SWEDISH & NORWEGIAN
TESTICULAR CANCER PROJECT
'SWENOTECA'
&
ONCOLOGIC CENTER
LUND, SWEDEN

TREATMENT OF NON-SEMINOMATOUS TESTICULAR CANCER

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No longer valid

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PREFACE

The idea of a Swedish-Norwegian testicular cancer project (SWENOTECA) dates back to January, 1980, when representatives from Det Norske Radiumhospital and the Departments of Oncology and Urology in Lund, Malmö and Göteborg met to discuss management of patients with non-seminomatous germ cell cancer. At that meeting it was felt desirable to try to create common treatment policies for these patients in the two countries. At subsequent meetings with participants from the various regional hospitals in Sweden and Norway the staging, treatment and follow-up, as described in this booklet, has been agreed upon.

The program has been approved by the Regional Oncologic Board of the Oncologic Center for South Swedish Medical Care Region, Sweden, and is effective as of April 1, 1981.

Printing and distribution of the program is arranged by the Oncologic Center and Regional Tumour Registry in Lund, where collection and analysis of data also will be carried out.

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CONTENTS

INTRODUCTION 7

BACKGROUND 9

1. Histopathologic classification 9
2. Principles of investigation 10
3. Staging 11
4. General principles of treatment 12
5. Radiotherapy 13
6. Second-line chemotherapy 14
7. General principles of follow-up 14

AIM OF THE STUDY 15

PATIENT SELECTION 16

PRINCIPLES OF REFERRAL 17

MANAGEMENT OF PATIENTS WITH TESTICULAR TUMOURS 19

1. Orchiectomy 19
2. Histopathological examination 20
3. Investigations of patients with histopathologically verified testicular NSGCT 20
4. Clinical staging (CS) 21
5. Pathological staging (PS) 21
6. Treatment according to stage 23
7. Retroperitoneal lymph node extirpation (RPLNE) 31

8. Follow-up 32

9. Treatment of relapse 32

ADDENDUM

1. SWENOTECA registration forms 37

2. Histopathological examination of NSGCT 57

3. Histopathological examination of the retroperitoneal nodes 59

4. CVB regimen 60

5. VP-16 - Cis-platinum regimen 63

6. VP-16 - Isophosphamide regimen 64

REFERENCES 67

INTRODUCTION

Malignant testicular tumours are rare neoplasms with a yearly incidence of 0.9-4.5 per 100 000 men. In men aged 20-40 years the incidence is, however, 7-10 per 100 000 per year, which makes it the most frequent cancer in males of that age group.

Non-seminomatous germ cell tumours (NSGCT) constitute about 50 % of all testicular cancer. The prognosis for patients with NSGCT has improved considerably during the last decade. New methods for staging, therapy and follow-up have been developed. These procedures are complicated and call for close collaboration between specialists in pathology, radiology, surgery and oncology. The treatment should therefore be centralized to centers fully equipped to meet the requirements of these patients and with a reasonable number of patients treated yearly.

Many aspects of the biologic behaviour of these neoplasms need to be studied further before the optimal treatment is found. As the number of patients with NSGCT is limited, a collaboration between several centers is a prerequisite for meaningful clinical research.

In the Swedish-Norwegian testicular cancer project, SWENOTECA, the management of patients with NSGCT is standardized as much as possible. This first program is focused on the impact on prognosis of the histopathologic type and extent of the primary tumour and of the use of tumour markers and various diagnostic procedures in staging and follow-up. If the SWENOTECA collaboration proves efficient, the aim is to include randomized, prospective therapeutic studies in the near future.

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BACKGROUND

1. HISTOPATHOLOGIC CLASSIFICATION

Several classification systems for the histopathologic subtyping of germ cells tumours are used. Most Swedish centers use the British Testicular Tumour Panel system (BTTP). Norwegian pathologists follow the WHO system. The subtypes of one system can not be directly translated into the other system. Table 1 is a comparison of the BTTP and the WHO classification of tumours of the testis (1).

Table 1. Comparison of WHO and BTT Panel Classifications of Tumors of Testes

WHO Panel	BTTP
Tumors of one histological type	Not used
Seminoma	Seminoma
Spermatocytic seminoma	Spermatocytic seminoma
Embryonal carcinoma	MTU excluding yolk sac tumors in adults
Yolk sac tumor—infantile embryonal carcinoma.	Yolk sac tumor in children (not in adults)
Teratoma	TD, MT1, MTT
Mature teratoma	TD, excluding epidermal cysts
Immature teratoma	TD
Teratoma with malignant transformation	MTI
Choriocarcinoma pure	Not recognized
Tumors of more than one histological type	Not used
Embryonal carcinoma and mature and/or immature teratoma	MTI
Yolk sac tumor with mature and/or immature teratoma	MTI
Seminoma and teratoma	Combined tumor
Seminoma and embryonal carcinoma	Combined tumor
Choriocarcinoma + ECA	MTT
Choriocarcinoma and teratoma	MTT
Choriocarcinoma and seminoma	Combined tumor

None of these classification systems has an obvious superiority over the other and therefore in this project we will use both classifications and by later cross-typing of the tumours be able to evaluate if there is a difference in prognostic significance between the two.

2. PRINCIPLES OF INVESTIGATION

2.1. Biochemical tumour markers

During the last years sensitive immunologic methods (RIA) for determination of small amounts of α-foeto-protein (AFP) and β-subunit of human choriongonadotropin (β-HCG) in serum have been developed. AFP is normally produced during fetal life by the liver, yolk-sac elements and gastrointestinal tissue. The biologic half-life of AFP in serum is 5 days. β-HCG is produced by normal placenta tissue and has a biologic half-life of 24 hours. In adult life the serum concentrations of these substances are <30 ng/ml. Since it has been shown that AFP and β-HCG are produced by non-seminomatous germ cell tumours (NSGCT) the monitoring of these substances in serum of patients with NSGCT is of great importance for staging, evaluation of response to therapy and follow-up (2). Elevated concentrations of AFP and/or β-HCG (>30 ng/ml) are found in 80-90 % of patients with clinically demonstrable NSGCT and in 50-60 % of patients with micrometastases, sometimes several months before the tumour is clinically obvious. When using the serum concentrations of these tumour markers for monitoring of tumour response to therapy it is mandatory to take their half-lives into consideration.

About 10 % of patients with seminoma have elevated titers of β-HCG. In such cases it is important to look very carefully for embryonal or chorioncarcinoma elements in the tumour. If such elements are found, the tumour is by definition a NSGCT. Production of AFP by pure seminoma has not been reported. This means that patients with elevated AFP always should be treated according to the principles of NSGCT even if no such elements can be found in the primary testicular cancer.

AFP and β-HCG may also be produced in some other diseases, e.g. AFP by hepatoma and by rapidly proliferating liver tissue and β-HCG by gestational chorioncarcinoma. Recently it has been reported that monitoring of serum LD might be of prognostic value in patients with NSGCT (3). S-LD is, however, non-specific and further studies are needed to assess its value in the treatment of these patients.

2.2. Diagnostic radiography

The regional lymph nodes of the testis are the paraaortic nodes in the renal hilar area and thus the first echolon for lymphogenic dissemination of tumour cells. Prior inguinal surgery may distort the lymphatic channels and alter the normal routes of metastatic spread. For

radiographic visualization of the paraaortic and pelvic nodes several methods are used. Lymphangiography, cavography and urography are well established methods in metastatic work-up in testicular cancer. Newer techniques such as computerized tomography (CT) and ultrasound have also been shown to be of value (4,5). The experience with these newer methods is, however, limited. For evaluation of the thorax there are preliminary results indicating a diagnostic gain with CT compared to plain x-ray and planar tomography of the lungs and mediastinum (5).

One of the aims of the SWENOTECA project is to evaluate the diagnostic value of the different methods for staging and follow-up of patients with testicular cancer.

2.3. "Diagnostic" surgery

For detection of micrometastases in regional lymph nodes available non-invasive methods are insufficient. Retroperitoneal lymphadenectomy increases the diagnostic accuracy by 10-20 % compared to lymphangiography (6). As treatment in this project is conditioned by the stage of the disease, a "diagnostic" retroperitoneal lymphadenectomy is to be performed to enable the distinction between stage I and II A. Furthermore, for the evaluation of the accuracy of the non-invasive diagnostic procedures it is important to get a histopathological verification.

3. STAGING

3.1. Staging of the primary testicular tumour

The local invasiveness of the primary tumour has a significant impact on prognosis (7,8). In testicular cancer staging of the primary tumour has not been performed and/or not been reported regularly, although this might be important for selecting high-risk patients. In this program staging according to UICC will be used and clinical stage (T1-4) and pathological stage (pT 1-4) of the primary tumour will be registered (see p. 57).

3.2. Staging according to extent of disease

The prognosis in testicular cancer is correlated not only to the extent of the disease but also to the size of the metastases. Patients with large retroperitoneal lymph node metastases (>2 cm diameter) have a high risk for disseminated disease. Furthermore, the efficacy of radiotherapy and chemotherapy is directly correlated to the size of the tumour and concerning radiotherapy there seems to be a border at 2 cm (9).

The staging system described by Peckham et al. (10) is based on the extent of tumour as well as on the size of the metastases (see p. 57-59).

In the present program the staging system according to Peckham will be used and constitute the base for the treatment principles.

4. GENERAL PRINCIPLES OF TREATMENT

4.1. Stage I

Most patients with stage I disease are cured by orchiectomy and retroperitoneal lymphadenectomy or radiotherapy to subdiaphragmatic nodes. Close follow-up after treatment is mandatory for such patients. Very good results are achieved with "salvage" chemotherapy for the few (about 20 %) patients who relapse. Today it seems possible to achieve a near 100 % survival for patients with stage I disease without the use of prophylactic (adjuvant) chemotherapy (11).

In this program adjuvant chemotherapy will not be given in stage I disease but the patients will be followed very closely after primary treatment in order to detect relapses early.

4.2. Stage II

For patients with limited retroperitoneal lymph node metastases (stage II A) the risk of relapse is 40-50 % after apparently complete excision of all retroperitoneal nodes. Relapse in the lungs is most frequent (12). Adjuvant chemotherapy seems to reduce the relapse rate and to improve survival (13). There are now ongoing prospective studies comparing survival with and without adjuvant chemotherapy.

Until more data are available patients with stage II A disease will be given adjuvant chemotherapy in this study.

For patients with extensive retroperitoneal lymph node metastases (stage II B-C) preoperative chemotherapy will reduce the bulk of tumour and make complete excision possible in most cases (14,15).

These patients also have a high frequency of subclinical metastases beyond the retroperitoneal nodes, which are erridicated by the chemotherapy.

In this program 4 cycles of CVB (Cis-platinum, Vinblastine and Bleomycin) will be given preoperatively in stage II B and C.

4.3. Stage III and IV

For patients with disseminated disease the main treatment is chemotherapy. During the last decade the prognosis for these patients has improved dramatically due to the development of effective chemotherapy regimens, one of which is CVB. Response rates in the order of 90-100 % and cure rates of 40-50 % may be achieved in patients with disseminated testicular cancer (16,17).

In stage III and IV disease metastases are usually found in the retroperitoneal lymph nodes at the staging investigation. As small metastases, residual after chemotherapy, are difficult to detect in this region with available non-invasive methods, a retroperitoneal lymph node extirpation should be performed even if a clinical complete remission is achieved with chemotherapy alone.

In the few cases where no metastases are found in retroperitoneal lymph nodes at the initial staging (CT, lymphography) retroperitoneal lymph node extirpation seems to be unnecessary (18).

Most of the patients who achieve a complete remission do so during the first 2-3 cycles of CVB chemotherapy. If a complete remission is not achieved after 4 cycles every attempt must be made to resect the remaining tumour tissue.

The chemotherapy may often reduce the tumour volume and make resection easier. Furthermore, in many cases the histology of the tumour has shifted towards a so-called "mature teratoma" (19,20).

Patients who achieve a complete remission after induction chemotherapy usually have received maintenance chemotherapy for longer or shorter periods. Einhorn et al. are now performing a randomized study comparing maintenance therapy with Vinblastine versus no maintenance for patients in complete remission after induction chemotherapy with 4 cycles of CVB. Preliminary data indicate no benefit of such maintenance chemotherapy (21).

In this study no maintenance chemotherapy will be given after complete remission with induction chemotherapy.

