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



# TREATMENT OF CLINICAL STAGE I (CS 1) NON–SEMINOMATOUS TESTICULAR CANCER

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# SWENOTECA

## Treatment of Clinical Stage I (CS1) Non-seminomatous Testicular Cancer

**A prospective, non-randomized study of;**

**A:** **Surveillance** for clinical stage I (CS1) non-seminomatous germ cell testicular cancer with **low risk** of metastases

**B:** **Retroperitoneal lymph node dissection** (RPLND) for patients with **intermediate risk** of metastases, and adjuvant chemotherapy if metastases are found at RPLND



**C:** **Prophylactic chemotherapy** for patients with a **high risk** of metastases.

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CONTENTS:

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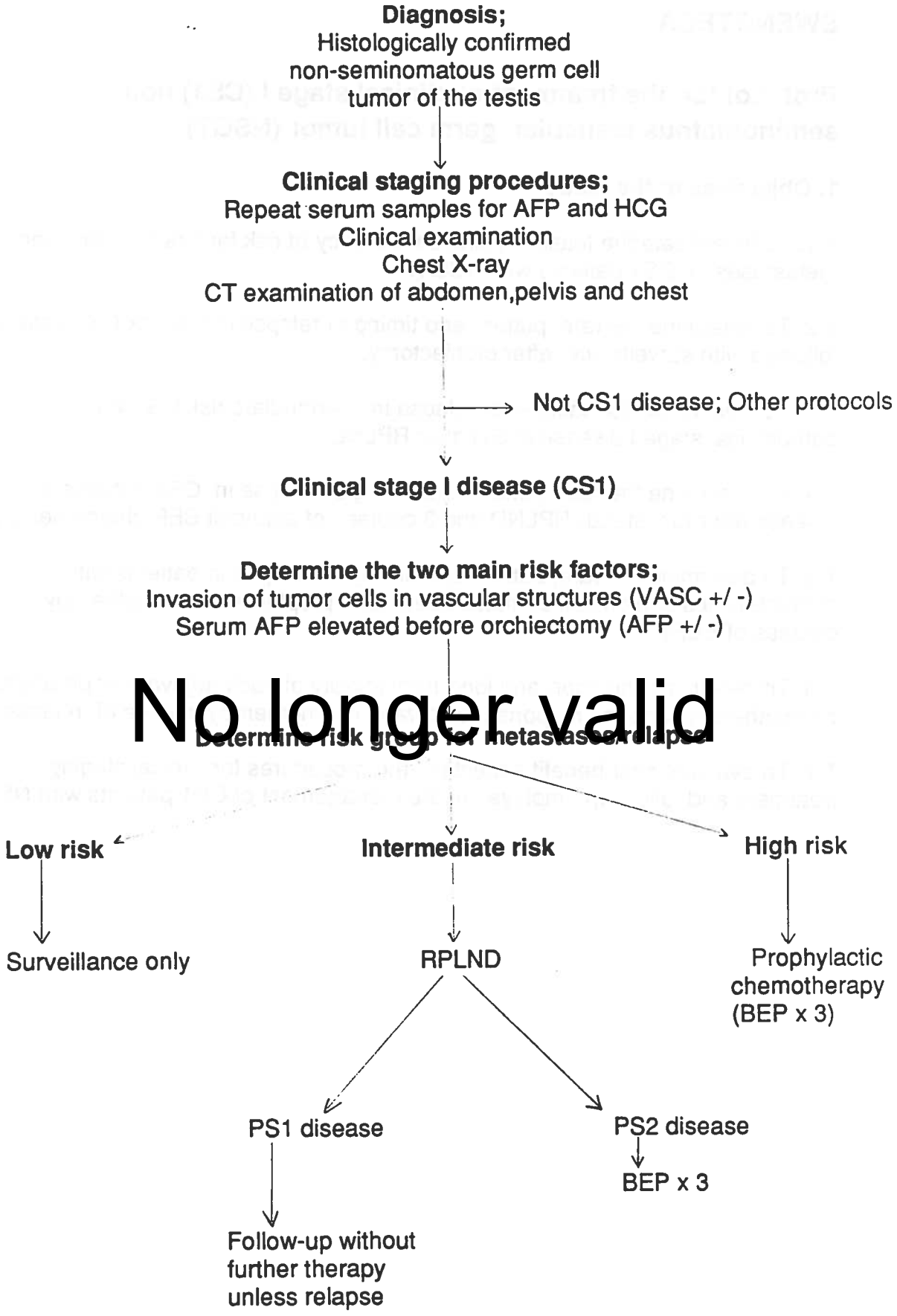

**SWENOTECA**

# Protocol for the treatment of clinical stage I (CS1) non-seminomatous testicular germ cell tumor (NSGT).

## 1. Objectives of the study

1.1. To investigate the feasibility and consistency of risk factors for prediction of metastases in CS1 patients with NSGT.

1.2. To determine the rate, pattern and timing of relapse in low risk CS1 patients followed with surveillance after orchiectomy.

1.3. To investigate risk factors for relapse in intermediate risk CS1 with pathological stage I disease (PS1) after RPLND.

1.4. To determine the rate, pattern and timing of relapse in CS1 patients with PS2 disease after (unilateral) RPLND and 3 courses of adjuvant BEP chemotherapy.

1.5. To determine the rate, pattern and timing of relapse in patients with characteristics of high risk of metastases, after prophylactic chemotherapy (3 courses of BEP).

1.6. To determine the short and long-term toxicity of such adjuvant or prophylactic chemotherapy and the response to salvage chemotherapy in case of relapse.



1.7. To evaluate cost-benefit aspects of the procedures for clinical staging, treatment and follow up employed in the management of CS1 patients with NSGT.

## 2. Background

### 2.1 Definition of clinical stage1 non-seminomatous germ cell tumors of the testis (NSGCT), for use in this protocol.

The revised version of the Royal Marsden Hospital Staging System [1,2] will be used:

Table I. The Royal Marsden Hospital Staging of testicular tumors.

| | |
|---|---|
| I | No evidence of metastases |
| 1Mk+ | Rising tumor markers with with no other evidence of metastases |
| II | Abdominal node involvement |
| A | < 2 cm diameter |
| B | 2-5 cm diameter |
| C | > 5 cm diameter |
| III | Supradiaphragmatic node involvement |
| M | Mediastinal |
| N | Supraclavicular/cervical/axillary |
| 0 | No abdominal lymphadenopathy |
| ABC | As above |
| IV | Extra-lymphatic metastases |
| Lung substage | |
| L1 | < or = 3 metastases |
| L2 | > 3 metastases, all < or = 2cm diameter |
| L3 | > 3 metastases, one or more >2 cm diameter |
| H+ | Liver mets |
| Br+ | Brain mets |
| Bo+ | Bone mets |



If one or both of the serum tumor markers alphafetoprotein (AFP) or human chorionic gonadotropin are elevated after orchiectomy, the level must be followed with at least 3 samples, taken with at least 5 days intervals if there are no other clear signs of metastatic disease. The normal serum half life is (maximum) 6 days for AFP and 2 days for HCG. If there is doubt regarding the fall of marker values, further samples must be taken until clear conclusions may be drawn. The patient can be classified as CS1 only if both markers are normal, or falling in accordance with expected half-life times.

CS1 constitutes about 50% of all NSGCT patients in Sweden and Norway, and CS1Mk+ about 5% [2]

## 2.2 Modern treatment strategies for NSGCT patients with CS1 disease.

### 2.2.1 Retroperitoneal lymph node dissection (RPLND) for determination of the pathological stage (PS)

This has been the traditional approach, and RPLND staging is still regarded as the standard option [3,4]. RPLND staging was performed in 345 evaluable patients with early clinical stages (CS1, CS1Mk+ and CS2A) of NSGCT included into the SWENOTECA project 1981-1986 [2,5]. Of 279 CS1 patients, 27% had retroperitoneal metastases (PS2 disease) revealed by RPLND. All the 122 PS2 patients who received adjuvant cisplatin-based chemotherapy stayed free of relapse despite the fact that 37 of them had only a unilateral RPLND [5]. Two out of 345 staging RPLND procedures resulted in lethal complications: One due to a ventilation failure during intubation and one due to a HIV-infected transfusion.

The risk of persistent dry ejaculation was 17% after unilateral and 56% after bilateral RPLND for the PS1 patients, significantly higher (28%) after a left unilateral operation than for the right-sided procedure (9%).

A total of 30 out of 217 PS1 (13.8%) patients relapsed within a median observation time of 5 years, 27 of the relapses were seen less than 18 months after the RPLND. Four (1.4%) of the 279 pathologically staged CS1 patients relapsed first in the retroperitoneum. Three of the 30 PS1 patients who relapsed died of progressive testicular cancer despite salvage chemotherapy. The 6-year cumulative tumor-specific survival for the 279 CS1 patients treated according to the first SWENOTECA protocol was 98.6%.



