since extensive staging procedures were not applied in all cases, due to either technical shortcomings or a clinical need for immediate treatment, these last-mentioned numbers are minimal figures. Fifty-three per cent had elevated AFP, 59 per cent elevated HCG in serum, while in 76 per cent of the cases at least one of the markers was found to be elevated at the start of the treatment.

The total doses of vinblastine, bleomycin, and cis-platinum were reduced by more than 20 per cent in 45, 15, and 15 per cent of the patients respectively (Fig. 4). Despite considerable subjective toxicity with severe nausea and vomiting the compliance to the treatment was thus reasonably good at all par-

**Table 7**

*DATECA, stage III*

| | Per cent |
|---|---|
| Histology | |
| Pure | 38 |
| Mixed | 63 |
| Components | |
| Embryonal carcinoma | 92 |
| Choriocarcinoma | 21 |
| Teratoma | 33 |
| Yolk sac | 19 |
| Seminoma | 31 |

**Table 8**

*DATECA, stage III. Response to treatment*

| | No. of cases | Per cent |
|---|---|---|
| 1. Complete remission | 34/50 | 68 |
| 2. Partial remission | 12/50 | 24 |
| 3. No change | 1/50 | 2 |
| 4. Progressive disease | 3/50 | 6 |
| 5. Partial remission → complete remission (surgery) | 2/50 | 4 |

1+5= 'complete remision': 72 per cent.

**Table 9**

*DATECA, stage III. Overall results*

| | No. of cases | Per cent |
|---|---|---|
| No evidence of disease | 30 | 60 |
| Alive with disease | 6 | 12 |
| Death (disease) | 12 | 24 |
| Death (toxicity)* | 2 | 4 |
| Total | 50 | |

* One uncertain, one pulmonary toxicity.

ticipating institutions. Two drug-related deaths were encountered; in one case bleomycin-induced lung toxicity contributed to death, the other toxic death was not fully evaluable. None of the other patients experienced clinically important pulmonary toxicity. Kidney function was evaluated in detail in 30 patients. A median reduction in CrEDTA clearance of 18 per cent (range 0–40) was found.

As was the case with stage II patients nearly all

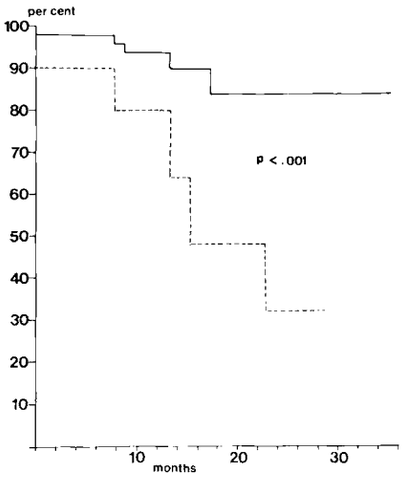



Fig. 6. Life table estimate of surgical percentages of stage III patients with choriocarcinoma (n=38 ——) and patients without choriocarcinoma (n=10 - - -) in the primary tumour.

primary tumours contained components of embryonal carcinoma. The distribution of histologic subtypes is shown in Table 7.

The results of treatment are described in Table 8. Five of the patients underwent surgery immediately after induction of chemotherapy because of radiologic evidence of residual tumour. In 3 cases, only fibrous tissue was found in the retroperitoneum, while in 2 cases benign teratomas were radically removed from the retroperitoneal area. All 5 patients are alive without evidence of disease.

Sixteen patients relapsed after achieving complete remission, the median time to relapse being 4 months (range 2–9). Eight of these died, 4 achieved a new complete remission after treatment with cisplatinum, VP-16, and bleomycin (response duration 5+, 7+, 16+, 31+ months), and 4 patients are alive with the disease currently under treatment.

Thus, the overall results revealed a 'cure rate' of over 60 per cent, i.e. patients alive without evidence of disease after primary or secondary chemotherapy. The overall results are given in Table 9. Life table estimates of crude survival and relapse-free survival appear in Fig. 5. The available information on each patient was tested with regard to prognostic significance. The diagnosis of liver metastases and extensive pulmonary disease carried a significantly negative prognostic influence ($p<0.05$). With regard to histology the presence of choriocarcinoma in the primary tumour (Fig. 6) was a bad prognostic sign. Finally, different levels of serum concentrations of AFP and HCG were tested for prognostic signifi-

**Table 10**

*DATECA. Negative prognosis factors*

| | |
|---|---|
| AFP >90 ng/ml | (stage II) |
| HCG >1 000 IU/ml | (stage III) |
| Extensive pulmonary disease | |
| Liver metastases | |
| Choriocarcinoma in primary tumour | |

cance and it was found that the best discrimination could be found at the levels depicted in Fig. 7, revealing a significantly negative influence on the prognosis of HCG levels exceeding 1 000 IU/l at the start of treatment. The prognostic factors are summarized in Table 10. Multivariate analysis will be carried out at the final analysis of the trial in order to define the interdependence of the individual negative prognostic factors. The findings are in agreement with earlier reports (3, 8) indicating that patients with extensive disease and with high tumour marker levels, especially HCG, have a bad prognosis.

## Discussion

The interim analysis of this trial indicated that a 'wait and see' strategy in patients orchiectomized for non-seminomatous testicular tumour and in clinicoradiologic stage I can safely be applied. Relapses occur at an expected rate of approximately 20 to 25 per cent. They occur early and can be successfully treated by combination chemotherapy. Irradiation seems to prevent recurrences in the retroperitoneal area and might reduce the total number of recurrences.