5. RADIOTHERAPY

The efficiency of radiotherapy in patients with NSGCT is dependent on the tumour size. The smaller the nodal deposits the greater the chance of local control with irradiation. In small tumours (<2 cm) absorbed doses of 40-50 Gy in 4-5 weeks are capable of irradicating the tumour in 80-85 % of the patients. Bulky deposits have, however, a significantly reduced radiosensitivity and even with absorbed doses of 50-55 Gy local control is achieved in only 30 % (9).

In this study radiotherapy will not be given as part of the primary treatment but will be used for small localised deposits residing after adequate chemotherapy and/or surgery. In these situations a minimum absorbed dose of 40 Gy to a limited target volume is recommended.

6. SECOND-LINE CHEMOTHERAPY

Until recently effective therapy for patients failing or relapsing after CVB treatment has not been available.

There are, however, now some encouraging reports on second-line therapy.

1 Patients who relapse after a comparatively long tumourfree interval (>6 months) may respond once more to treatment with Cis-platinum (22).

2 The alkylating agent isophosphamide (Holoxan®) has been used in the treatment of testicular cancer especially in Germany. A response rate of 90 %, with 45 % complete remissions has been reported (23). The duration of response has, however, often been short.

A limiting factor in the use of isophosphamide has been its pronounced toxicity on the uroepithelium. Since a few years an antidot (Mitexan) to this toxic effect is available, which has rendered isophosphamide more useful.

3 Another drug, the epipodophyllotoxin VP-16 has recently been reported to be active in testicular cancer. As a single agent or in combination with other cytotoxic drugs (Adriamycin, Cis-platinum, Bleomycin) VP-16 is reported to induce complete remissions in 30 % in patients who had prior extensive chemotherapy (24,25).

The combination of isophosphamide and VP-16 has been used in phase I and phase II studies in various types of tumours during the last few years. The combination is comparatively well tolerated by the patients even if they are heavily pretreated with other cytostatic drugs. The limiting factor has been myelosuppression while urotoxicity has not been a problem when the uroprotecting drug Mitexan has been given simultaneously (26,27).

There are some early reports on the efficacy of the combination of isophosphamide and VP-16 also in disseminated testicular cancer (28).

7. GENERAL PRINCIPLES OF FOLLOW-UP

Ninety per cent of the relapses will appear within the first 2 years after treatment, most of them within 1 year. Relapses in the abdomen after retroperitoneal lymph node extirpation is unusual and the first relapse is usually located in the lungs.

As the efficiency of therapy is dependent on tumour mass at detection, a close follow-up, especially during the first 2 years, is important.

AIM OF THE STUDY

1. The aim of this SWENOTECA project is to standardize the staging procedure, treatment and follow-up in an unselected group of patients with non-seminomatous germ cell tumour (NSGCT) to gain further knowledge of the biological behaviour of these tumours as a base for optimizing the treatment in various disease presentations.

   The following points will be evaluated:

   1 The prognostic influence of histopathologic type, site and extent of the primary testicular tumour.

   2 The prognostic value of the British testicular tumour panel (BTTP) classification and the WHO classification respectively.

   3 The value of biologic serum markers (β-HCG, AFP, LD) for staging, therapy and follow-up.

   4 The diagnostic significance of different radiological methods at the initial staging of the disease and early detection of relapse after therapy.

2. After an initial period the intention is to expand the project to include prospective randomized therapeutic studies.

PATIENT SELECTION

1. Included in the study:

   All adult patients with histopathologically proven testicular NSGCT.

   1 All germ cell tumours with other elements than pure seminoma are classified as NSGCT.

   2 Patients with elevated serum AFP are included even if only seminomatous elements are found histopathologically.

   3 Patients with present or prior disease, necessitating deviation from the protocol are included but will be analysed separately.

2. Excluded from the study:

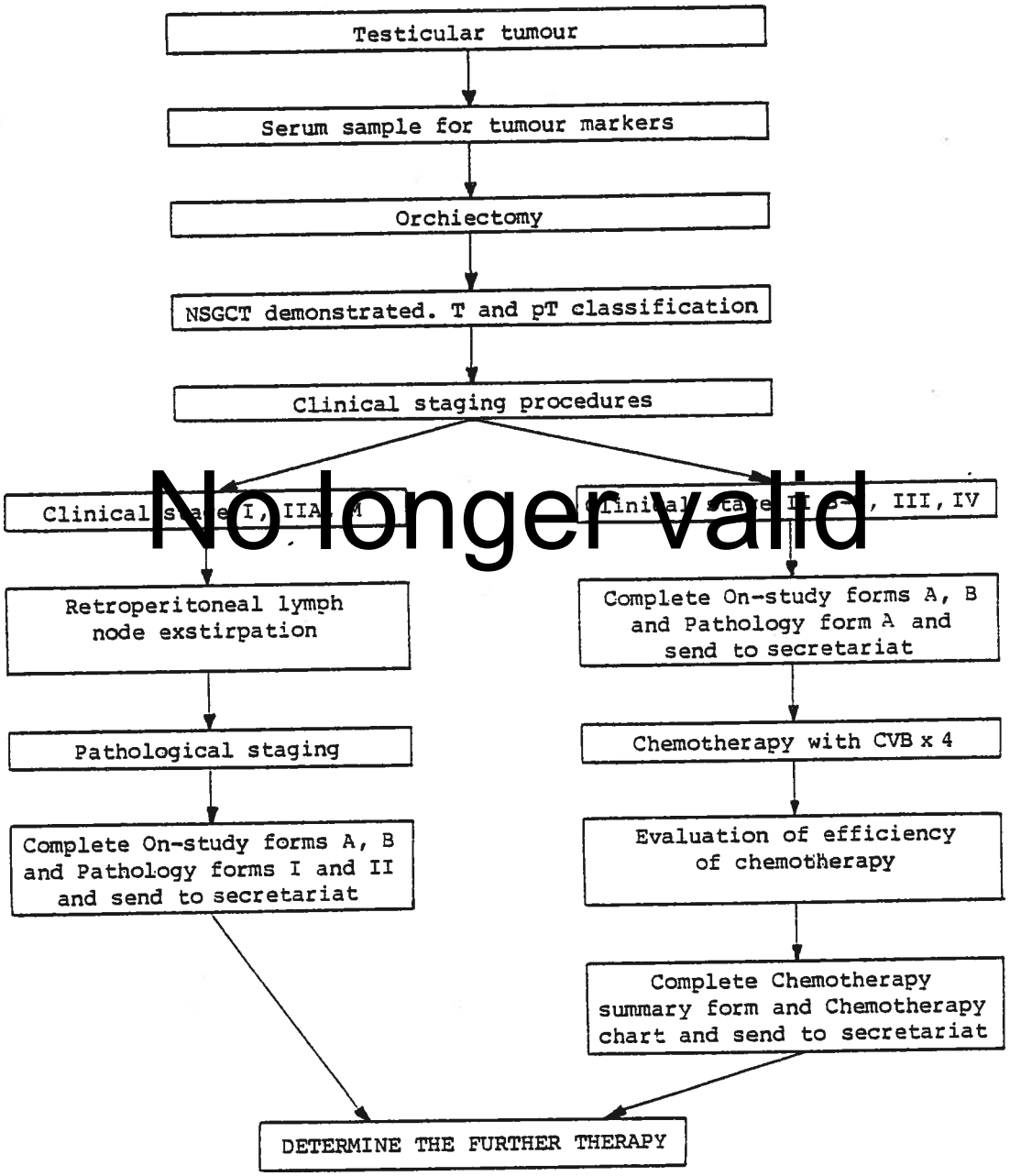
   No primary tumour found in the testes (extragonadal NSGCT).

PRINCIPLES OF REFERRAL

1. The patient should preferably be referred to an urologic department for evaluation.

2. In case of absence of the contralateral testicle the patient should always be referred to a urologic department where a frozen section examination can be performed before orchiectomy.

PRINCIPLES OF DIAGNOSIS, STAGING, INITIAL THERAPY AND REGISTRATION



MANAGEMENT OF PATIENTS WITH TESTICULAR TUMOURS

1. ORCHIECTOMY

1.1. Exploration of the testis should be carried out when a testicular tumour cannot be excluded clinically.

1.2. Transscrotal biopsy or fine needle aspiration should never be performed.

1.3. Serum for analysis of tumour markers (β-HCG, AFP, LD) should be drawn before orchiectomy.

1.4. Notify the path.lab. that an orchiectomy will be performed.

1.5. The surgical procedure demands general anesthesia.

1.6. Surgical procedure:

A long incision identical to that performed on patients with inguinal hernia is done. A scrotal incision increase the risk of tumour spread and should not be performed. If an earlier incision biopsy has been performed, hemiscrotectomy should be done.

The anterior wall of the inguinal canal is divided. The proximal part of the funicle is dissected free. The funicular vessels are clamped proximally.

The funicle and its surrounding fascia, the testis and the epididymis are dissected free. The fascia containing the testis and the epididymis is lifted out of the scrotum and put into a sterile bowl.

If a testicular tumour is found clinically, the funicle is divided proximally. Increased vascularity of the tunica albuginea indicates the presence of a testicular tumour. An incision in the testis should be avoided, but if uncertainty exists, the testicle may be divided and a specimen sent for frozen section examination while the funicle is clamped. Even a suspicion of malignancy makes orchiectomy warranted, especially if the patient has another normal testis. The testis is replaced in the scrotum only if both macro- and microscopic examination reveals a benign lesion. The funicle is divided after crushing at the proximal aperture of the inguinal canal. Tie with non-resorbable sutures. It is easier to identify the proximal part of the funicle if such material is used, when a later retroperitoneal lymph node extirpation is performed. Extremely careful hemostasis should be performed before the suturing to avoid infections.

Phlebography of the testicular vein is recommended, preferably combined with urography.

The surgeon should not cut into the tumour or the testicle except when a frozen section examination is needed. The macroscopic examination should be done by the pathologist. The surgical specimen should be sent immediately unfixed to the path. lab. (provided that it can be handled immediately).

A testis prothesis should preferably not be placed in the scrotum before 2 years after the orchiectomy in order to make later clinical evaluation easier.

2. HISTOPATHOLOGICAL EXAMINATION

2.1. The diagnosis of non-seminomatous germ cell tumour (NSGCT) is established by histopathologic examination of the removed testicle.

2.2. The tumour is classified according to BTTP and WHO classification (see p. 9).

2.3. Staging of the tumour is done according to UICC 1978 (see p. 57).

3. INVESTIGATION OF PATIENTS WITH HISTOPATHOLOGICALLY VERIFIED TESTICULAR NSGCT

3.1. Postoperatively serum marker analysis (AFP, β-HCG, LD) once weekly until clinical staging procedures are completed.

3.2. Laboratory tests: B-Hb, B-Leucocytes, B-Trombocytes, S-Creatinine, S-GT, S-ALP.

3.3. Diagnostic radiography:

- Chest x-ray
- CT of chest
- CT of abdomen and pelvis
- Ultrasound of abdomen and pelvis
- Foot lymphography
- Urography

If CT is not available chest planar tomography and vena cava phlebography are performed.

Liver scintigraphy if liver metastasis is clinically suspected.

CT of brain or brain scintigraphy if brain metastasis is clinically suspected.

4. CLINICAL STAGING (CS)

Based on all findings except retroperitoneal lymphadenectomy.

CS I — No evidence of metastases.

CS M — α-foetoprotein and/or β-subunit of HCG persistently elevated (>30 ng/ml) but no metastases demonstrable.

CS II — Metastases confined to abdominal lymph nodes. Three subgroups recognized:

A. Maximal diameter of metastases <2 cm

B. Maximal diameter of metastases 2-5 cm

C. Maximal diameter of metastases >5 cm

For determination of the A, B and C status of the abdominal lymph nodes lymphangiogram and CT (if available) should be used.

CS III — Involvement of supradiaphragmatic lymph nodes. Note: subdiaphragmatic lymph nodes may not be demonstrable.
Abdominal status: 0 (no mets.), A, B, C, as for stage II.

CS IV — Extralymphatic metastases. For the lungs 3 subgroups are recognized:

L_1 ≤3 metastases

L_2 >3 metastases, no one >2 cm maximum diameter

L_3 >3 metastases, at least one >2 cm maximum diameter

Abdominal status: 0 (no mets.), A, B, C, as for stage II.