### 2.2.2 Surveillance after orchiectomy

Due to the availability of effective salvage chemotherapy and in order to avoid RPLND, the so-called surveillance policy has gained popularity during the 1980's. NSGCT patients in clinical stage 1 are only followed closely after the orchiectomy until relapse according to this treatment option at some centres. A recent overview[4] of 680 surveilled CS1 patients reported in the litterature concluded that the overall relapse rate was 26% and at least 50% of the first relapses occurred in the retroperitoneum. As the median observation time in some of the surveillance studies was comparatively short, the overall relapse rate and not the actuarial was evaluated and possibly due to some selection of low-risk CS1 patients, the 26% relapse rate should probably be regarded as a minimum figure. Some very experienced urologists[6,7] have warned about the risk of comparatively high relapse rate in the retroperitoneum, detected only at a relatively advanced size, and/or with a relatively high secondary relapse rate after salvage chemotherapy.

According to Pizzocaro[6], very resource-demanding follow-up procedures are mandatory if surveillance is to be regarded as a safe option for routine treatment. This viewpoint is supported by the experience from the first SWENOTECA treatment program: If a surveillance policy had been

followed for the same CS1 population, the cummulative relapse rate would have been about 38%, with at least a 27% risk of relapse in the abdomen [8].
One conclusion of the Consensus Conference on Testicular Cancer in Hull (April 1989 [3]) was that the surveillance option should not be regarded as routine treatment for all CS1 NSGCT cases, but seemed suitable for selected low-risk populations of patients.

### 2.2.3 Risk-adapted treatment choice

If the likelihood of metastases could be determined from clinical and/or histopathological characteristics at the time of diagnosis and staging, a more rational treatment option could be offered to the individual CS1 patient. Vascular invasion, presence of undifferentiated tumor cells, absence of yolk sac or teratoma elements in the primary tumor, primary tumor pT stage above 1, and/or normal pre-orchiectomy AFP serum level are current candidates for prognosticators in CS1 patients [2,4,6-10]. Some studies of primary "prophylactic" chemotherapy after orchiectomy in CS1 patients regarded as having a high risk of subclinical metastases have been published [4,11].
The British Medical Research Council has recently activated a study[12] of primary chemotherapy to high-risk CS1 patients, defined as having 3 or all of the following 4 parameters:

Tumor invasion of testicular veins
Tumor invasion of testicular lymphatics
Undifferentiated cells present
Absence of yolk sac elements



### 2.2.4 Risk factor analyses from the first SWENOTECA study

The 345 evaluable cases with early stages of NSGCT included into the first SWENOTECA treatment program (1981-86) have been subject to multivariate risk factor analyses regarding subclinical metastases [2,2,8,13].
Vascular invasion in the primary tumor and normal pre-orchiectomy AFP serum level predicted retroperitoneal disease as found by RPLND in the CS1 patients. If pre-orchiectomy AFP was excluded, absence of yolk sac elements and of teratoma elements predicted PS2 disease in addition to vascular invasion. Vascular invasion, absence of teratoma elements and a short orchiectomy to RPLND time interval predicted increased risk of relapse in PS1 patients after RPLND. If all the PS2 cases, and the PS1 patients who relapsed are evaluated as having subclinical disease despite CS1 status before RPLND, the following factors predicted metastases in multivariate analyses: Vascular invasion in the primary tumor, normal pre-orchiectomy AFP level, absence of teratoma elements and a short orchiectomy to RPLND interval.

Based upon the SWENOTECA study, the following simplified risk assessment for subclinical metastases could be formulated [8] :

Table 2. Risk estimates for CS1 patients regarding PS2 disease, Relapse in PS1 or the combined risk (MET), for different combinations of the main prognostic variables vascular invasion in primary tumor (VASC) and pre-orchiectomy AFP elevation.

| Combination of variables | % of the CS1 cases. | % Risk of PS2 (95% CI) | % Risk of relapse if PS1 (95% CI) | % Risk of MET (95% CI) |
|---|---|---|---|---|
| VASC- AFP+ | 39 | 11 ( 6- 9) | 10 ( 5-20) | 20 (13-30) |
| VASC- AFP- | 34 | 32 (22-43) | 10 ( 4-21) | 38 (28-50) |
| VASC+ AFP+ | 14 | 34 (21-50) | 35 (18-56) | 58 (42-72) |
| VASC+ AFP- | 14 | 66 (50-79) | 34 (15-60) | 77 (62-87) |

The main purpose of the present SWENOTECA protocol is to evaluate these findings in a new prospective study, and use the information obtained in the first study to reduce the need for RPLND staging procedures in the patient with either a low risk or a very high risk of metastases.

### 2.2.5 Detection of relapse

After staging RPLND there is a low risk of retroperitoneal relapse in PS1 cases. The risk of relapse in PS2 cases who receive 3 courses of adjuvant cisplatin-based chemotherapy after RPLND is less than 1% (none out of 122 PS2 SWENOTECA cases, see. section 2.2.1 and ref.8). The detection of relapse in PS1 as experienced in the first SWENOTECA study[5] is shown in Table 3.



Table 3. First symptom or positive examination indicating relapse in the 30 PS1 patients who relapsed (excluding 2 patients with new contralateral primary tumor)

| First or main indication of relapse | Number of patients (%) | Supportive role* Number of patients |
|---|---|---|
| Chest X-ray | 12 (40%) | 2 |
| Elevated serum AFP and/or HCG | 10 (33%) | 4 |
| Clinical examination | 4 (13%) | 2 |
| Pain | 1 ( 3%) | 1 |
| Lactate dehydrogenase (LD) elev. | 1 ( 3%) | 2 |
| Patient noted palpable tumor | 1 ( 3%) | |
| Routine CT examination of abdomen | 1 ( 3%) | 1 |

* Stated on the flow sheets as secondary or supplementary to the first indication

Analyses of the serum tumor markers AFP and HCG and the more unspecific lactate dehydrogenase (LDH) were useful in early detection of relapse, even in patients who had normal

serum tumor markers at the time of orchiectomy. Routine CT examinations in the follow-up period was little cost-effective in patients who had undergone RPLND[5].

For patients surveilled after orchiectomy (no staging RPLND) repeated CT examinations are mandatory in order to detect retroperitoneal relapses at an early stage of development[6].

## 3. Therapeutic strategy for CS1 patients in this study.

### 3.1 Low risk patients: Surveillance

Patients with no tumor cell invasion of vascular stuctures in the testis and with elevated level of AFP before orchiectomy that falls to normal levels or declines according to normal half-life (6 days) of AFP in serum. This group will constitute about 40% of the CS1 population. A policy of close surveillance after orchiectomy only is proposed , with an expected risk of relapse of about 20%. Relapses are presumed to be detected at a low volume state, with very good chances of being cured by chemotherapy.

### 3.2 Intermediate risk patients: Unilateral RPLND

Patients with no vascular invasion and a normal AFP level at orchiectomy (staying normal), and

Patients with vascular invasion and elevated pre-orchiectomy AFP level (falling to normal levels).



This combined group will constitute about 45% of the CS1 patients and have a 38-58% risk of relapse if only surveilled. About 33% will have retroperitoneal lymph node metastases (PS2) at RPLND.

The PS1 patients will have from about 10 % ( patients with no vascular invasion , constituting 2/3 of these PS1 population) to about 35% risk of relapse ( the patients with vascular invasion). Nearly all of these relapses will occur during the first 18 months after RPLND, and very few will relapse in the abdomen.

#### *3.2.1 Time interval from orchiectomy to RPLND*

***NOTE: In order to increase the chances for subclinical metastases to become manifest before a staging RPLND, there should be an interval of at least 6 weeks between the orchiectomy and the RPLND. Serum tumor markers and CT of the abdomen should be taken and evaluated less than two weeks before the planned RPLND, and the RPLND omitted or delayed if there is any sign of active disease. If active metastases are verified, chemotherapy is started, and RPLND only performed if there is any sign of residual abdominal tumor masses.***

### 3.3 High risk patients: Prophylactic chemotherapy

Patients with vascular invasion and a normal AFP level at orchiectomy.

This group constitutes about 15% of the CS1 population and will have more than 60% risk of developing metastases if only surveilled. Three full courses of BEP chemotherapy have a very good chance of curing low volume metastases with acceptable side effects. The patients should be followed rather closely after chemotherapy however, as there theoretically may be some risk of late and slow-growing abdominal metastases.

### 3.4 Patients with unknown "peri-orchiectomy" AFP level

One must expect that the referring physicians may forget to obtain a serum sample for tumor marker analysis at time of orchiectomy in some cases. As the serum half-time of AFP is 5-6 days, it may take some time before normalization if the level was elevated before orchiectomy. Any clearly elevated level found after orchiectomy that subsequently falls to normal limits according to normal half-times may be taken as significantly elevated with normalization. If the first AFP level was obtained within 3 days after orchiectomy and that level was normal, it should be considered as "normal at orchiectomy". If the first level was obtained later than 3 days after orchiectomy and that level was normal, the "peri-orchiectomy" AFP levels should be considered as unknown. **All such cases with unknown AFP level should be included in the study and treated according to the principles of the intermediate risk group.**



### 3.5 Patients with persistently raised or rising AFP and/or HCG levels.

If the serum levels of AFP and/or HCG rises or do not fall according to normal half-times (6 days for AFP, two days for HCG), the patients should be classified as having CS1M+ disease and not be included in the study.