It is still too early to define high risk groups in which the application of adjuvant treatment could be considered in the future. It might be most advantageous to focus on patients with elevated tumour markers and a less favourable histology in the primary tumours. The present trial is planned to continue for at least another 18 months in order to provide tentative answers to some of these questions.

The preliminary results are in accordance with the data published by the Royal Marsden Group (17), where selected patients were followed after orchiectomy without further treatment. The relapses in that series were successfully treated and the overall results were excellent.

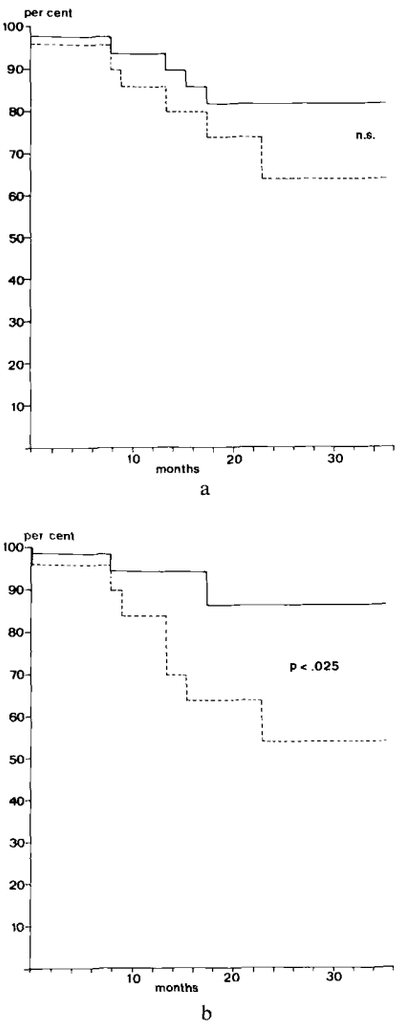



Fig. 7. Life table estimate of survival percentages in patients with a) AFP<90 ng/ml (n=28 ——) and >90 ng/ml (n=20 - - -) and b) with HCG <1 000 IU/l (n=30 ——) and >1 000 IU/l (n=18 - - -).

The results of the present investigation confirmed the reports of other centres (16), in that the prognosis of patients with stage II non-seminomatous testicular tumours can be considerably improved when chemotherapy is applied early in the treatment plan. Adjuvant irradiation towards the tumour area carries in this strategy no therapeutic benefit and leads to significant reduction in the total dose of chemotherapy given. All patients in this trial who had a serum level of AFP below 90 ng/ml are alive without evidence of disease. The need for more intensive treatment can thus be restricted to patients with increased AFP. Reduction of treatment intensity in subgroups of patients with small tumours should be considered on the basis of careful studies of the

impact of chronic toxicity such as reduction in kidney function and fertility.

In the Danish multicentre project for the analysis of testicular malignancy it has been possible to confirm on a nation-wide basis the improved results in the treatment of stage III non-seminomatous germ cell tumours. Even though the present report deals with a preliminary analysis we feel confident that the improvement in treatment strategy will be substantiated and confirmed in the final analysis. The short time span between induction of complete remission and occurrence of the relapses enables fairly safe conclusions to be drawn with regard to the long-term survival of the patients. In this investigation, all relapses occurred within 9 months after induction therapy.

The future direction for clinical research will focus on the definition and treatment of 'high risk groups'. The preliminary analysis now carried out suggests that extensive lung metastases and high levels of serum markers, especially HCG, may be predictors of a group of patients with a bad prognosis. This group should be treated more intensively than with the standard PVB regimen.

Earlier studies indicated activity of other drugs in this disease, in particular VP-16 (6, 14). The present results with treatment of patients relapsing after PVB therapy, where cis-platinum plus VP-16 was employed, give rise to some optimism with regard to the inclusion of VP-16 in the primary treatment. Drugs such as actinomycin-D might also be of value in particular cases.

Another possibility of improving the therapeutic results is the use of high-dose cis-platinum. In a pilot study at NIH (15) cis-platinum in doses of 40 mg/ml daily for 5 days, given in high chloride solutions, proved feasible with no deleterious effects on kidney function and with promising results. Intensive use of myelosuppressive drugs such as vinblastine and VP-16 might conceivably be supplemented by the use of autologous bone-marrow transplantation. In theory, high risk patients with testicular malignancy should be well suited for this procedure since bone-marrow metastases are extremely unusual.

Another avenue of research is to develop less toxic agents with equal or better antineoplastic activity as, for instance, new platinum analogues with less renal toxicity and new bleomycin analogues with less lung toxicity. It is in this connection of utmost importance to define in more detail the degree to which the toxicity in terms of infertility and chronic renal dysfunction will prove to be a lasting problem in the management of these patients. Increased risk of secondary leukemia, which has been reported in the treatment of, for instance, lymphomas, small cell lung carcinoma, and ovarian carcinoma (1, 4, 18) has not been reported in the treatment of patients with testicular malignancy, which probably reflects the fact that alkylating agents are not included in the modern treatment strategy.

The improved results in the treatment of testicular tumours is one of the greatest achievements in modern oncology. It is obvious that attempts to reduce toxicity or duration of treatment should be carried out in such a way that this therapeutic gain can be preserved.

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