5. PATHOLOGICAL STAGING (PS)

Based on macro- and microscopic findings at retroperitoneal lymphadenectomy.

PS I — No evidence of metastases.

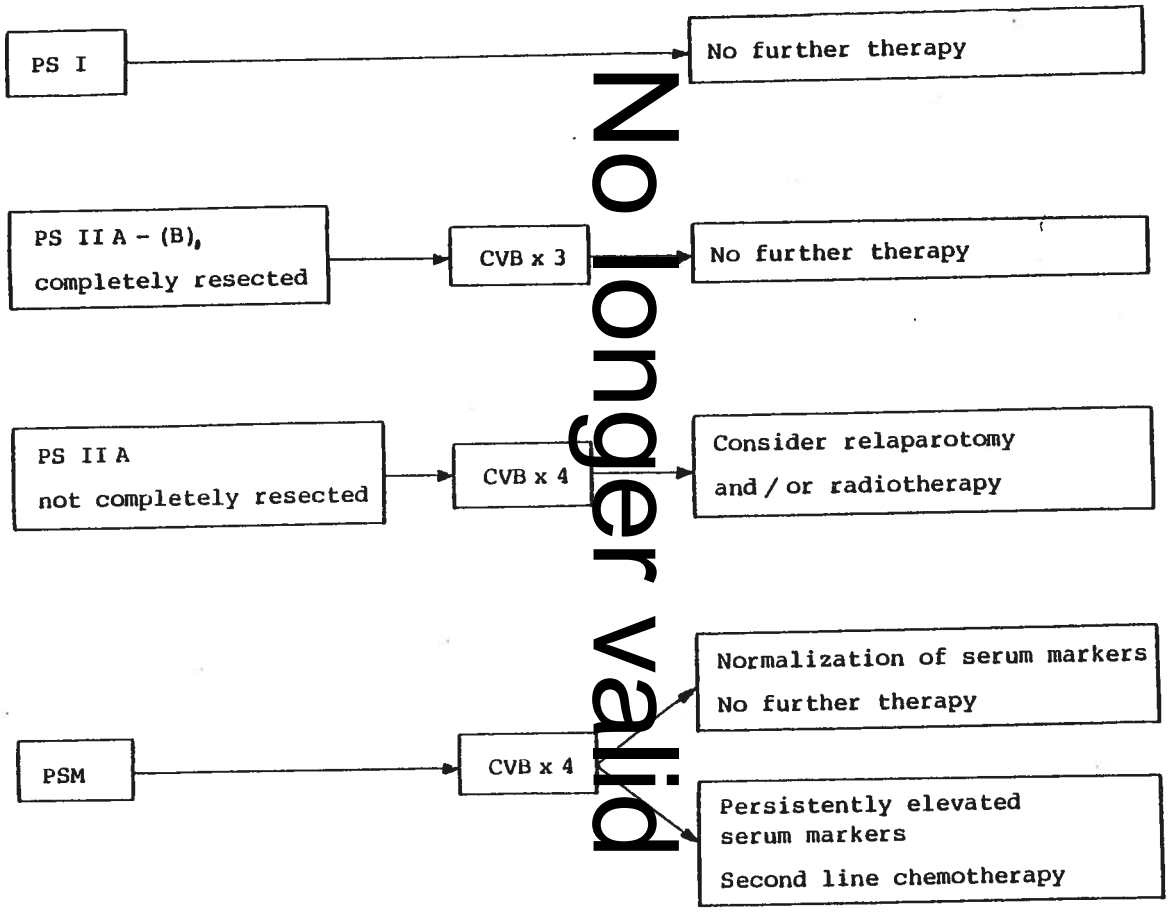
PS M — α-foetoprotein and/or β-subunit of HCG persistently elevated after retroperitoneal lymphadenectomy but no metastases demonstrable.

PS II — Metastases confined to retroperitoneal lymph nodes. α-foetoprotein and β-subunit of HCG normalized after retroperitoneal lymphadenectomy. A, B, and C status of abdominal nodes determined by measurement of the operative specimen.

PS III — Not recognized in this program.

PS IV — Metastases in extralymphatic organs (e.g. liver) found at lymphadenectomy.

TREATMENT PRINCIPLES AFTER RETROPERITONEAL LYMPH NODE EXTIRPATION (RPLNE)
FOR PATIENTS IN PATHOLOGICAL STAGE I, II A, M AND UNEXPECTED II B



CVB = Cisplatinum, Vinblastine, Bleomycin combination chemotherapy.

6. TREATMENT ACCORDING TO STAGE

6.1. CS I, CS M, CS II A

1 Perform retroperitoneal lymph node extirpation (RPLNE) (see p.31). If lymph node metastases larger than 2 cm are found at laparotomy, RPLNE should not be attempted.

2 Serum markers should be analyzed once weekly if elevated, until further therapy is decided. Persistently elevated AFP and/or β-HCG after RPLNE implies residual tumour.

6.2. PS I

No further treatment. Follow-up according to schedule (see p. 33).

6.3. PS II A

1 After radical RPLNE 3 cycles of chemotherapy with CVB are given (see p. 60).

Serum markers are analyzed prior to each cycle of chemotherapy.

At start of third cycle perform chest x-ray.

If relapse during CVB treatment change to second-line chemotherapy (see p. 14). Consider also radiotherapy and/or surgery for localized relapse.

2 If continuous complete remission after CVB, no further treatment is indicated. Follow-up according to schedule (see p. 33).

3 If radicality was not achieved at RPLNE consider local radiotherapy or relaparotomy after 4 cycles of CVB.

6.4. PS M

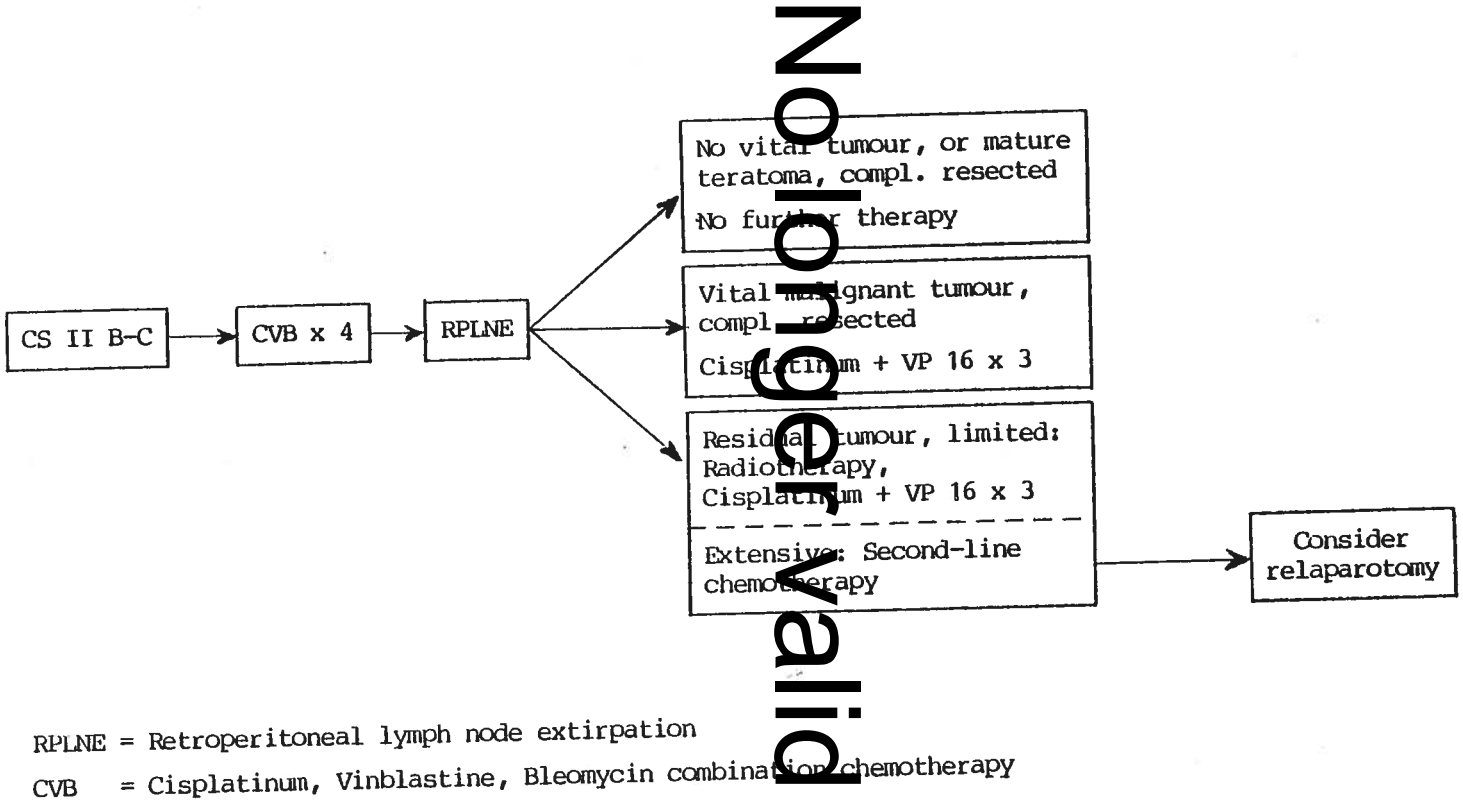
1 Four cycles of CVB are given (see p. 60). Serum markers are analyzed prior to each cycle of chemotherapy.

If progressive disease after the second or fourth cycle of CVB change to second-line chemotherapy (see p. 14).

2 If complete remission after CVB, no further treatment is indicated. Follow-up according to schedule (see p. 33).

3 If a decrease to less than 50 % of the initial level(s) of AFP and β-HCG is not achieved at start of third cycle of CVB change to second-line chemotherapy (see p. 14).

TREATMENT PRINCIPLES FOR PATIENTS IN CLINICAL STAGE II B-C



RPLNE = Retroperitoneal lymph node extirpation

CVB = Cisplatinum, Vinblastine, Bleomycin combination chemotherapy

6.5. CS II B and II C

1 Four cycles of CVB are given (see p. 60). Serum markers are analyzed prior to each cycle of chemotherapy. Before start of third cycle and after the fourth cycle the effect of CVB is evaluated with chest x-ray and CT of abdomen and pelvis.

If CT is not available perform plain x-ray and/or ultrasound of abdomen and pelvis.

If progressive disease after the second or fourth cycle of CVB change to second-line chemotherapy (see p. 14).

N.B. Unchanged or even some increase of tumour size does not necessarily imply progressive disease, since fibrosis and/or "maturization" of the tumour might cause some enlargement. A decrease to less than 50 % of the initial tumour marker level at start of third cycle implies efficacy of the therapy.

2 Perform RPLNE (see p. 31).

Mark with clips areas with questionable radicality.