One should remember that a few patients have their "normal" AFP level slightly above the usual limit of 20 nanogram/liter ( up to 40 nanogram/liter). Patients with persistent AFP levels in this range should be followed very closely. If there is no normalization, or no significant rise during 4-5 weeks after orchiectomy, the patients should undergo RPLND.

## 4. Inclusion Criteria

**The following criteria are required for entry into this study:**

4.1 Age 18 and higher

4.2 Histologically confirmed non-seminomatous germ cell tumor of the testis. If both seminomatous and non-seminomatous elements are present, the patient is eligible for the study.

Slides of the tumor specimen must be available for review by a panel of pathologists.

4.3 No (other) prior or concomitant malignancy, including a germ cell tumor in the contralateral testis

4.4 Evaluable regarding presence or abscence of tumor cell invasion of the testis

4.5 Evaluable regarding "peri-orchiectomy" AFP-level (see 3.4 and 3.5)

4.6 No medical, psychological , social and/or geographical factor making the proposed treatment and/or close follow up for at least 5 years impossible or very difficult. (Patients exluded for such reasons should preferably undergo RPLND and otherwise be treated and followed up according to the principles for intermediate risk patients ( see sections 3.2 and 7.2 )

4.7 Clinical stage I disease.;

4.7.1 No evidence of metastatic disease on clinical examination

4.7.2 Normal Chest X-ray (and chest CT in any doubtful case)

4.7.3 Normal CT scan of abdomen

4.7.4 Normal tumor markers after orchiectomy (see 3.5)



4.8 The interval between markers becoming normal and entry to the study should not exceed 6 weeks.For patients whose markers are normal at time of referral to the collaborating hospital, the interval between orchiectomy and entry should not exceed 8 weeks.

4.9 Consent to the proposed treatment and follow-up.

## 5. Pre-treatment assessments

5.1 The following investigations are mandatory and must be carried out prior to registration:

5.1.1 Assay of serum AFP and (beta) HCG (until normal) and assay of LDH

5.1.2. Chest X-ray

5.1.3 CT examination of abdomen and pelvis

5.1.5 Liver function tests ( alkaline phosphatase, ALAT, Gamma GT)

5.1.6 Serum creatinine

5.1.7 Haemoglobin, white cell count and platelet count

**5.2 Optional investigations:**

5.2.1 Sperm analysis prior to elective sperm banking in patients wishing to undertake this.

5.2.2 Ultrasound examination of abdomen and pelvis (NOTE: CT examination is mandatory!)

5.2.3 CT of the chest

## 6. Registration

6.1. Both for the safety of the individual patient and for study purposes it is extremely important that there is accurate and prospective registration of all mandatory parameters before choice of therapy and during follow up. There must be a comprehensive written file and optionally a computer file for all of the patients enrolled in the study at the departement/hospital in charge of the individual patients. A computer database will be estabiiashed in Lund for Swedish and in Trondheim for Norwegian patients included in the study. Both the national central secretariats will use the MEDLOG medical database and statistical program (for personal computers) for registration. The databases will have common structure and parameter definitions, in order to pool the data ( patient names omitted) from the two countries for statistical analysis.

6.2 Routines (macro functions in MEDLOG and manual procedures) will be established at the national secretariats in order to ascertain the completeness of follow-up for the patients included from the participating hospitals. ***The participating hospitals have the full responsibility (medical, formal and legal) for the following of the individual patients they include in the study. The national secretariats will only have the formal responsibility for completeness of the data collection from a scientific point of view, and not for the medical consequences in case of missed follow up of the individual patient.***



The national secretaries will strive to give prompt reminders to the clinicians in charge of the patient in case of missing follow-up information, but will not undertake any formal medicolegal responsibility.

6.3. The system(s) and procedures chosen must be approved by the national data inspection board, including guidelines for transfer of patient data between the two countries.

6.4 The registration and follow-up forms are **simplified** versions of the forms used in the first SWENOTECA protocol, with emphasis on the comparatively few parameters regarded as important for the endpoints of the present study.

6.5 A working party of pathologists from the participating centers will be organized, and all procedures and forms concerning histopathological parameters should be discussed between this working party and the clinicians. (Section 6.5 will be further specified in the final protocol..)

## 7. Surgical procedures

### 7.1 Orchiectomy

Exploration of the testis should be carried out when a testicular tumor cannot be excluded clinically or (preferably) by ultrasound scanning.

*The surgeon must check that serum for analysis of the tumor markers AFP and beta-HCG is obtained before the orchiectomy.*

The surgeon is reponsible for the delivery to the pathologist of the fresh specimen, without fixative, within an hour from the orchiectomy. If transfer of fresh specimen to the Dept. of Pathology is not feasible, the fixation of the removed testis must be in accordance with guidelines from the Dept. of Path.

#### 7.1.1 Surgical procedures at orchiectomy

A long inguinal incision, identical to the one used when an operation for inguinal hernia is performed. The anterior wall of the inguinal canal is incised and the funicle is dissected free and clamped. The fascia tunica vaginalis containing the testis and epidydimis is dissected free and lifted up from scrotum and incised.

Increased vascularity of the tunica albuginea indicates presence of a testicular tumor. An incision of the testis should be avoided. However, if GREAT uncertainty exists, a specimen may be sent to frozen section examination while the funicle is clamped.



Note that **even suspicion of malignancy makes orchiectomy warranted**, especially if the patient has a normal testicle on the other side. Only if both macroscopic and microscopic examination reveals a benign lesion can the testicle be replaced into the scrotum.

The orchiectomy is brought to an end by dividing the gubernaculum testis.Thereafter the funicle is divided at the proximal aperture of the inguinal canal and tied with a non-resorbable ligature, which is easy to identify at a later retroperitoneal lymphadenectomy. The inguinal canal and skin are closed by single sutures.

Observe that the testicle is now sent FRESH, WHOLE and UNFIXED without any delay to the Pathology laboratory (provided that there is one at the same hospital) If the transport to the patologist will take more than an hour, the testis should be fixated according to guidelines.

### 7.2 Retroperitoneal lymph node dissection (RPLND)

**Unilateral RPLND**

**Only performed in Clinical Stage 1 (CS1) intermediate risk**

Abdominal mid-line incision.

The right colon is made free up to the right flexure and the small intestine is dissected free up to the duodenal-jejunal junction and these bowels are placed in a parcel of clothing on the breast of the

patient. According to the SWENOTECA 1 study the borderline between the two halves is a sagittal plane through the aorta. A right-sided unilateral RPLND leads to dry ejaculation in about 9% of the PS1 patients while 28% of patients with left-sided RPLND may risk dry ejaculation. The overall risk of dry ejaculation after unilateral RPLND is about 17%, versus 56% for patients undergoing bilateral RPLND. The risk of dry ejaculation after unilateral RPLND can probably be further reduced by employing a modified nerve-sparing procedure[14]. This procedure involves more extensive surgery above A. Mesenterica inf., which is preserved, and less extensive surgery below that artery.

The upper border for the unilateral RPLND is above the renal vessels. The ureter constitutes the lateral border. Caudally the dissection is performed down to the groin where the funicle with its knotted end is found and removed.
Examinations with frozen sections of any suspect node or evident metastases is recommended.

*If retroperitoneal metastases are histologically verified during RPLND there are two options regarding further operation:*

**7.2.1 Continue with a bilateral RPLND**
This is the traditional approach, and should be performed in any case with contralateral metastases or extensive ipsilateral disease.

**7.2.2 Unilateral RPLND despite PS2 status:**
If there is only ipsilateral (must be considered on an individual basis) disease ipsilaterally, evidence from the first SWENOTECA study indicates that it is safe to perform only unilateral RPLND provided that the patient receives effective adjuvant chemotherapy afterwards. A total of 37 patients with PS2 were operated unilaterally only. They all received 3-4 courses of adjuvant CVB chemotherapy and none of them relapsed. Most of these cases had no macroscopic disease ipsilaterally, but final examination of the nodes revealed microscopic retroperitoneal metastases. At least 10 of these 37 patients also had macroscopic ipsilateral metastases at RPLND, however.



**7.3 PS2B or PS2C disease at RPLND**
If unexpected PS2B (diameter 2-5 cm) or even PS2C (diameter >5 cm) is found at laparatomy, RPLND should not be performed, but chemotherapy given first. If the tumor masses are estimated to be easily removed, the RPLND could be continued, with adjuvant chemotherapy given post-operatively.

**7.4 Mounting of removed specimens**
As the specimens are removed during the operation, they should be arranged on a sterile cork plate which has an anatomic sketch on it. The mounted tissue should be covered by a wet cloth during the operation.

When surgery is finished the plate with the specimen is sent to the pathologist, who decides whether he/she wants it fresh or in a fixative.