3 Subsequent treatment depends on surgical and histopathological findings:

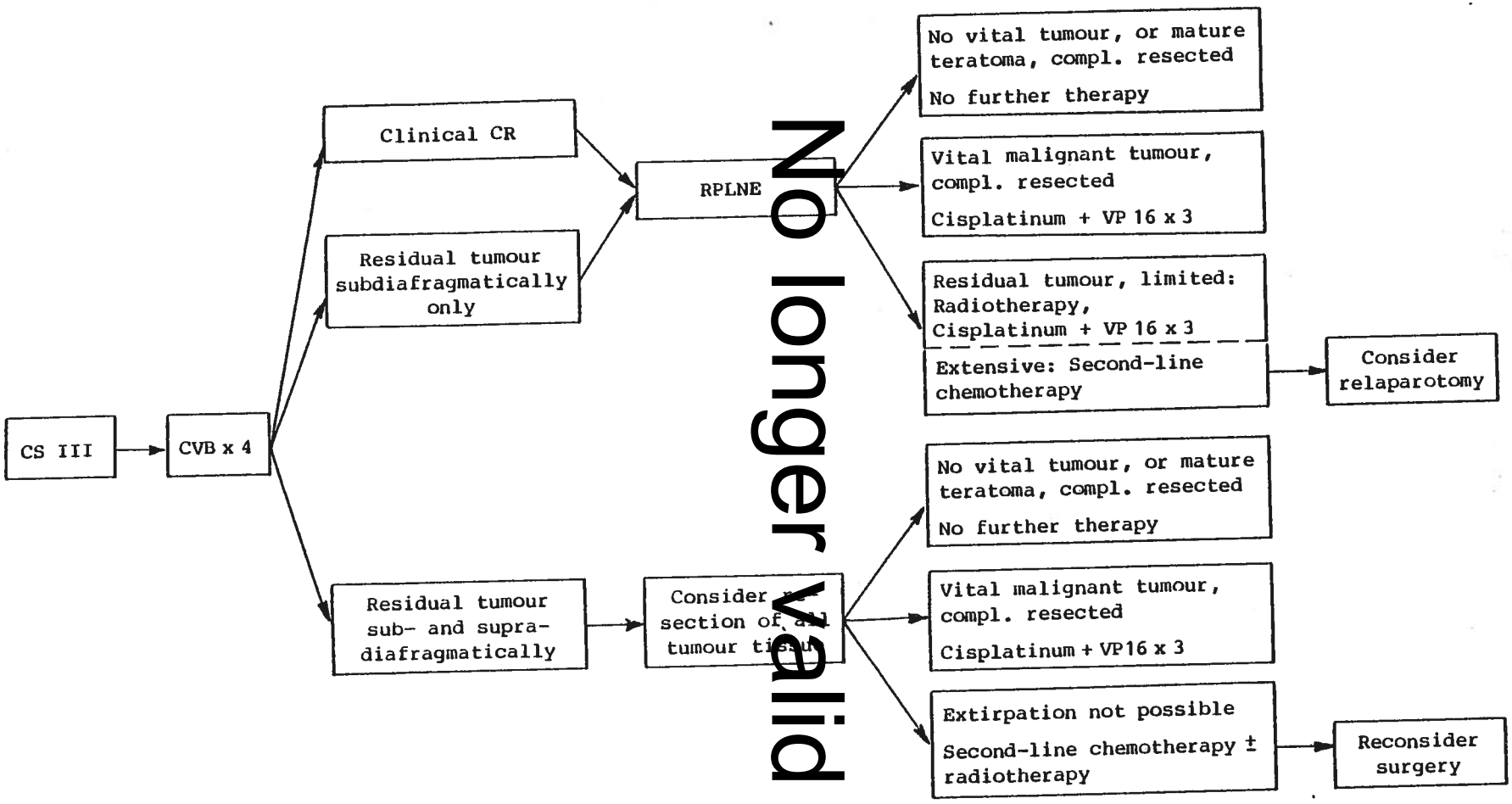
If complete remission or resectable mature teratoma is found histopathologically, no further treatment. Follow-up according to schedule (see p. 33).

If the operative specimen contains areas of vital tumour growth, completely resected macro- and microscopically, 3 cycles of chemotherapy with Cis-platinum and VP-16 are given (see p. 63). Follow-up according to schedule (see p. 33).

If all tumour tissue cannot be resected completely at RPLNE further treatment is conditioned by the bulk of tumour left. If limited residual tumour, give radiotherapy to this region (see p. 13), followed by 3 cycles of chemotherapy with Cis-platinum and VP-16 (see p. 63). If more extensive disease give second-line chemotherapy (see p. 14). Therapeutic efficacy should be evaluated every second month. Thereafter consider second look laparotomy.

If complete remission after these measures, no further treatment. Follow-up according to schedule (see p. 33).

TREATMENT PRINCIPLES FOR PATIENTS IN CLINICAL STAGE III



RPLNE = Retroperitoneal lymph node exstirpation

CVB = Cisplatinum, Vinblastine, Bleomycin combination chemotherapy

6.6. CS III

1 Induction chemotherapy with CVB according to 6.5.

2 If complete clinical remission after 4 cycles of CVB perform RPLNE.

N.B. If the retroperitoneal lymph nodes were not involved pretherapeutically, RPLNE is not performed.

Subsequent treatment depends on surgical and histopathological findings:

If complete remission or resectable mature teratoma is found histopathologically, no further treatment. Follow-up according to schedule (see p. 33).

If the operative specimen contains areas of vital malignant tumour, completely resected macro- and microscopically, 3 cycles of chemotherapy with Cis-platinum and VP-16 are given (see p.63). No further treatment. Follow-up according to schedule (see p.33).

If all tumour tissue cannot be resected completely at RPLNE, further treatment is conditioned by the bulk of tumour left. If limited residual tumour, give radiotherapy to this region followed by 3 cycles of chemotherapy with Cis-platinum and VP-16 (see p. 63). If extensive residual disease left, give second-line chemotherapy (see p.14). Therapeutic efficacy should be evaluated every second month. Thereafter consider second look laparotomy. If complete remission after these measures, no further treatment. Follow-up according to schedule (see p. 33).

3 If complete clinical remission is not achieved after 4 cycles of CVB further therapy is dependent on the region(s) with persistent disease:

If only retroperitoneal tumour persists after chemotherapy, treatment is the same as stated for patients in complete clinical remission (see above 2.).

If tumour persists sub- as well as supradiaphragmatically after chemotherapy consider surgery to all regions:

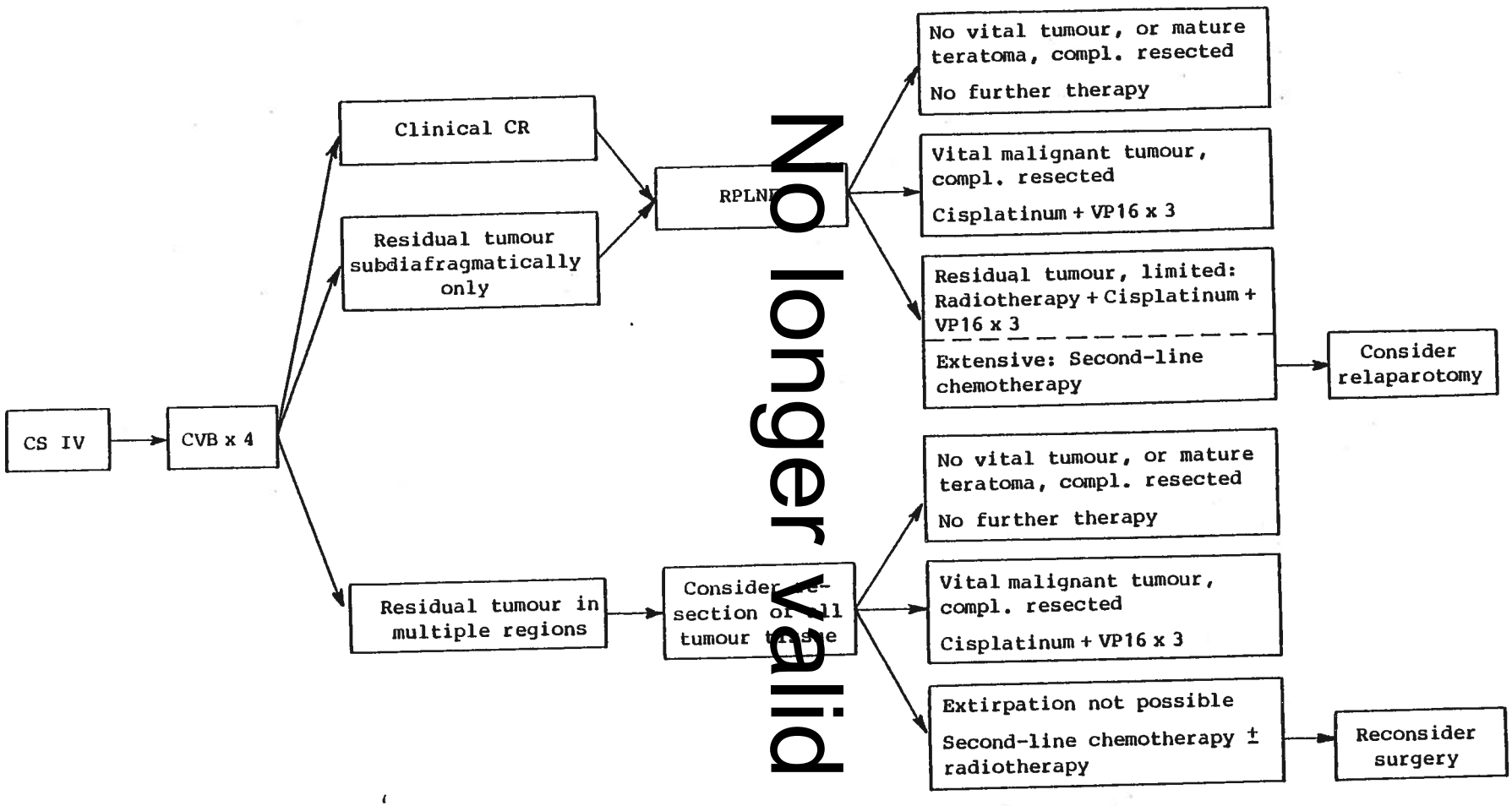
Alt 1. At surgery no malignant tumour or only resectable mature teratoma is found histopathologically. No further treatment.

Alt 2. At surgery vital malignant tumour is found in one or more regions, which can be completely resected, macro- as well as microscopically. Three cycles of chemotherapy with Cis-platinum and VP-16 (see p. 63) are given.

Alt 3. Surgery not possible. Give second-line chemotherapy first (see p. 14) and then reconsider surgery. Radiotherapy should also be considered to limited residual tumour.

If complete remission after these measures, no further treatment. Follow-up according to schedule (see p. 33).

TREATMENT PRINCIPLES FOR PATIENTS IN CLINICAL STAGE IV



RPLNE = Retroperitoneal lymph node exstirpation

CVB = Cisplatinum, Vinblastine, Bleomycin combination chemotherapy

6.7. CS IV

1 Induction chemotherapy is given according to 6.5.

2 If complete clinical remission after 4 cycles of CVB perform RPLNE (see p. 31).

N.B. If the retroperitoneal lymph nodes were not involved pretherapeutically, RPLNE is not performed.

Subsequent treatment depends on the surgical and histopathological findings:

If complete remission or only resectable mature teratoma is found histopathologically no further treatment. Follow-up according to schedule (see p. 33).

If the operative specimen contains areas of vital malignant tumour, completely resected macro- and microscopically, give 3 cycles of chemotherapy with Cis-platinum and VP-16 (see p. 63). If continuous complete remission after this chemotherapy, no further treatment. Follow-up according to schedule (see p. 33).

If radical surgery is not possible further therapy is conditioned by the bulk of tumour left. If limited residual tumour give radiotherapy to this region (see p. 13), followed by 3 cycles of chemotherapy with Cis-platinum and VP-16 (see p. 63). If extensive residual tumour give second-line chemotherapy (see p. 14) and thereafter consider second look laparotomy. If complete remission after these measures no further therapy is given. Follow-up according to schedule (see p. 33).

3 If complete remission is not achieved after 4 cycles of CVB further therapy is dependent on the region(s) with persistent disease:

If tumour persists only in subdiaphragmatic lymph nodes treatment is the same as stated for patients in complete clinical remission (see above 2.).

If tumour persists also in other regions (lung, liver, supradiaphragmatic lymph nodes etc.) consider surgery to all regions:

Alt 1. At surgery no malignant tumour or only resectable mature teratoma is found histopathologically. No further treatment.

Alt 2. At surgery resectable vital malignant tumour is found in one or more regions. Three cycles of chemotherapy with Cis-platinum and VP-16 are given (see p. 63).

Alt 3. Radical surgery not possible. Give second-line chemotherapy (see p. 14) and then reconsider surgery. Radiotherapy should also be considered to limited residual tumour.

If complete remission after these measures, no further treatment. Follow-up according to schedule (see p. 33).

N.B. If tumour markers are normalized after induction chemotherapy but there is residual tumour clinically every attempt should be made to resect persistent tumour. It might be only necrotic and fibrotic tissue or mature teratoma.