## 8. Chemotherapy

The chemotherapy schedules are same for the adjuvant and the prophylactic (see section 3.3) indications. Chemotherapy will consist of 3 courses of cisplatin, etoposide and bleomycin according to the standard BEP-20 regimen. *See Addendum 1 for schedule and dose modification*

## 9. Patient follow-up

9.1 The date of entry will be used as the starting point for calculating follow-up;
For patients in the low risk group and the high risk group the date of entry will be the date when clinical staging is finished, at most 8 weeks since orchiectomy. For patients in the intermediate risk group the date of RPLND will be the date of entry.

9.2 The follow-up intervals and procedures for the different groups are detailed in Flow sheets 1, 2 and 3.

Additional CT and/or other pertinent examinations must of course be performed if there is any hint of relapse clinically or by serum tumor marker levels.



*9.3 In every case of relapse encountered, the central register(s) must be notified immediately. Such patients should be thoroughly investigated to document the site and extent of relapse, and promptly be treated with chemotherapy. Patients who have received prior BEP-20 chemotherapy (adjuvant or prophylactic) should be treated with the regimen(s) for poor risk metastatic non-seminomatous testicular cancer used at the center and time in question.*
*Patients who have only been surveilled may be treated with standard chemotherapy if not the volume of disease nor other factors at relapse indicate more intensive chemotherapy.*

## 10. End points

The principal end points of the study will be relapse rate, which should be low. Survival is expected to be at least 98 per cent. The study will be monitored at least every 6 months. **Should there be clear evidence that either;**

10.1 The relapse rate for exceeds 30% for surveillance patients
10.2 Relapses are detected late and at a state where curative therapy is difficult
10.3 Relapse rate after RPLND and PS1 disease exceeds 30%
10.4 Relapse rate after adjuvant chemotherapy for PS2 exceeds 5%
10.5 Relapse rate after prophylactic chemotherapy for high risk patients exceeds 5 %, or
10.6 **Any** death due to testicular cancer progression occur,
**a review of the whole study will be performed and termination will be considered.**

## 11. Numbers

11.1 According to the experience from the first SWENOTECA study, current incidence rates and referral practice to the centers interested to participate, about 40 new patients with CS1 non-seminomatous testicular cancer could probably be included per year. There is no evidence that the proposed treatment strategies will be unethical or out of fasion for the first 5 years, and there are good arguments for not changing treatment strategies too often.
During a 5 year period, starting 1990, it should therefore be possible to accrue about 200 patients.

11.2 Surveillance group

The expected relapse rate for this group should be below 20% ( about 17%).
In order to have a 95% confidence limit for a presumed relapse rate of 20% within the 10-30% range, the minimum group (sample) size must include 62 patients. As the surveillance group is expected to constitute about 40% of the CS1 patients, the size of this group should be within realistic goals for a 5 year period of accrual.

**If 19 or more of the first 62 surveillance patients relapse, the surveillance option must be reconsidered.**

**(A relapse rate above a percentage reflecting the upper 95% confidence interval limits, before the minimum number is accrued will of course lead to close monitoring of the development and reconsideration of further patient inclusion. This principle concerns all the treatment groups ).**



11.3 RPLND group

About 90 patients should be accrued during 5 years. About 30 of these will have PS2 disease and receive adjuvant chemotherapy after RPLND. The expected rate of relapse after 3 courses of BEP should be in the order of 1% . To have the upper limit of the 95% confidence interval below 5%, a minimum group size of 24 must be accrued.

**If 2 or more of the first 24 patients receiving adjuvant chemotherapy relapse, this treatment option must be reconsidered.**

Of the about 60 patients with PS1 disease, the relapse rate is expected to be in the order of 15%, and should not exceed 30%. The minimum group size needed for having the upper limit of the 95% confidence interval (of a 15% relapse rate) below 30% is 22.

**If 7 or more of the first 22 PS1 patients relapse, this treatment option should be reconsidered.**

11.4 High risk group (prophylactic chemotherapy)

Only about 30 patients are expected to be included in this group during a 5 year period. The expected relapse rate relapse rate should be in the order of 1%, and should not exceed 5%. The minimum group required will be about 24, in order to ensure an upper 95% limit of 5%.

**If 2 or more of the first 24 patients receiving prophylactic chemotherapy relapse, this treatment option must be terminated or at least reconsidered**

## 12. Publication

The results from the different participating centers will be analyzed together and published as soon as the data are considered mature. Individual clinicians must not publish data concerning their patients that are directly relevant to questions posed by the study, until the SWENOTECA working committee has published its report. Named authors for the definitive publication will include the study co-ordinator, one or more members of the pathology review panel and all collaborators contributing 10% or more of the patients. Other contributors will be acknowledged, and other named authors may be considered by the working committee.

## 13 Ethical considerations

13.1 Before entering patients in the study, clinicians must ensure that the protocol has received clearance from their regional ethical committee.. The patient's consent to participate in the study should be obtained after a full explanation of other treatments options has been given.



13.2 Clearance from the national agency of data security must be obtained from the Swedish and Norwegian study coordinators.

13.3 The right of the patient to refuse to participate without giving reasons must be respected. After the patient has entered the study, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if she/he feels it to be in the patient's best interest. The reason for doing so should be recorded and the patient will remain in the study for the purpose of follow-up and data analysis.Similarly, the patient must feel free to withdraw at any time from protocol treatment without giving reasons and without prejudicing his further treatment.

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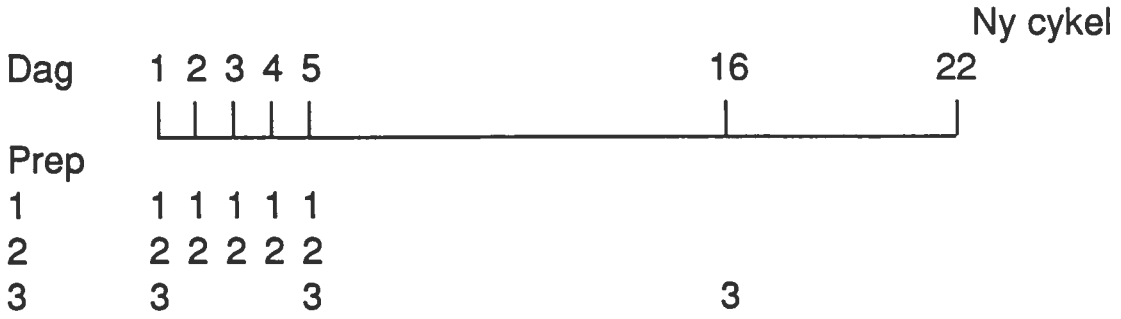
Non-seminomatös testikel cancer. Kliniskt stadium I. SWENOTECA II.

# BEP

| Preparat | Dos mg/m² | Maxdos mg | Administrering | |
|---|---|---|---|---|
| 1 Cisplatinum | 20 | | iv inf 1/2–1 tim | dag 1–5 |
| 2 Etoposid | 100 | | iv inf 1/2–1 tim | dag 1–5 |
| 3 Bleomycin | 30* | | iv/im inj | |

* = totaldos




3 cykler gives. Cykellängd: 21 dagar



*Speciella åtgärder:*

F-kreatinin inför varje cykelstart. Om patologiskt utföres Cr-EDTA-clearance.

Cisplatinum gives med forcerad diures.

CAVE: aminoglykosid skall ej givas under och en månad efter cisplatinumbehandling.

Bleomycin: om toxisk reaktion vid bleomycintillförsel (feber, frossa) gives steroider exempelvis 100 mg Solu-Cortef. Fortsättningsvis gives steroider profylaktiskt före bleomycin.

## Dosreduktionsrekommendationer:

| LPK x $10^9$/l | TPK x $10^9$/l | Prep 1 | 2 | 3 |
|---|---|---|---|---|
| | | % av fulldos | | |
| 3.0–3.5 | 75–99 | 100 | 75 | 100 |
| 2.0–2.9 | 50–74 | 100 | 50 | 100 |
| <2.0 | <50 | Behandlingen uppskjutes | | |
| clearance: 70–79 | | 100 dag 1–4 | 100 | 100 |
| ml/min 60–69 | | 100 dag 1–3 | 100 | 50 |
| <60 cisplatinum gives ej | | | | |

No longer valid

# FORMS FOR REPORTING

**Flow sheets**

1. For surveillance patients (Low risk)
   A) English version
   B) Swedish version

2. After RPLND (Intermediate risk)
   A) English version
   B) Swedish version

3. After chemotherapy (High risk)
   A) English version
   B) Swedish version



**Forms**

**1** On study form

**2** Surgery form

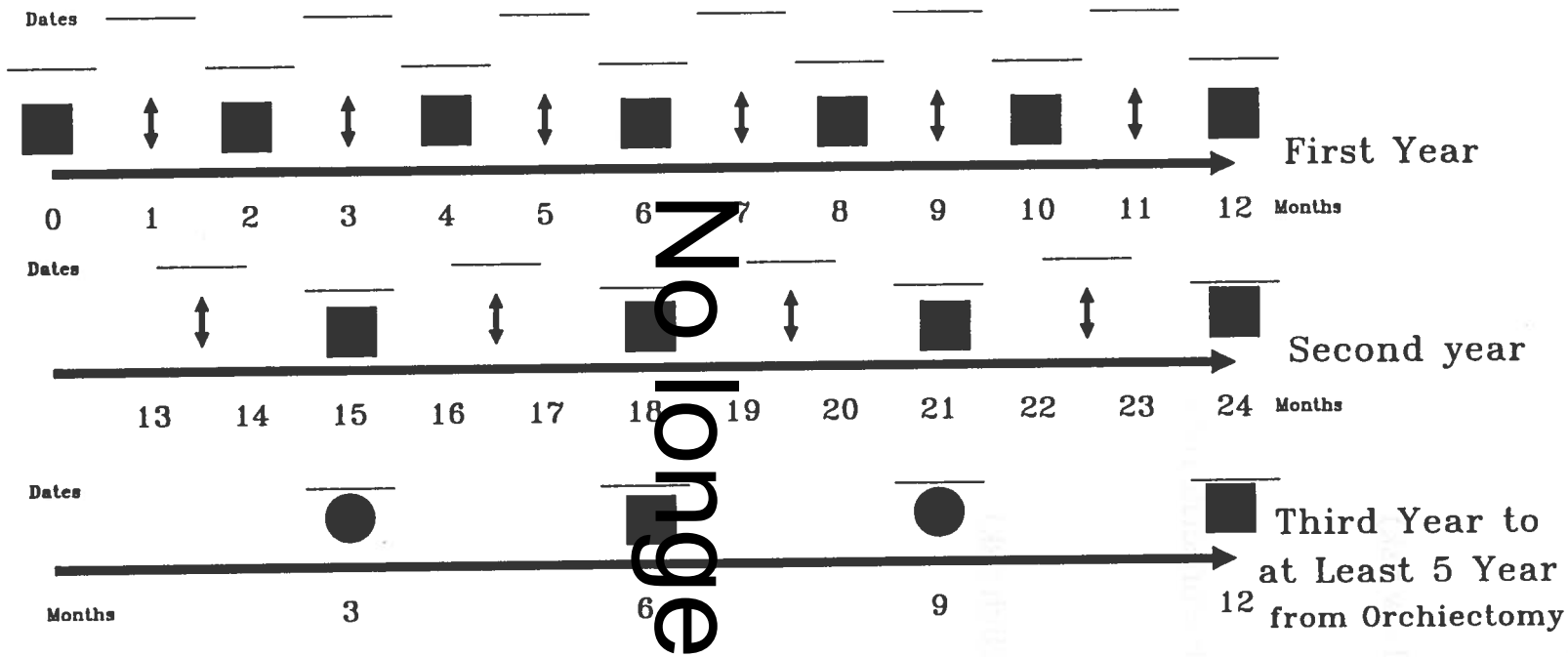
**3A** Pathology form

**3B** Pathology form B

**4** Chemotherapy summary form

**5** Follow-up form

# Flow Sheet for Surveillance Patients






■ Physical examination
Chest X-ray
CT of abdomen and pelvis
Serum markers (AFP,HCG and LDH)
Alk.phosphatase,GT,Creatinine

↕ Serum markers (AFP, HCG, LDH)

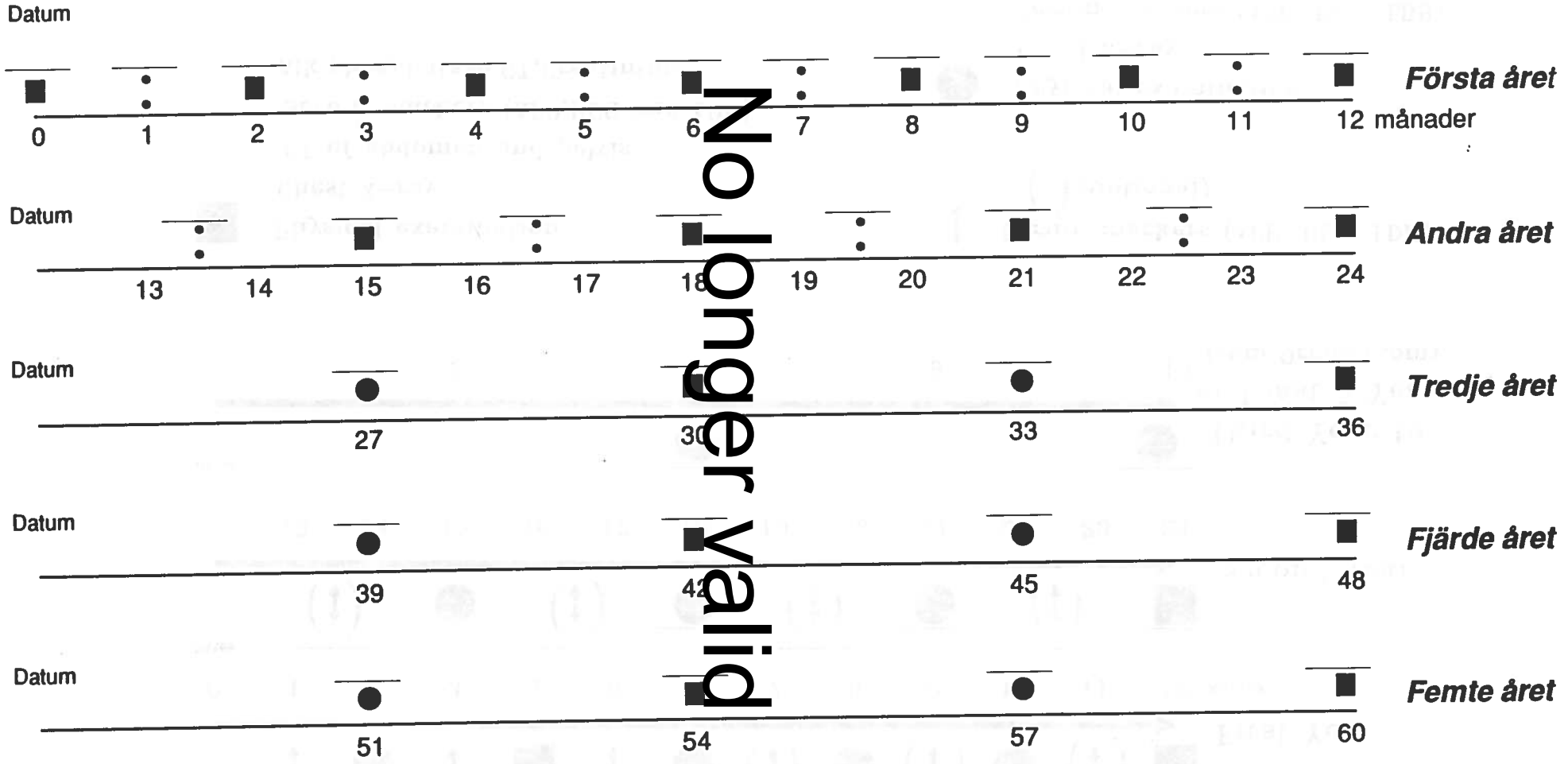
● Physical examination
Chest X-ray
Serum markers (AFP, HCG, LDH)

Name:_____P.nbr._____

Kärlinv. –
AFP +

# Uppföljning för intensivövervakade patienter (surveillance)

Lågrisk CS1 (ej RPLND – ej cytostatikabeh patienter)






■ Fysisk undersökning
Lungröntgen
CT av buk och bäcken
Serummarkörer (AFP, HCG, LDH)
Alk. Fosf., GT, Kreatinin

● Fysisk undersökning
Lungröntgen
Serummarkörer (AFP, HCG, LDH)