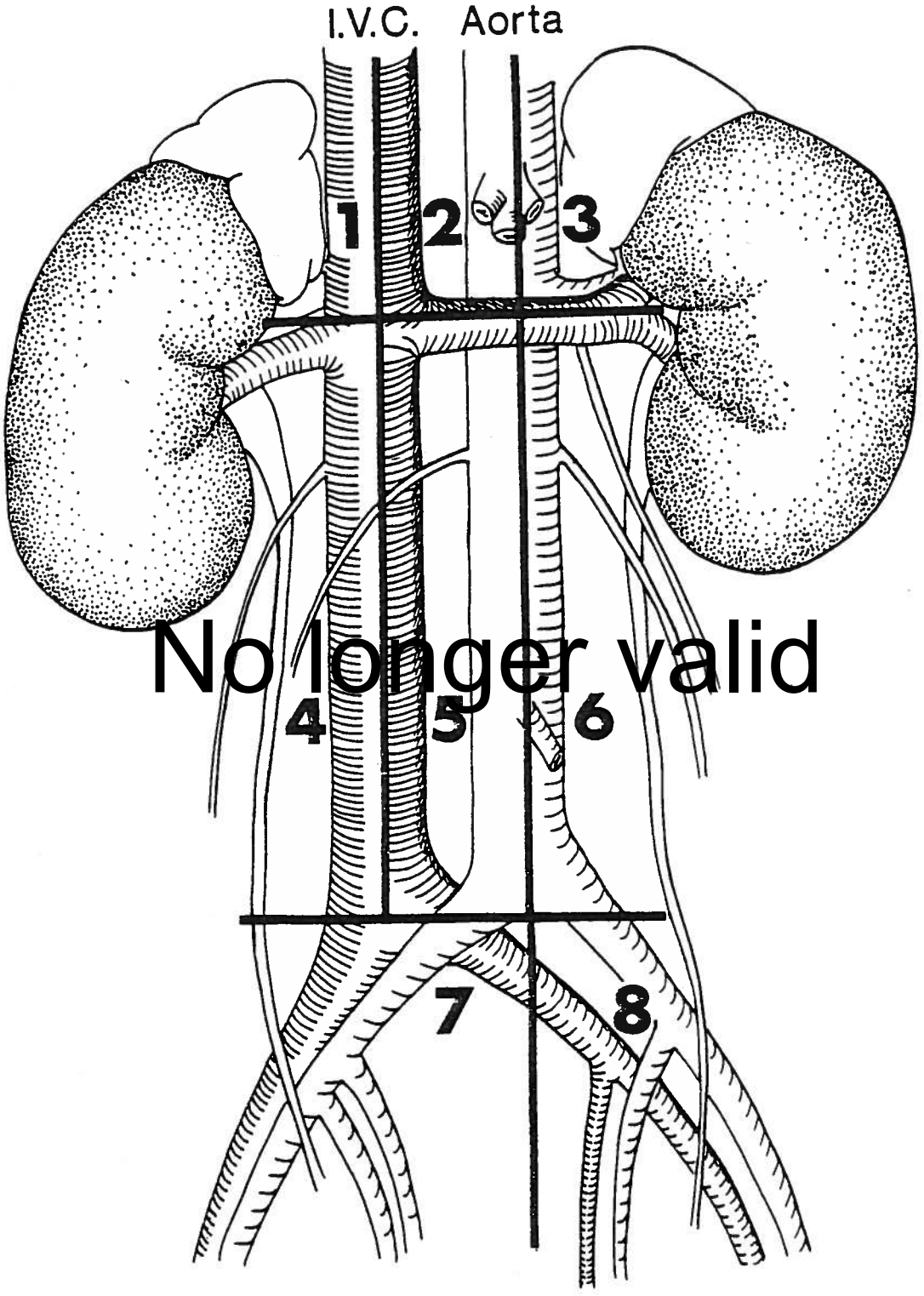


Fig 1. Lymph node regions in RPLNE

7. RETROPERITONEAL LYMPH NODE EXTIRPATION (RPLNE)

7.1. For pathological staging in CS I, M, II A.

Each center selects one out of two alternatives:

Alternative 1: Bilateral RPLNE

The RPLNE is performed bilaterally and extensively. Tissue around aorta and inferior caval vein is removed from above the upper mesenteric artery to the bifurcation of aorta. The tissue around iliacal vessels on the tumour side is removed down to the inguinal ligament removing the remaining part of the funicle. The tissues along the iliacal vessels on the contralateral side is only removed if retroperitoneal tumour growth is obvious macroscopically. The lateral boundaries are the ureters.

Frozen section examination during the operation allows a better evaluation of the extent of tumour growth. Lumbar vessels and the inferior mesenteric artery are always divided.

Alternative 2: Unilateral RPLNE

Only in clinical stage I (CS I).

The borderline between the two halves is a sagittal plane through aorta. The upper border is above the renal vessels. Consecutive examinations with frozen section must be performed during the operation, and if positive for metastases bilateral RPLNE according to Alt. 1. should be performed.

If microscopic tumour tissue is found only at the final histopathological examination, and there were no sign of contralateral lymph node metastases by the pre- and peroperative examinations, one can consider to give only 3 cycles of CVB chemotherapy postoperatively, with no further laparotomy if the patient is in CR after chemotherapy.

If unexpectedly stage II B or C is found at laparotomy, RPLNE should not be performed but chemotherapy given first, according to treatment for CS II B, C (see p. 25).

Exceptionally, if the tumour mass is easily removable RPLNE could be done before chemotherapy.

The surgeon must carefully record the extent of tumour and the extent of the extirpation performed, measure the diameter of the largest metastasis and evaluate whether a radical removal of all evident tumour tissue was achieved. Any residual tumour tissue should be marked with metal clips (preferably tantalum) in order to be able to outline radiation fields etc.

As the specimens are removed during operation, they should be arranged on a sterile anatomic sketch (see p. 59) mounted on a cork plate. The mounted tissues should be covered by a cloth soaked in saline solution. The plate should then be sent to the path. lab.

The cork plate with the whole specimen should preferably be x-rayed which will make it easier to correlate the preoperative lymphographic findings with the histopathological findings. At the end of the RPLNE a plain x-ray of abdomen will reveal if all contrast filled nodes have been removed.

7.2. RPLNE after initial treatment with chemotherapy in CS II B and C, III and IV.

It is imperative that the oxygen content of the ventilation gas does not exceed 20-25 % if the patient has been treated with Bleomycin.

Lung complications may occur up to one year after the administration of Bleomycin.

The RPLNE is performed according to Alternative 1 (see p. 31). The tissue around the iliacal vessels is removed bilaterally.

8. FOLLOW-UP

8.1 Tumourfree patients are followed according to the schedule (see p. 33).

The aims of this close follow-up are to detect relapses as early as possible and to evaluate which investigations are the most effective for early detection.

9. TREATMENT OF RELAPSE

9.1. Chemotherapy:

Patients who have not received chemotherapy previously (PS I) should receive CVB regimen (see p. 60).

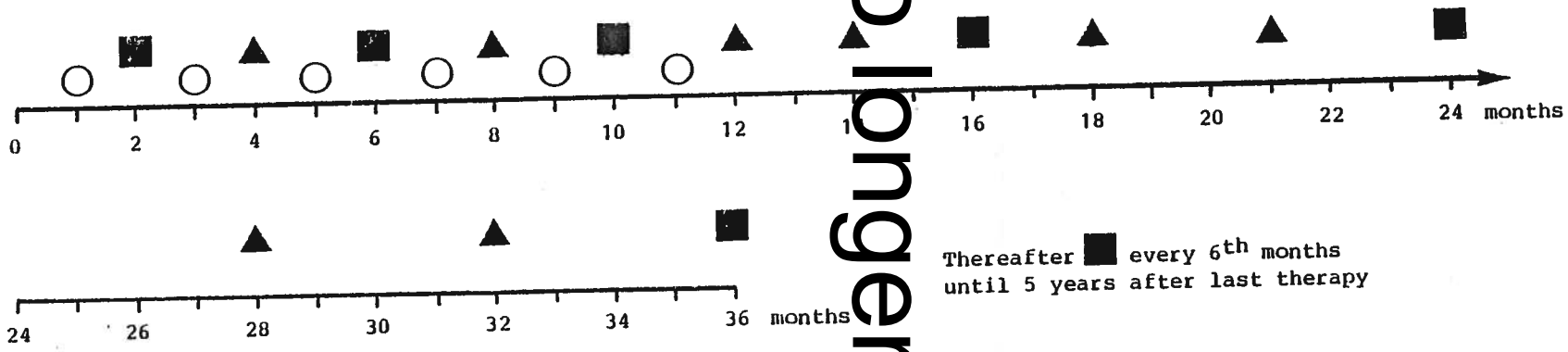
Patients who achieve a complete remission during CVB chemotherapy but relapse more than 6 months after chemotherapy, should receive a re-induction with Cis-platinum and VP-16 (see p. 63).

Patients who do not achieve a complete remission, or who relapse after 4 cycles of CVB within the first 6 months should receive second-line chemotherapy (VP-16 + Iphosphamide) (see p. 64).

9.2. Radiotherapy and surgery:

Strict rules for the use of radiotherapy and surgery in treatment of relapses cannot be established due to the variations of relapse presentations. Concerning general principles for radiotherapy, see
The surgical approach should be aggressive. Even resection of metastases in brain, liver, bone etc. might be of value.

FLOW SHEET FOR FOLLOW-UP OF PATIENTS OFF THERAPY



Thereafter ■ every 6th months
until 5 years after last therapy

○ = Serum markers
(AFP, β-HCG and LD)

■ = Physical examination
Chest X-ray
CT of abdomen and pelvis
(Ultrasound if CT not available)
Serum markers
S-creatinine, GT, alkaline phosphatase
CT of chest and/or planar tomography
is optional
Leucocyte and thrombocyte count, HGb

Note: If there is any hint of relapse - the interwals should be shortened and the investigations "intensified".

▲ = Physical examination
Chest X-ray
Plain X-ray of abdomen and pelvis
(or ultrasound)
Serum markers
GT, alkaline phosphatase

No longer valid

ADDENDA

No longer valid

No longer valid

1. SWENOTECA registration forms

FORM	CONTENTS	REPORTING PHYSICIAN
On-study form A and B	Patient data, investigation, clinical and pathological staging	Completed by urologist or oncologist after retroperitoneal lymphadenectomy (CS I, IIA and M) or after complete clinical evaluation (CS II B, C III and IV)
Surgery form	Retroperitoneal lymphadenectomy and other surgery for metastatic disease	Completed by surgeon after each surgical procedure except orchiectomy
Pathology form A	Histopathological examination of orchiectomy specimen, T and pT classifications	Completed by pathologist
Pathology form B	Histopathological examination of all surgical specimens, except orchiectomy specimens	Completed by pathologist after each surgical procedure
Chemotherapy chart	Details of each chemotherapy cycle	Completed by oncologist after each cycle and sent together with summary form after completion of each chemotherapy program
Chemotherapy summary form	Complication and results of each completed chemotherapy program	
Radiotherapy form	Data on target volume, target dose, complications and result	Completed by oncologist after each course of radiotherapy
Follow-up form	Clinical evaluation of patients in complete remission after therapy	Completed by examining physician at each follow-up visit

Submit forms to:

SWENOTECA sekretariat
Regionala tumörregistret
Lasarettet i Lund
S-221 85 Lund

No longer valid

TESTICULAR CANCER PROGRAM 1A

On study form A

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

PATIENT DATA

Family history of malignancy
☐ no ☐ yes ☐ unknown — testicular ca · ovarian ca — ☐ father ☐ mother ☐ brother(s) ☐ sister(s) ☐ son(s) ☐ daughter(s)

Prior malignant tumour
☐ no ☐ yes, specify:

Other disease(s) that will modify treatment
☐ no ☐ yes, specify:

Retentio testis
☐ no ☐ yes — ☐ dx ☐ sin — ☐ inguinal ☐ abdominal

Surgery for retentio testis
☐ no ☐ yes, date:

Op. for ing. hernia/hydrocele
☐ no ☐ yes ☐ sin ☐ dx

Prior orchitis
☐ no ☐ yes

Prior known infertility
☐ no ☐ yes ☐ not evaluable

Gynecomastia
☐ no ☐ yes ☐ sin ☐ dx

PRIMARY SURGERY

Side of present tumour
☐ sin ☐ dx

Contralat. testis normal
☐ no ☐ yes

Fine needle aspiration biopsy performed
☐ no ☐ yes

Transscrotal surgery
☐ no ☐ yes

Inguinal orchiectomy
☐ no ☐ yes

Date | Hospital, dept

SERUM MARKERS

Before orchiectomy:

Date:

	Value			
AFP	µg/l	☐ normal	☐ elevated	☐ not performed
ß-HCG	IU/l	☐ normal	☐ elevated	☐ not performed
LDH	µcat/l	☐ normal	☐ elevated	☐ not performed

After orchiectomy:

Date	Value	Value	Value
	AFP 1 µg/l	ß-HCG 1 IU/l	LDH 1 µcat/l
Date	AFP 2 µg/l	ß-HCG 2 IU/l	LDH 2 µcat/l
Date	AFP 3 µg/l	ß-HCG 3 IU/l	LDH 3 µcat/l

Serum markers indicate active disease before start of other therapy
☐ no ☐ yes

After lymphadenectomy (2-4 weeks):

Date:

AFP	☐ normal	☐ elevated, value:	µg/l
ß-HCG	☐ normal	☐ elevated, value:	IU/l
LDH	☐ normal	☐ elevated, value:	µcat/l

1981-10-16 Skandia Tryckeri AB 66439

No longer valid

TESTICULAR CANCER PROGRAM 1B

On study form B

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

PROCEDURES PERFORMED FOR CLINICAL STAGING

Investigation	Performed	Metastatic disease demonstrated	~~Microscopic~~ verification
Chest X-ray	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
Chest CT	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	☐ no ☐ yes
Chest planar tomography	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
CT of abdomen & pelvis	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
Ultrasound of abdomen & pelvis	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
Foot lymphography	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	☐ no ☐ yes
Cavography	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
Phlebography of testicular vein	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	
Other, specify:	☐ no ☐ yes	☐ no ☐ yes ☐ doubtful	☐ no ☐ yes

METASTASES

LYMPHNODES	Metastases	Size of largest metastasis (cm × cm)	EXTRA LYMPHATIC	Metastases	Size of largest metastasis (cm × cm)
Inguinal	☐ no ☐ yes		Lung	☐ no ☐ yes	
Iliac	☐ no ☐ yes		Liver	☐ no ☐ yes	
Paraaortic	☐ no ☐ yes		Brain	☐ no ☐ yes	
Mediastinal	☐ no ☐ yes		Bone	☐ no ☐ yes	
Supraclav	☐ no ☐ yes		Skin	☐ no ☐ yes	
Other	☐ no ☐ yes		Other	☐ no ☐ yes	

CLINICAL STAGE (CS): ①

Stage: ☐ I ☐ II ☐ III ☐ IV ☐ M

Abdominal status: ☐ 0 ☐ A ☐ B ☐ C

Serum markers: ☐ pos AFP ☐ neg AFP ☐ pos ß-HCG ☐ neg ß-HCG

Lung status: ☐ L_0 ☐ L_1 ☐ L_2 ☐ L_3

RPLNE

Retroperitoneal lymph node extirpation performed

☐ no ☐ yes ☐ bilat ☐ unilat

PATHOLOGICAL STAGE (PS): ②

Stage: ☐ I ☐ II ☐ IV ☐ M

Abdominal status: ☐ 0 ☐ A ☐ B ☐ C

Serum markers: ☐ pos AFP ☐ neg AFP ☐ pos ß-HCG ☐ neg ß-HCG

Lung status: ☐ L_0 ☐ L_1 ☐ L_2 ☐ L_3

PERFORMANCE ③

Karnofsky index:

☐ 100 ☐ 80 ☐ 60 ☐ 40 ☐ 20 ☐ Impairment mostly due to other disease

FURTHER TREATMENT

Patient proceeds to:

☐ No further treatment ☐ Surgery ☐ Radiotherapy ☐ Chemotherapy

1981-10-15 Skrivpa Tryckeri AB 86440

① CLINICAL STAGING (CS)

Based on all findings except retroperitoneal lymphadenectomy.

CS I No evidence of metastases.

CS M α-foetoprotein and/or ß-subunit of HCG persistently elevated but no metastases demonstrable.

CS II Metastases confined to abdominal lymph nodes. Three subgroups recognized:

A. Maximal diameter of metastases < 2 cm

B. Maximal diameter of metastases 2–5 cm

C. Maximal diameter of metastases > 5 cm

For determination of the A, B and C status of the abdominal lymph nodes lymphangiogram and CT (if available) should be used.

CS III Involvement of supradiaphragmatic lymph nodes. Note: subdiaphragmatic lymph nodes may not be demonstrable.
Abdominal status: 0 (no mets.), A, B, C, as for stage II.

CS IV Extralymphatic metastases. For the lungs 3 subgroups are recognized:

L_1 ≤ 3 metastases

L_2 > 3 metastases, no one > 2 cm maximum diameter

L_3 > 3 metastases: 0 (no mets.), A, B, C, as for stage II.

② PATHOLOGICAL STAGING (PS)

Based on macro- and microscopic findings at retroperitoneal lymphadenectomy

PS 1 No evidence of metastases.

PS M α-foetoprotein and/or ß-subunit of HCG persistently elevated after retroperitoneal lymphadenectomy but no metastasesdemonstrable.

PS II Metastases confined to retroperitoneal lymphnodes. α-foetoprotein and ß-subunit of HCG normalized after retroperitoneal lymphadenectomy. A, B, and C status of abdominal nodes determined by measurement of the operative specimen.

PS III Not recognized in this program.

PS IV Metastases in extralymphatic organs (e. g. liver) found at lymphadenectomy.

③ PERFORMANCE INDEX ACCORDING TO KARNOFSKY

100 = Normal, no complaints

80 = Normal activity with effort

60 = Requires occasional assistance, but is able to care for most of his needs

40 = Disabled, requires special care and assistance

20 = Very sick, hospitalisation and active supportive treatment necessary

TESTICULAR CANCER PROGRAM 2

Surgery form

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

RPLNE

Date of surgery | Department of surgery

Pathology institution | Specimen (=PAD) No. | Date

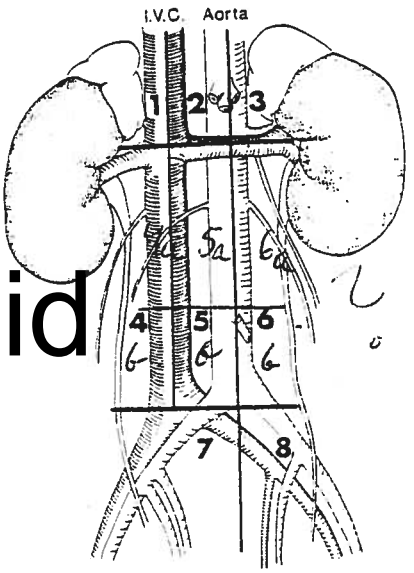
Type of RPLNE

☐ Unilateral ☐ Bilateral

☐ For pathological staging in CS I, M and II A. ☐ After initial chemotherapy in CS II B-C, III and IV.

Macroscopic findings

Region	Number of metastases	Size of largest metastasis (cm x cm)
1		
2		
3		
4		
5		
6		
7		
8		
Other:		



OTHER SURGICAL PROCEDURE

Type of surgery, specify: | Code No.

RADICALITY

Tumour completely extirpated macroscopically

☐ No ☐ Yes

SURGICAL COMPLICATIONS

☐ No ☐ Yes: ☐ Wound infection ☐ Wound rupture

☐ Bleeding ☐ Ileus demanding surgery ☐ Thromboembolia

☐ Other, specify:

FURTHER TREATMENT PLAN

Patient proceeds to

☐ No further treatment ☐ Surgery ☐ Radiotherapy ☐ Chemotherapy

Comments:

1981-10-28 Skurups Tryckeri AB 06441

No longer valid

TESTICULAR CANCER PROGRAM 3A

Pathology form A

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

PATHOLOGY INSTITUTION AND SPECIMEN

Institution | Specimen (=PAD) No. | Date

MACRO

Laterality
☐ Left testis ☐ Right testis

Size of tumour: mm × mm

T-CLASSIFICATION ①

☐ T0 ☐ T1 ☐ T2 ☐ T3 ☐ T4a ☐ T4b ☐ TX

pT-CLASSIFICATION ②

☐ pT0 ☐ pT1 ☐ pT2 ☐ pT3 ☐ pT4a ☐ pT4b ☐ pTX

RADICALITY

Macroscopic infiltration of proximal funicle
☐ No ☐ Yes

Microscopic infiltration of proximal funicle
☐ No ☐ Yes

Margins of excision free of tumour
☐ Yes ☐ No

Tumour cells invading vascular structures
☐ No ☐ Yes

IMMUNE-PEROXIDASE-STAINING

AFP
☐ Positive ☐ Negative ☐ Not performed

ß-HCG
☐ Positive ☐ Negative ☐ Not performed

WHO-CLASSIFICATION

☐ Seminoma — Number of mitoses per field:
Syncytiotrophoblastic cells: ☐ No ☐ Yes

☐ Spermatocytic seminoma

☐ Embryonal carcinoma

☐ Yolk sac tumour (embryonal carcinoma, infantile type; endodermal sinus tumour)

☐ Polyembryoma

☐ Teratoma, immature ☐ Teratoma, mature ☐ Teratoma with malignant transformation

☐ Choriocarcinoma

☐ Combined tumour – indicate components above

PUGH/BTTP CLASSIFICATION

☐ TD ☐ MTI ☐ MTU ☐ MTT ☐ Combined tumour

1991-09-27 Swedish Infokon AB 86442

① MACROSCOPIC STAGING		② HISTOLOGIC STAGING
T_0	no primary tumour	pT_0
T_1	limited to the body of testis	pT_1
T_2	invading beyond the tunica albuginea	pT_2
T_3	invading rete testis or epididymis	pT_3
T_4	infiltrating spermatic cord and/or the scrotal wall	pT_4
T_{4a}	infiltrating spermatic cord	pT_{4a}
T_{4b}	infiltrating the scrotal wall	pT_{4b}
TX	minimum requirements to assess stage can not be met	pTX

TESTICULAR CANCER PROGRAM 3B

Pathology form B

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

SPECIMEN FROM RETROPERITONEAL LYMPH NODE EXTIRPATION

Pathology institution | Specimen (=PAD) No. | Date

Type of retroperitoneal lymph node extirpation

☐ Unilateral ☐ Bilateral

Microscopic findings:

Region (see figure) below ①	No of nodes	No of nodes with met	Size of largest metastasis (cm × cm)	Size of necrotic or fibrotic tissue (cm × cm)	Vital tumour tissue	Microscopic radicality achieved
1					☐ no ☐ yes	☐ no ☐ yes
2					☐ no ☐ yes	☐ no ☐ yes
3					☐ no ☐ yes	☐ no ☐ yes
4					☐ no ☐ yes	☐ no ☐ yes
5					☐ no ☐ yes	☐ no ☐ yes
6					☐ no ☐ yes	☐ no ☐ yes
7					☐ no ☐ yes	☐ no ☐ yes
8					☐ no ☐ yes	☐ no ☐ yes

Identical metastases and primary tumour
☐ no ☐ yes

Mature teratoma only
☐ no ☐ yes

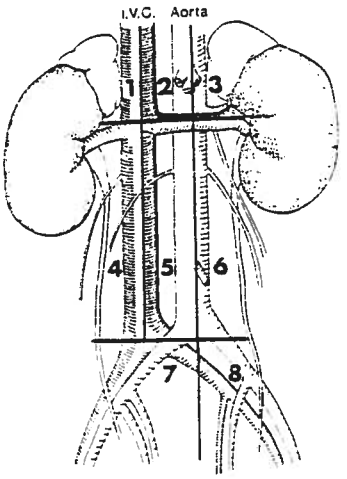
OTHER OPERATIVE SPECIMEN

Pathology institution | Specimen (=PAD) No. | Date

Microscopic findings:

Sites	Vital tumour tissue	Microscopic radicality achieved
Lymph nodes:		
☐ Inguinal	☐ no ☐ yes	☐ no ☐ yes
☐ Mediastinal	☐ no ☐ yes	☐ no ☐ yes
☐ Supraclavicular	☐ no ☐ yes	☐ no ☐ yes
☐ Other:	☐ no ☐ yes	☐ no ☐ yes
☐ Other:	☐ no ☐ yes	☐ no ☐ yes
Extra lymph tissue:		
☐ Liver	☐ no ☐ yes	☐ no ☐ yes
☐ Lung	☐ no ☐ yes	☐ no ☐ yes
☐ Bone	☐ no ☐ yes	☐ no ☐ yes
☐ Other:	☐ no ☐ yes	☐ no ☐ yes

① Regions of RPLNE



Identical metastases and primary tumour
☐ no ☐ yes

Mature teratoma only
☐ no ☐ yes

1981-10-16 Skandia Tryckeri AB 86443

No longer valid

TESTICULAR CANCER PROGRAM 4A

Chemotherapy chart

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

CHEMOTHERAPY PROGRAM

Starting date	Aponym	Length of cycle
		days
Length of patient	**Weight of patient**	**Surface area**
cm	kg	m^2