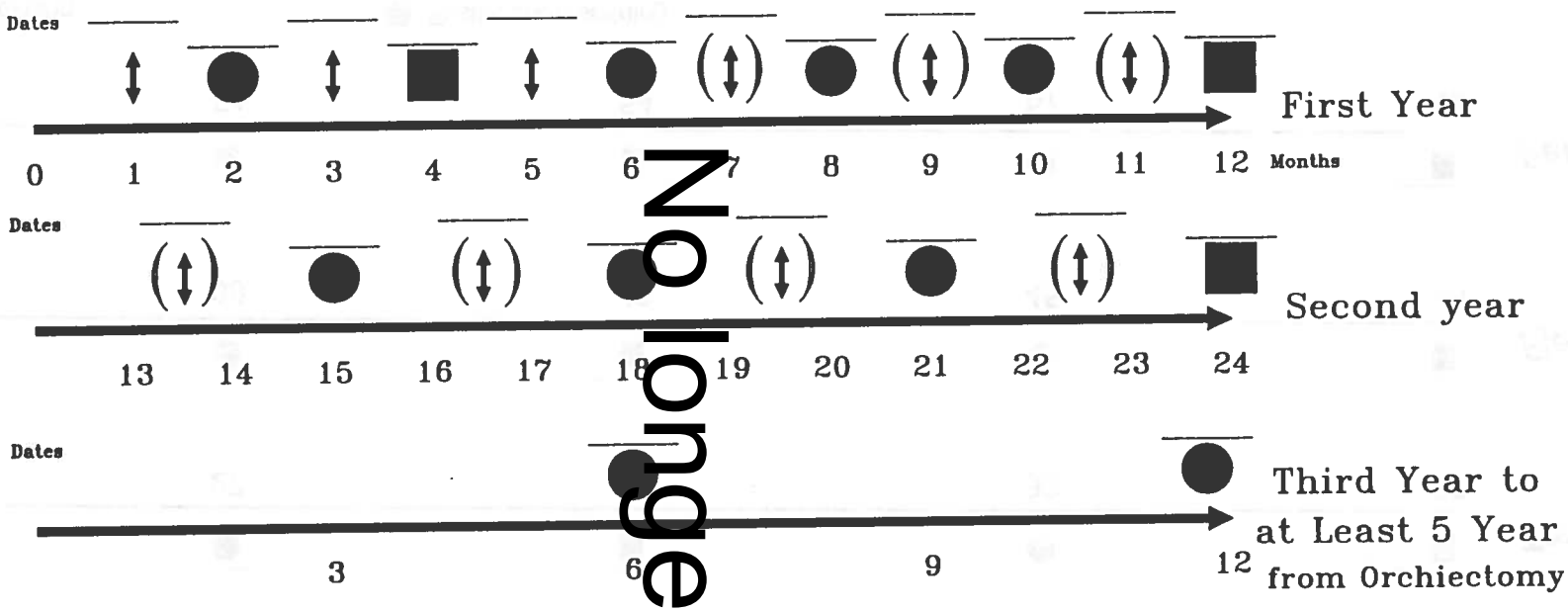
⋮ Serummarkörer (AFP, HCG, LDH)

Patientens personnr: ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ – ⌊⌋⌊⌋⌊⌋⌊⌋

Namn: _____

*Denna blankett förvaras i patientjournalen*

# Follow-up after RPLND, PS1 Patients (Intermediate Risk)






■ Physical examination
Chest X-ray
CT of abdomen and pelvis
Serum markers (AFP,HCG and LDH)
Alk.phosphatase,GT,Creatinine

↕ Serum markers (AFP, HCG, LDH)
( ) (Optional)

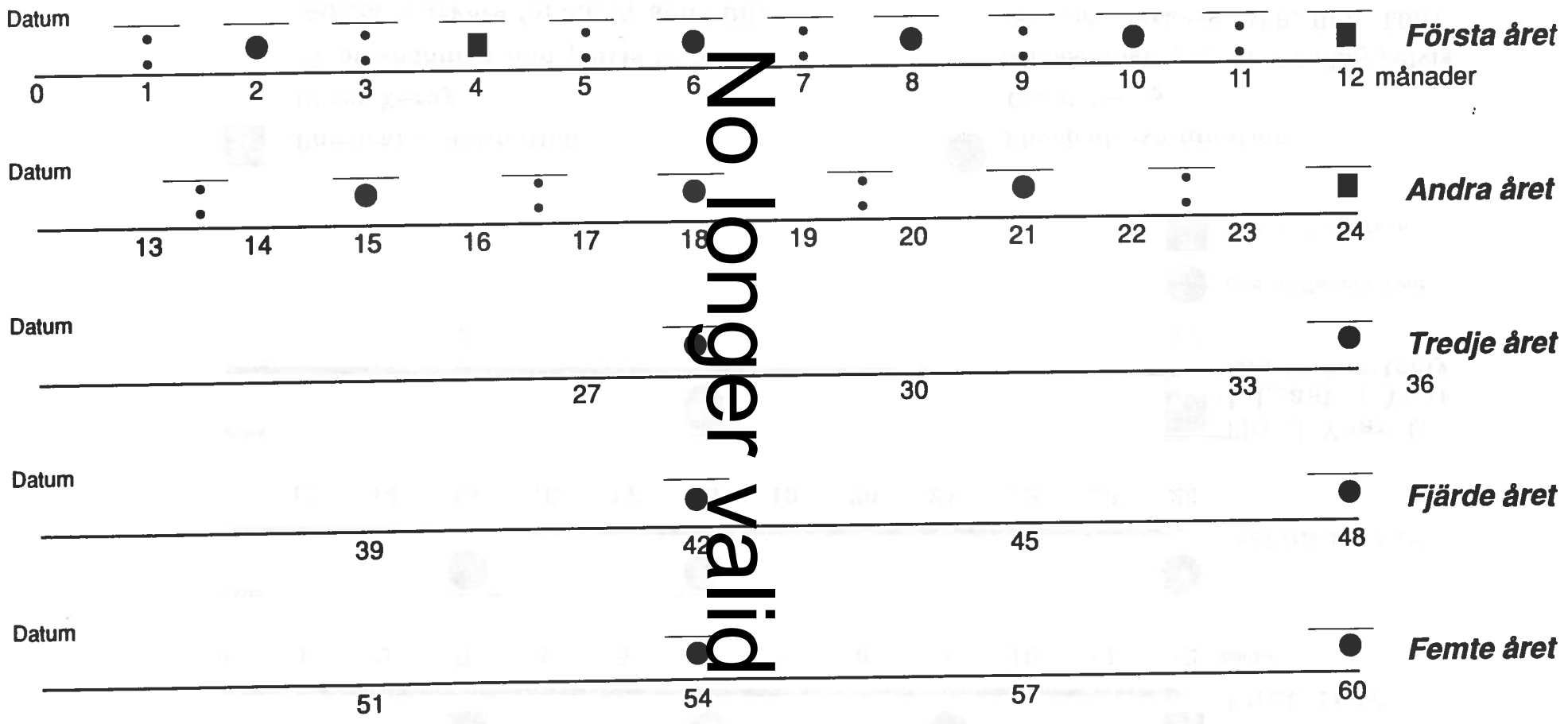
● Physical examination
Chest X-ray
Serum markers (AFP, HCG, LDH)

Name:_____P.nbr._____

# Uppföljning efter RPLND (körtelutrymning)

PS 1 patienter (intermediär risk)

| | |
|---|---|
| Kärlinv. | – |
| AFP | – |
| alt | |
| Kärlinv. | + |
| AFP | + |






■ Fysisk undersökning
Lungröntgen
CT av buk och bäcken
Serummarkörer (AFP, HCG, LDH)
Alk. Fosf., GT, Kreatinin

● Fysisk undersökning
Lungröntgen
Serummarkörer (AFP, HCG, LDH)

⋮ Serummarkörer (AFP, HCG, LDH)

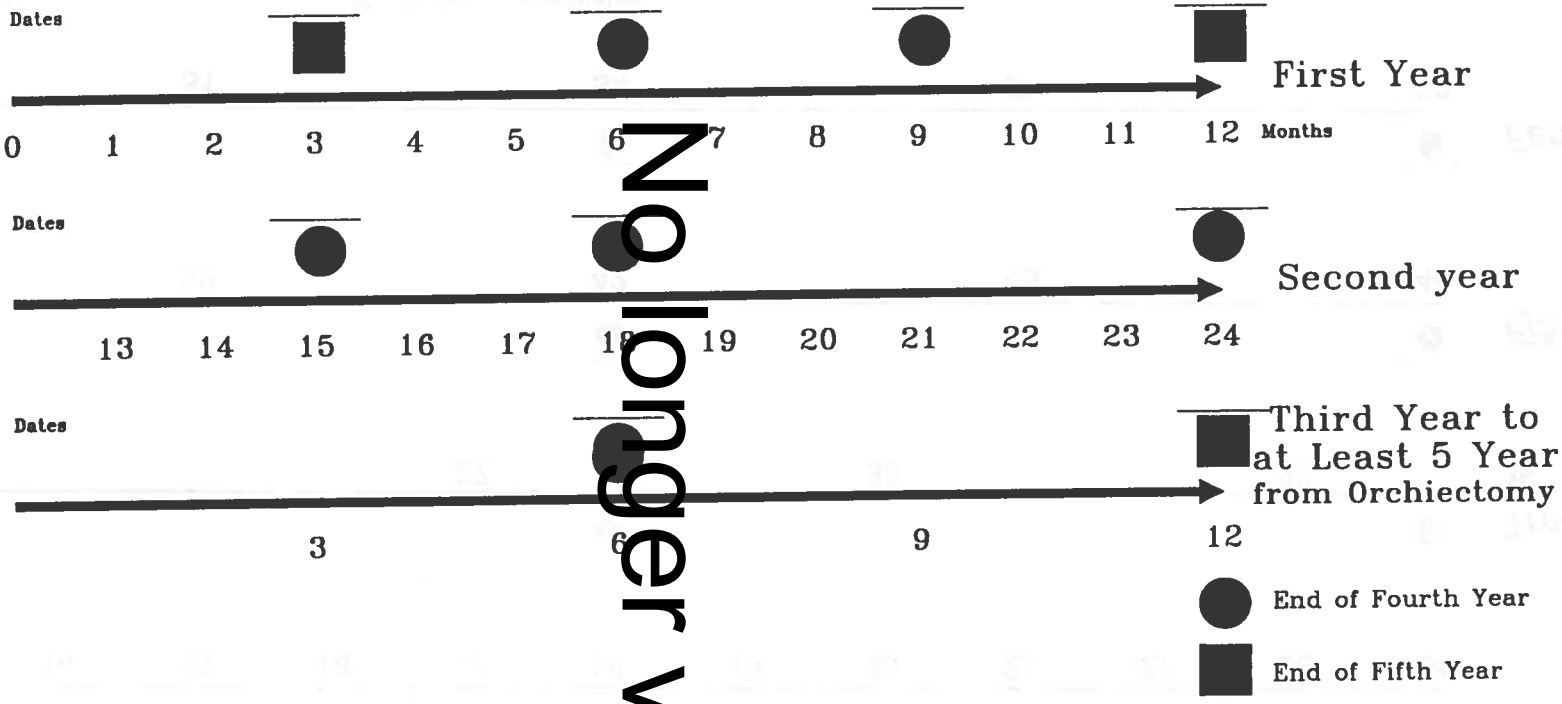
Patientens personnr: ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ – ⌊⌋⌊⌋⌊⌋⌊⌋

Namn: _____

*Denna blankett förvaras i patientjournalen*

# Follow-up After Chemotherapy

## High-Risk CS1 (No RPLND) and PS2 Patients (After RPLND)






■ Physical examination
Chest X-ray
CT of abdomen and pelvis OBLIGATORY!
Serum markers (AFP,HCG and LDH)
Alk.phosphatase,GT,Creatinine

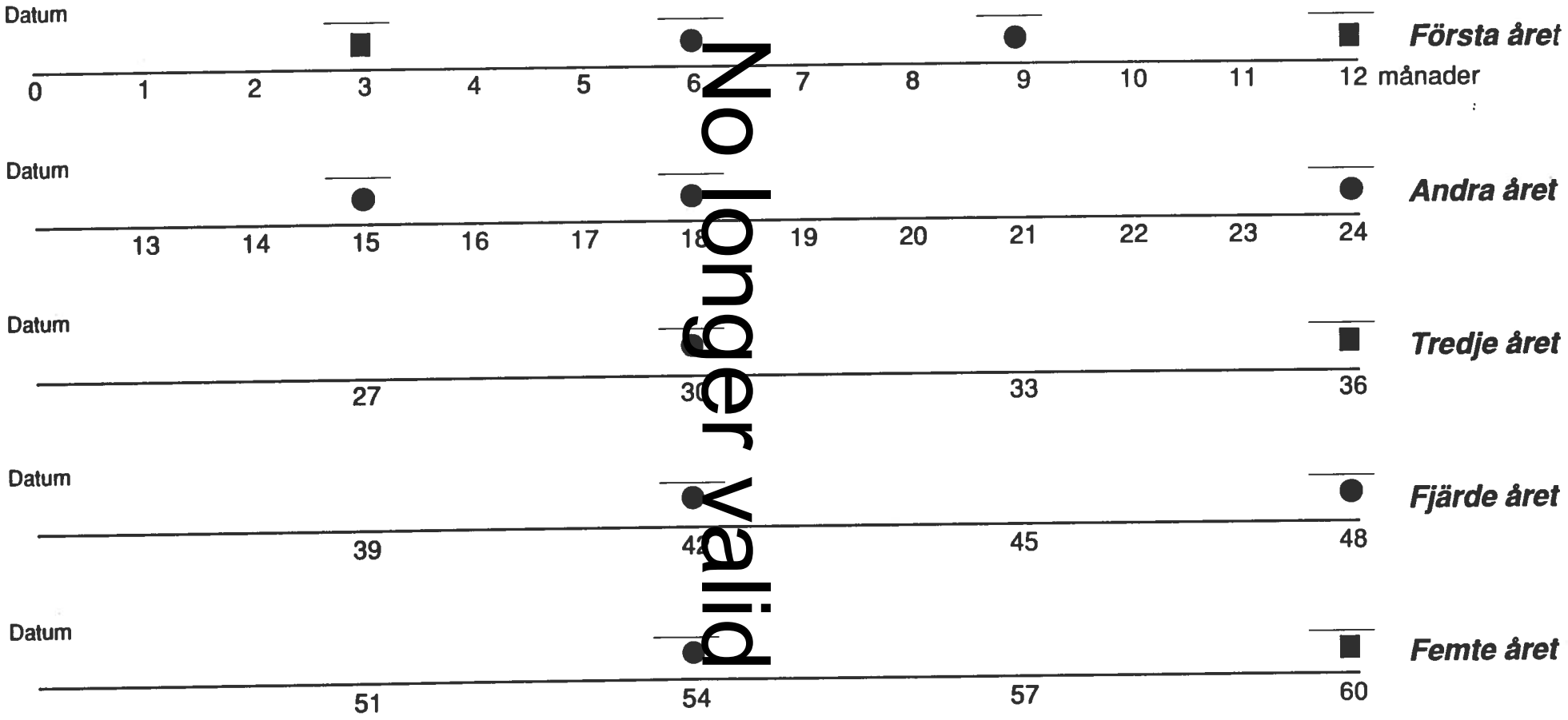
● Physical examination
Chest X-ray
Ultrasonography or CT abd/pelvis
Serum markers (AFP, HCG, LDH)

Name_____ P.nbr_____

Kärlinv. +
AFP –

# Uppföljning efter Cytostatikaterapi

## Högrisk CS1 (ej RPLND) och PS2 patienter (efter RPLND)






■ Fysisk undersökning
Lungröntgen
CT av buk och bäcken
Serummarkörer (AFP, HCG, LDH)
Alk. Fosf., GT, Kreatinin

● Fysisk undersökning
Lungröntgen
Ultraljud eller CT av buk/bäcken
Serummarkörer (AFP, HCG, LDH)

Patientens personnr: ⌊⌋⌊⌋⌊⌋⌊⌋⌊⌋ – ⌊⌋⌊⌋⌊⌋⌊⌋

Namn: _____

*Denna blankett förvaras i patientjournalen*

No longer valid

**SWENOTECA PROGRAM II** 1

**On study form**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet | Kreftsekretariatet |
| Tumörregistret, Lasarettet I Lund | Kreftavdelingen |
| S–221 85 LUND | N–7006 Trondheim |

Hospital and Department

Physician | Date

## PRIMARY SURGERY

| Side of present tumour | Fine needle biopsy performed | Transscrotal surgery | Scrotectomy performed |
|---|---|---|---|
| ☐ sin ☐ dx | ☐ no ☐ yes | ☐ no ☐ yes | ☐ no ☐ yes |
| **Spermiogram performed** | **Inguinal orchiectomy** | **Date of orchiectomy** | **Hospital, department** |
| ☐ no ☐ yes | ☐ no ☐ yes | | |

## SERUM MARKERS

Upper normal limit of lab. and unit;
AFP ..... HCG-beta: ..... LD: .....

Before orchiectomy:

| Date: | | | |
|---|---|---|---|
| AFP | ☐ normal | ☐ elevated | ☐ not performed |
| HCG | ☐ normal | ☐ elevated | ☐ not performed |
| LD: | ☐ normal | ☐ elevated | ☐ not performed |

After orchiectomy:

| Date: | AFP 1 | HCG 1 |
|---|---|---|
| | AFP 2 | HCG 2 |
| | AFP 3 | HCG 3 |
| | AFP 4 | HCG 4 |
| | AFP 5 | HCG 5 |



Markers indicate active disease
☐ no ☐ yes ☐ ?

## METASTASES

| Lymphnodes metastases | | | Largest metastasis (mm x mm) | Extralymphatic metastases | | | Largest metastasis (mm x mm) |
|---|---|---|---|---|---|---|---|
| Inguinal | ☐ no | ☐ yes | x | Lung | ☐ no | ☐ yes | x |
| Iliac | ☐ no | ☐ yes | x | Number of metastases in lungs | | | |
| Paraaortic | ☐ no | ☐ yes | x | Brain | ☐ no | ☐ yes | |
| Retrocrural | ☐ no | ☐ yes | x | Bone | ☐ no | ☐ yes | |
| Mediastinal | ☐ no | ☐ yes | x | Liver | ☐ no | ☐ yes | |
| Supraclav | ☐ no | ☐ yes | x | Other | ☐ no | ☐ yes , site(s)..... | |

## CLINICAL STAGE (CS)① – PATHOLOGICAL STAGE (PS)②

Risk group for metastases

| | | | | |
|---|---|---|---|---|
| ☐ CS I | ☐ low | ☐ medium | ☐ high | ☐ uncertain |

| Abdominal lymph node status | | | | |
|---|---|---|---|---|
| ☐ CS Mk+ | ☐ CS II | ☐ CS III | ☐ CS IV | ☐ 0 ☐ A ☐ B ☐ C |

Further therapy
☐ Surveillance ☐ RPLND ☐ Chemotherapy

| Staging RPLND performed | Date | | Nerve- |
|---|---|---|---|
| ☐ no ☐ yes | | ☐ Unilateral ☐ Bilateral | ☐ sparing ☐ Other |

| PS at RPLND | Abdominal lymph node status |
|---|---|
| ☐ PS I ☐ PS II ☐ PS IV | ☐ 0 ☐ A ☐ B ☐ C |

Further therapy
☐ No further therapy ☐ Chemotherapy ☐ Other, specify:.....