Day	Drug	Dose (mg/m^2 or kg)	Full dose (mg)	Mode of administration

Start of treatment	End of treatment	Drug	Given dose (mg)	Accumulated dose (mg)	Dose reduction
CYCLE 1:					
					no yes
					no yes
					no yes
					no yes
					no yes
CYCLE 2:					
					no yes
					no yes
					no yes
					no yes
					no yes
CYCLE 3:					
					no yes
					no yes
					no yes
					no yes
					no yes

1981-10-16 Stenqvist Tryckeri AB 68444

No longer valid

TESTICULAR CANCER PROGRAM 4B

Chemotherapy summary form

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

SUMMARY OF CHEMOTHERAPY

Aponym of chemotherapy (CHT) program	Start of treatment; date	End of treatment; date

REASON FOR STARTING CHT

CHT given as initial treatment

☐ Adjuvant (IIA) ☐ Induction (IIB–IV) ☐ Initial treatment for relapse after CR

CHT given for other reasons

☐ Elevated AFP/ß-HCG as only indicator of tumour

☐ Minimal (< 2 cm) tumour persistent after prior treatment	☐ Lymph nodes	☐ Brain	☐ Bone	☐ Other, specify:	
	☐ Liver	☐ Lung	☐ Skin		
☐ Bulky (> 2 cm) tumour persistent after prior treatment	☐ Lymph nodes	☐ Brain	☐ Bone	☐ Other, specify:	
	☐ Liver	☐ Lung	☐ Skin		

PERFORMANCE ①

Karnofsky index at start of CHT

☐ 100 ☐ 80 ☐ 60 ☐ 40 ☐ 20 ☐ Impairment mostly due to other disease

Karnofsky index at end of CHT

☐ 100 ☐ 80 ☐ 60 ☐ 40 ☐ 20 ☐ Impairment mostly due to other disease

REASON FOR TERMINATING CHT

☐ Planned program completed ☐ Progressive disease ☐ Unacceptable toxicity

☐ Treatment refused ☐ Other, specify:

Major violation of protocol

☐ no ☐ yes, specify:

RESPONSE

☐ Not evaluable ☐ Complete Remission Date: ☐ Partial Remission Date: ☐ Stationary disease Date: ☐ Progression Date:

Site(s) with persistent disease

Lymph nodes: ☐ Inguinal ☐ Iliac ☐ Paraaortic ☐ Mediast. ☐ Supraclav ☐ Other, specify:

Other organs: ☐ Liver ☐ Lung ☐ Brain ☐ Bone ☐ Skin ☐ Other, specify:

TOXICITY ②

	Grade				
Hematological toxicity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Gastrointestinal toxicity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Renal toxicity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pulmonary toxicity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Neurologic toxicity	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Infection	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

FURTHER TREATMENT

Patient proceeds to

☐ No further treatment ☐ Surgery ☐ Radiotherapy ☐ Chemotherapy

1981-10-16 Skanpa Trycksa AB 66446

① PERFORMANCE INDEX ACCORDING TO KARNOFSKY

100 = Normal, no complaints

80 = Normal activity with effort

60 = Requires occasional assistance, but is able to care for most of his needs

40 = Disabled, requires special care and assistance

20 = Very sick, hospitalisation and active supportive treatment necessary

② RECOMMENDATIONS FOR GRADING OF ACUTE AND SUBACUTE TOXIC EFFECTS (WHO 1979)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
HEMATOLOGICAL:					
Haemoglobin (g/l)	≥110	95-109	80-94	65-79	<65
Leucytes (× 10^9/l)	≥4.0	3.0-3.9	2.0-2.9	1.0-1.9	1.0
Platelets (× 10^9/l)	>100	75 - 99	50 - 74	25 - 49	<25
GASTROINTESTINAL:					
Nausea/vomiting	None	Nausea	Transient vomiting	Vomiting, requiring therapy	Intractable vomiting
Diarrhoea	None	Transient, < 2 days	Tolerable but > 2 days	Intolerable, requiring therapy	Haemorrhagic dehydration
RENAL:					
S-creatinine	1.25 × N[a]	1.26-2.5 × N[a]	2.6-5 × N[a]	5-10 × N[a]	10 × N[a]
Proteinuria	No change	1+ <3 g/l	2-3+ <3-10 g/l	4+ >10 g/l	Nephrotic syndrome
Haematuria	No change	Microscopic	Gross	Gross + clots	Obstructive uropathy
PULMONARY:	No change	Mild symptoms	Exertional dyspnoea	Dyspnoea at rest	Complete bed rest required
NEUROLOGIC:					
Peripheral	None	Paraesthesias and/or decreased tendon reflexes	Severe paraesthesias and/or mild weakness	Intolerable paraesthesias and/or marked motor loss	Paralysis
Constipation[b]	None	Mild	Moderate	Severe	Intractable
INFECTION:					
(Specify site)	None	Minor infection	Moderate infection	Major infection	Major infection with hypotension

[a] N = upper limit of normal value of population under study.

[b] = This does not include constipation resultant from narcotics.

TESTICULAR CANCER PROGRAM 5

Radio therapy form

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

RADIATION TREATMENT

Prior radiotherapy

☐ no ☐ yes, specify:

Reason for starting radiotherapy

☐ Not resectable bulky tumour ☐ Minor tumour rest after surgery/chemotherapy

Starting date | Ending date | No. of series

Target volumes	Target absorbed dose, Gy	No. of fractions	No. of days

COMPLETION OF TREATMENT

Treatment completed as planned

☐ yes ☐ no; discontinued at a target absorbed dose of _____ Gy

Reason for discontinuation of radiotherapy

☐ Progressive disease ☐ Unacceptable toxicity ☐ Treatment refused

☐ Other, specify:

RESPONSE TO RADIOTHERAPY

Date of evaluation

Degree of response

☐ Complete remission ☐ Partial remission ☐ Stationary disease ☐ Progressive disease ☐ Not evaluable

FURTHER TREATMENT PLAN

Patient proceeds to

☐ No further treatment ☐ Surgery ☐ Chemotherapy ☐ Radiotherapy

1981-10-14 Skurups Tryckeri AB 66448

No longer valid

TESTICULAR CANCER PROGRAM 6

Follow-up form

Submit this form to:
SWENOTECA sekretariatet
Regionala tumörregistret
Lasarettet i Lund, S-221 85 LUND

Hospital and department

Physician | Date

CLINICAL EVALUATION ①

Investigation	Performed	Relapse	Not evaluable
Physical exam	☐ no ☐ yes	☐ no ☐ yes	☐
Chest X-ray	☐ no ☐ yes	☐ no ☐ yes	☐
CT of chest	☐ no ☐ yes	☐ no ☐ yes	☐
Abdominal X-ray	☐ no ☐ yes	☐ no ☐ yes	☐
CT of abdomen & pelvis	☐ no ☐ yes	☐ no ☐ yes	☐
Ultrasound of abdomen & pelvis	☐ no ☐ yes	☐ no ☐ yes	☐
Other, specify:	☐ no ☐ yes	☐ no ☐ yes	☐

Date of evaluation

	Level	Normal	Elevated
AFP			
ß-HCG			
LDH			

PERFORMANCE ②

Karnofsky index
☐ 100 ☐ 80 ☐ 60 ☐ 40 ☐ 20 ☐ Impairment due mostly to other disease

LATE EFFECTS OF TREATMENT ③

Dry ejaculate
☐ no ☐ yes

Reduced libido
☐ no ☐ yes

Impotence
☐ no ☐ yes

Other.
☐ specify:

STATUS

Tumour status
☐ No evidence of disease ☐ Relapse ☐ Not evaluable

IN CASE OF RELAPSE

LYMPHNODES	Metastases	Size of largest metastasis (cm×cm)	EXTRA LYMPHATIC	Metastases	Size of largest metastasis (cm×cm)
Inguinal	☐ no ☐ yes ☐ not evaluable		Lung	☐ no ☐ yes ☐ not evaluable	
Iliac	☐ no ☐ yes ☐ not evaluable		Liver	☐ no ☐ yes ☐ not evaluable	
Paraaortic	☐ no ☐ yes ☐ not evaluable		Brain	☐ no ☐ yes ☐ not evaluable	
Mediastinal	☐ no ☐ yes ☐ not evaluable		Bone	☐ no ☐ yes ☐ not evaluable	
Supraclav.	☐ no ☐ yes ☐ not evaluable		Skin	☐ no ☐ yes ☐ not evaluable	
Other, specify:			Other, specify:		

Symptom(s) or examination(s) that gave first hint of relapse:

FURTHER TREATMENT PLAN

Patient proceeds to:
☐ Continued follow-up off therapy ☐ Surgery ☐ Radiotherapy ☐ Chemotherapy

Skrutupa Tryckeri AB 86447

① FLOW SHEET FOR FOLLOW-UP OF PATIENTS OFF THERAPY

	Months																										
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	24	28	32	36	42	48	54	60
Physical exam.		X		X		X		X		X		X		X		X		X			X	X	X	X	X	X	X	X	X
Chest X-ray		X		X		X		X		X		X		X		X		X			X	X	X	X	X	X	X	X	X
CT of abdomen & pelvis		X				X				X						X						X			X	X	X	X	X
CT of chest		(X)				(X)				(X)						(X)						(X)			(X)	(X)	(X)	(X)	(X)
Serum markers	X	X	X	X	X	X	X	X	X	X	X	X		X		X		X			X	X	X	X	X	X	X	X	X
GT, alkaline phosphatase		X		X		X		X		X		X		X		X		X			X	X	X	X	X	X	X	X	X
Leukocyte & thrombocyte count		X				X				X						X						X			X	X	X	X	X
S-creatinine		X				X				X						X						X			X	X	X	X	X

② PERFORMANCE INDEX ACCORDING TO KARNOFSKY

100 = Normal, no complaints

80 = Normal activity with effort

60 = Requires occasional assistance, but is able to care for most of his needs

40 = Disabled, requires special care and assistance

20 = Very sick, hospitalisation and active supportive treatment necessary

③ Evaluated one year after completion of all treatment.

2. Histopathological examination of NSGCT

2.1. Macroscopic examination

It is important that all NSGCTs are handled in the same way by the pathologist.

The pathologist should examine the specimen and locate the cord, head, body and tail of epididymis and rete testis. The testis should be dissected longitudinally through the rete testis if possible. Measure the size of the tumour with two perpendicular diameters (cm x cm). Describe macroscopically the cut surface of the tumour (necrosis, haemorrhage, color etc.).

Describe the relation between the tumour and the tunica albuginea, rete testis, epididymis and cord.

A T-staging according to UICC is done macro- and microscopically.

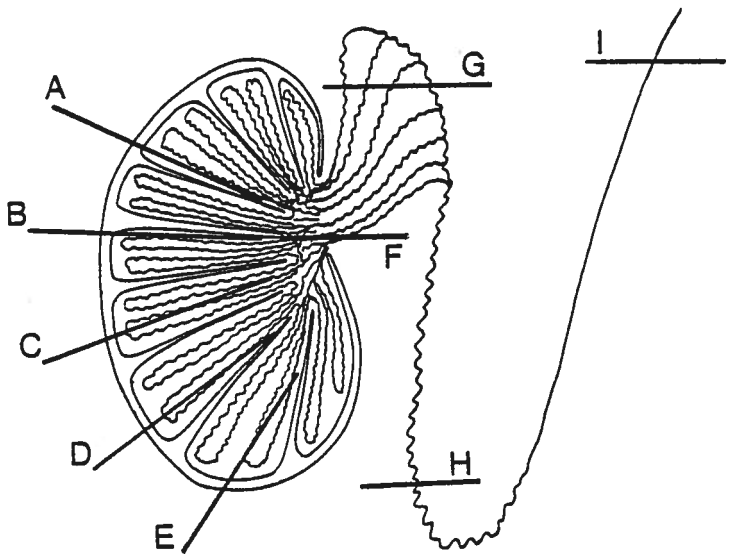
Macroscopic staging		Histologic staging
T_0	no primary tumour	pT_0
T_1	limited to the body of testis	pT_1
T_2	invading beyond the tunica albuginea	pT_2
T_3	invading rete testis or epididymis	pT_3
T_4	infiltrating spermatic cord and/or the scrotal wall	pT_4
T_{4a}	infiltrating spermatic cord	pT_{4a}
T_{4b}	infiltrating the scrotal wall	pT_{4b}
TX	minimum requirements to assess stage can not be met	pTX

2.2. Histological methods

The testis must be fixed in 10 % buffered formalin solution.

Perform five sections from the tumour (see fig.), and also sections so that the histological relation between the tumour and tunica albuginea and rete testis and epididymis can be established (see fig.).

Perform immunoperoxidase stain for AFP and β-HCG (optional).



A-E 5 sections through tumour tissue

F rete testis

G epididymis at the level of the upper pole of the testis

H epididymis at the level of the lower pole of the testis

I cord - upper margin of resection

Fig 2. Position of sections for histopathological examination

2.3. Histological evaluation

The classification of the tumour is made according to the British Testicular Tumour Panel (BTTP) and/or according to WHO. Evaluation of blood vessel and lymphatic invasion should be performed. The extent of tumour growth is based on the histological examination and determines the pathological stage (pT).

3. Histopathological examination of the retroperitoneal nodes

3.1. Lymph node specimens

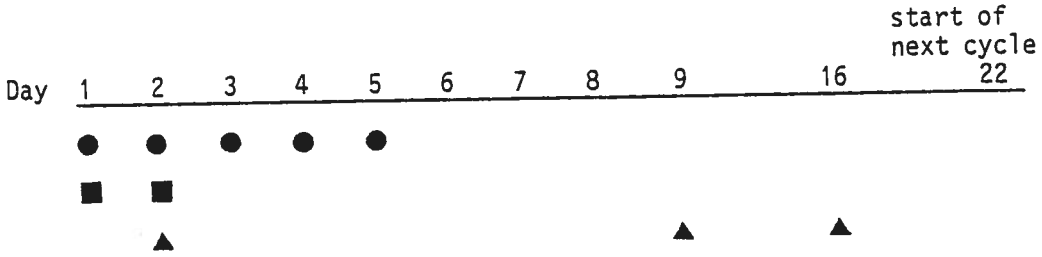
The lymph node specimens submitted to the pathologists are mounted on a sterile piece of cork. The larger vessels are labelled. Radiological pictures of the operative specimen should also be submitted. Macroscopic evaluation should be performed and suspected metastases measured. Each lymph node is longitudinally bisected. The number of lymph nodes are counted. The metastases are classified histologically according to BTTP and/or WHO. The presence of perinodular growth is recorded as well as if the margins of excision are free from tumour. The size of the largest metastasis is measured in mm (largest diameter).

Immunoperoxidase stain should be performed on the metastases (optional). All blocks should be saved.

Duphaston 30 mg x1
Fluxyl 200 mg x3

4. CVB regimen

Cis-platinum	●	20 mg/m^2 i.v. day 1-5. Rapid infusion.
Vinblastine	■	0.15/kg i.v. day 1 and 2. Rapid infusion.
Bleomycin	▲	30 mg i.v. once a week. Rapid infusion. N.B. in the 4th cycle preoperatively the dose is reduced to 10 mg/week. Total given dose must not exceed 300 mg.



Spec. precautions during CVB treatment:

a. before starting and after completion of CVB treatment investigate: renal function (creatinine clearence), pulmonary function (dynamic spirometry), auditory function (audiogram). (Audiogram is optional).

b. before every cycle check serum creatinine and if pathologic, creatinine clearence should be done and the dose of Cis-platinum adjusted according to schedule.

c. if surgery is planned after CVB or CVB is given profylactically (stage II A) the max. given total dose of Bleomycin should be 300 mg.

d. CVB is given with hydration and mannitol diuresis. See spec. form.

e. administration of aminoglycoside should be avoided during and one month after CVB treatment.

Dose reduction schedule:

level at start of cycle	Cis-platinum	Vinblastine	Bleomycin
	percentage of full dose		
leucocytes x 10^9/l			
3,0 - 3,4	100	75	100
2,0 - 2,9	100	50	100
<2,0	postpone treatment one week		

Cont. next page

Dose reduction schedule cont:

level at start of cycle	Cis-platinum	Vinblastine	Bleomycin
	percentage of full dose		
thrombocytes x 10^9/l			
75 - 100	100	75	100
50 - 75	100 for 3 days	75	100
<50	postpone treatment one week		
creatinine clear.*) ml/min			
70 - 80	100 for 4 days	100	100
60 - 70	100 for 3 days	100	50
<60	no more Cis-platinum (except when the reduced renal function is due to tumour obstruction)		

*) Note: Reduction is performed only when Cis-platinum is given in an adjuvant setting. When given for manifest tumour Cis-platinum should be given in full dose even if creatinin clearance is <60 ml/min. Reduction is made only when renal toxicity is life-threatening.

4.1. Schedule for hydration

The fluid balance is followed closely, input and output of fluid are measured.

1 Prehydration: 1000 ml NaCl 0.9 % i.v. during 2-4 hours before infusion of Cis-platinum.

2 Cis-platinum is infused in 2000 ml NaCl 0.9 % together with 75 g (500 ml) mannitol. Infusion time 4 hours.

3 Diuresis is measured and should not drop below 400 ml/4 hours. If urine output is less, diuretics should be given (e.g. 0.25 mg Burinex).

4 After the infusion the patient should drink at least 100 ml/hour the rest of the day. If not possible fluid should be given i.v.

5 Vinblastine and Bleomycin are given immediately prior to Cis-platinum days 1+2 and 2, respectively.

4.2. Toxicity of drugs in CVB regimen

Cis-diamine dichloroplatinum (Cis-platinum, DDP, Platinol®).

1 The most important side-effect is nephrotoxicity, which is often irreversible. A good renal function and a high urine output during the treatment reduce the risk. Note: other nephrotoxic drugs e.g. aminoglucosides potentiate the nephrotoxic effect and must be avoided in patients during treatment or previously treated (within 4 months) with Cis-platinum.

2 Modest myelosuppression, in particular thrombocytopenia.

3 Ototoxicity. Tinnitus and a high pitch hearing loss may occur.

4 Peripheral neuropathy. Unusual.

5 Hypomagnesemia and hypocalcemia. Cramps have been reported.

6 Anaphylactic reactions. Unusual.

7 Alopecia.

8 Modest-severe nausea and vomiting is a rule.

Vinblastine (Velbe)

1 Significant myelosuppression, in particular granulocytopenia with potential hazard of sepsis. Nadir reached at day 7-11.

2 Constipation with abdominal pains. Paralytic ileus may occur.

3 Myalgia, sometimes severe enough to require analgetics.

4 Peripheral neuropathy.

Bleomycin

1 The most important side-effects are pneumonitis and pulmonary fibrosis, which are irreversible in most cases and may be fatal. The risk increases at a cumulative dose of 400 mg. Note: Anesthesia may cause a serious acute respiratory distress syndrome. High concentration of oxygen (>35%) in the ventilating gas and possibly also a high ratio of crystalloid compared to colloid fluid replacement intraoperatively increase the risk for this complication.

2 Febrile reaction shortly after injection of Bleomycin is common. May be prevented by giving glucocorticoids (100 mg Solucortef).

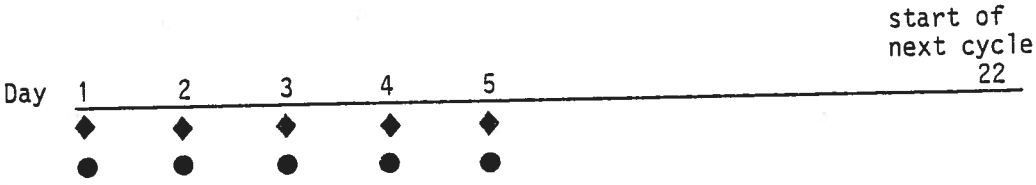
3 Anaphylactic reaction.

5. VP-16 - Cis-Platinum regimen

Used as second-line chemotherapy at late relapses (>6 months after last CVB) and as consolidation chemotherapy in stage III and IV patients with less than complete remission after CVB.

VP-16 ◆ 100 mg/m^2 i.v. day 1-5. Infusion time 2 hours. Added to the hydration fluid before infusion of Cis-platinum.

Cis-platinum ● 20 mg/m^2 i.v. day 1-5. Hydration schedule as for CVB.



As consolidation chemotherapy to "tumourfree" patient 3 cycles are given. As chemotherapy for relapse 2 cycles are given after achieved CR, at least 4 cycles.

Dose reduction schedule:

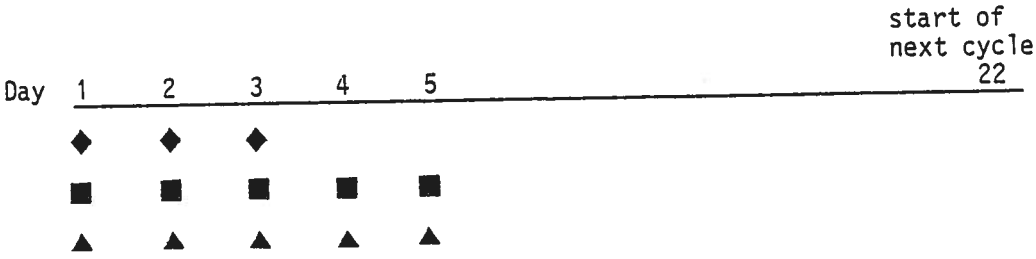
level at start of each cycle	VP-16 percentage of full dose	Cis-platinum
leucocytes x 10^9/l		
3,0 - 3,4	75 day 1-5	100 day 1-5
2,0 - 2,9	50 day 1-5	100 day 1-5
<2,0	postpone treatment one week	
thrombocytes x 10^9/l		
75 - 100	75 day 1-5	100 day 1-5
50 - 75	50 day 1-5	100 day 1-3
<50	postpone treatment one week	
creatinine clear. ml/min *)		
70 - 80	100 day 1-5	100 day 1-4
60 - 70	100 day 1-5	100 day 1-3
<60	no more Cis-platinum	

*) Note: Reduction is performed only when Cis-platinum is given in an adjuvant setting. When given for manifest tumour Cis-platinum should be given in full dose even if creatinine clearance is <60 ml/min. Reduction is made only when renal toxicity is life-threatening.

6. VP-16 - Isophosphamide regimen

Second-line chemotherapy used at early relapse (<6 months after CVB) or at progressive disease during CVB treatment.

VP-16	◆ 100 mg/m^2 i.v. day 1-3. Infusion time 2 hours.
Isophosphamide	■ 1500 mg/m^2 i.v. day 1-5. Rapid infusion.
Mitexan	▲ 300 mg/m^2 (20 % of the administered Isophosphamide dose) is given i.v. at 0, 4 and 8 hours after Isophosphamide injection, day 1-5.



Two cycles are given after achieved CR, at least 4 cycles.

Fluid intake should exceed 2 l. daily during Isophosphamide administration. If not possible, fluid should be given i.v.

Urine should be checked for haematuria every other day during Isophosphamide administration. If microhaematuria increase diuresis. If macrohaematuria discontinue treatment.

Dose reduction schedule:

level at start of each cycle	VP-16 percentage of full dose	Isophosphamide
leucocytes x 10^9/l		
3,0 - 3,4	75 day 1-3	100 day 1-4
2,0 - 2,9	50 day 1-3	100 day 1-3
<2,0	postpone treatment one week	
thrombocytes x 10^9/l		
75 - 100	75 day 1-3	100 day 1-4
50 - 75	50 day 1-3	100 day 1-3
<50	postpone treatment one week	

6.1. Toxicity of drugs in VP-16 - Isophosphamide regimen

VP-16-213 (Vepesid®)

1 Myelosuppression, mainly leucopenia.

2 Nausea, vomiting and infrequently diarrhoea.

3 Alopecia.

4 Hypotension when VP-16 is administered as a rapid infusion has been reported. Prevented by slowing the infusion rate.

Isophosphamide (Iphosphamide, Holoxan®)

1 Toxic effect on lower urinary tract (haemorrhagic cystitis), caused by renal elimination of toxic metabolites of Isophosphamide. This toxicity is effectively reduced by simultaneous administration of the uroprotector Mitexan (Mesna), which traps the toxic metabolites.

2 Myelosuppression, mainly leucopenia.

3 Reversible cerebral symtoms (confusion) has been reported.

4 Alopecia.

5 Nausea.

No longer valid

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No longer valid