## ① CLINICAL STAGING (CS)

Based on all findings except retroperitoneal lymphadenectomy.

CS I No evidence of metastases.

CS MK+ α-foetoprotein and/or β-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 abdominal lymph nodes CT 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, >2 cm maximum diameter
Abdominal status: 0 (no mets.), A,B,C, as for stage II.

## ② PATHOLOGICAL STAGING (PS)

Based on macro- and microscopic findings at retroperitoneal lymphadenectomy.



PS I No evidence of metastases

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.

**SWENOTECA PROGRAM II** 2

**Surgery form**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet | Kreftsekretariatet |
| Tumörregistret, Lasarettet i Lund | Kreftavdelingen |
| S–221 85 LUND | N–7006 Trondheim |

Hospital and Department

Physician | Date

RPLND for pathological staging

Date of surgery | Department of surgery

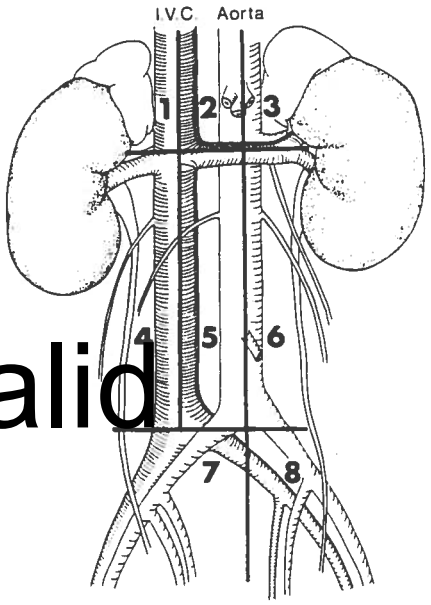
Pathology institution | Specimen (=PAD) No. Year | Date

Type of RPLND

☐ Unilateral ☐ Bilateral

**Macroscopic findings**

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






RADICALITY

Tumour completely exstirpated 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

No longer valid

**SWENOTECA PROGRAM II** **3A**
**Pathology form**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet | Kreftsekretariatet |
| Tumörregistret, Lasarettet i Lund | Kreftavdelingen |
| S–221 85 LUND | N–7006 Trondheim |

Hospital and Department

Physician (pathologist) | Date

## PATHOLOGY INSTITUTION AND SPECIMEN

| Institution | Specimen (=PAD) No. Year | Date |
|---|---|---|
| | ⌊⌊⌊⌊⌊⌊⌊⌊⌋ - ⌊⌊⌋ | ⌊⌊⌊⌊⌊⌊⌋ |

## MACRO

Laterality
☐ Left testis ☐ Right testis Size of tumour: ⌊⌊⌊⌋ x ⌊⌊⌊⌋ mm

## MICRO

| Rete structures present in the section | Invasion of rete testis | Spermiogenes present |
|---|---|---|
| ☐ No ☐ Yes | ☐ No ☐ Yes | ☐ No ☐ Yes |

## pT-CLASSIFICATION ①

☐ pT0 ☐ pT1 ☐ pT2 ☐ pT3 ☐ pT4a ☐ pT4b ☐ pTx

## RADICALITY

Macroscopic infiltration of proximal funicle
☐ No ☐ Yes

Microscopic infiltration of proximal funicle
☐ No ☐ Yes

Tumour cells invading vascular structures
☐ No ☐ Yes



## IMMUNE–PEROXIDASE – STAINING

| AFP | β-HCG |
|---|---|
| ☐ Positive ☐ Negative ☐ Not performed | ☐ Positive ☐ Negative ☐ Not performed |

## WHO-CLASSIFICATION

☐ Seminoma — Syncytiotrophoblastic cells: ☐ No ☐ Yes

☐ Ca in situ lesion present

☐ 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

## CONTRALATERAL TESTIS

| Biopsy performed | Ca in situ lesion present |
|---|---|
| ☐ No ☐ Yes | ☐ No ☐ Yes |

## pTNM Pathological Classification (WHO 1987)

### pT – Primary Tumour

pTX Primary tumour cannot be assessed (in the absence of radical orchiectomy TX is used)
pT0 Histological scar or no evidence of primary tumour
pTis Intratubular tumour: preinvasive cancer

pT1 Tumour limited to testis, including rete testis
pT2 Tumour invades beyond tunica albuginea or into epididymis
pT3 Tumour invades spermatic cord
pT4 Tumour invades scrotum

### pN – Regional Lymph Nodes

The pN categories correspond to the N categories.

### pM – Distant Metastasis

The pM categories correspond to the M categories.

**SWENOTECA PROGRAM II** **3B**
**Pathology form B**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet | Kreftsekretariatet |
| Tumörregistret, Lasarettet i Lund | Kreftavdelingen |
| S–221 85 LUND | N–7006 Trondheim |

Hospital and Department

Physician | Date

## SPECIMEN FROM RETROPERITONEAL LYMPH NODE DISSECTION

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

Type of retroperitoneal lymph node dissection
☐ Unilateral ☐ Bilateral

Microscopic findings:

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

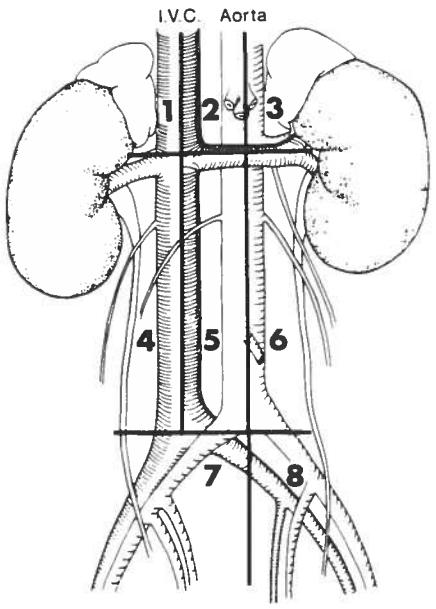


Identical metastases and primary tumour
☐ no ☐ yes

Mature teratoma only
☐ no ☐ yes

Regions of RPLND

①




② includes carcinoma as well as mature teratoma

No longer valid

**SWENOTECA PROGRAM II** **4**

**Chemotherapy summary form**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet<br>Tumörregistret, Lasarettet I Lund<br>S–221 85 LUND | Kreftsekretariatet<br>Kreftavdelingen<br>N–7006 Trondheim |

Hospital and Department

Physician | Date

## SUMMARY OF CHEMOTHERAPY

| Aponym of chemo-therapy regimen: ..... | Start of treatment; date | End of treatment; date | No. of cycles given |
|---|---|---|---|

## REASON FOR STARTING CHT

☐ CS I high-risk group ☐ CSMk+ ☐ CS II ☐ PS II ☐ CS III ☐ CS IV ☐ Relapse after CR

## 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 ☐ Unaccetable toxicity

☐ Treatment refused ☐ Other, specify:

Major violation of protocol

☐ no ☐ yes, specify:



## RESPONSE

| ☐ Not evaluable | ☐ Complete Remission<br>Date: | ☐ Partial remission<br>Date: | ☐ Stationary disease<br>Date: | ☐ Progression<br>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

## 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 |
| Leucocytes ($x10^9$/l) | ≥4.0 | 3.0–3.9 | 2.0–2.9 | 1.0–1.9 | 1.0 |
| Platelets ($x10^9$/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 x N[a] | 1.26–2.5 x N[a] | 2.6–5 x N[a] | 5–10 x N[a] | 10 x 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 |

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

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

**SWENOTECA PROGRAM II** **5**
**Follow-up form**

| **Swedish patients:** | **Norwegian patients:** |
|---|---|
| Swenoteca sekretariatet | Kreftsekretariatet |
| Tumörregistret, Lasarettet i Lund | Kreftavdelingen |
| S–221 85 LUND | N–7006 Trondheim |

Hospital and Department

Physician | Date

## CLINICAL EVALUATION

| **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 | | | |
| β-HCG | | | |
| LDH | | | |

## PERFORMANCE ①

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



## LATE EFFECTS OF TREATMENT ②

| Dry ejaculate | Reduced libido | Impotence |
|---|---|---|
| ☐ no ☐ yes | ☐ no ☐ yes | ☐ no ☐ yes |

Other,
☐ specify:

## STATUS

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

## IN CASE OF RELAPSE

| **Lymphnodes** | Metastases | Size of largest metastasis (mm x mm) | **Extra Lymphatic** | Metastases | Size of largest metastasis (mm x mm) |
|---|---|---|---|---|---|
| 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 evaluavle | | 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 ☐ Surgery ☐ Radiotherapy ☐ Chemotherapy

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 Evaluated one year after completion of all treatment.