SWEDISH & NORWEGIAN TESTICULAR CANCER PROJECT

SWENOTECA V

TREATMENT AND SURVEILLANCE OF CLINICAL STAGE I and IIA (CS I & CS IIA) SEMINOMATOUS TESTICULAR CANCER

TREATMENT OF CLINICAL STAGE IIB-IV (CS IIB - IV) IN SEMINOMATOUS TESTICULAR CANCER AND RELAPSE IN PREVIOUSLY IRRADIATED PATIENTS OR IN SURVEILLANCE PATIENTS

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PREFACE

The Swedish & Norwegian Testicular Cancer Project, the SWENOTECA started in 1981 with programs for staging, treatment and follow-up of non-seminomatous germ cell cancer.
The present program provides an expansion of the cooperation within the SWENOTECA to include seminomatous germ cell cancer.

The working committee initially conducted a survey on current staging and treatment practice amongst the participating centers in the SWENOTECA. This survey was the starting point for the work with the program presented below.

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CONTENTS: **Page**

Diagram of staging and treatment principles 4

1 Introduction 5

2 Objectives (CS I and CS IIA) 6

3 Principles of investigation 6

4 Principles of treatment (CS I and CS IIA) 8

5 Clinical/Pathological staging 11

6 Surgical procedures 13

7 Criteria for inclusion 14

8 Pre-irradiation assessments 14

9 Radiotherapy 15

10 A Follow-up - Seminoma CS I and CS IIA after radiotherapy 18

10 B Follow-up - Seminoma CS I. Surveillance 19

10 C Follow-up - Seminoma CS IIB – CS IV 20

11 Treatment of advanced seminoma 21

12 Treatment of relapse after surveillance or after radiotherapy 23

13 Conclusion with regard to treatment of advanced seminoma 23

REFERENCES 24

ADDENDUM:

Reporting forms

Information to patients

DIAGNOSIS

Histopathologically confirmed seminomatous testicular cancer
with normal AFP before orchiectomy

Vascular invasion or not (Vasc+/Vasc-)
Size of tumor

Note:

1) If possible, biopsy of the contralateral testis should be performed
2) Blood samples for determination of LH, FSH, testosterone and SHBG should be obtained before orchiectomy
3) Patients should preferentially be admitted for sperm count and cryopreservation, depending on the patient's choice

CLINICAL STAGING PROCEDURES

Repeated serum samples for tumour markers - β-HCG, AFP, LDH, PlAP
Clinical investigation
CT scan and X-ray of the chest
CT scan of the abdomen and pelvis
(Ultrasound or MRI if uncertainty with regard to findings with the CT scan)
TNM - classification

CLINICAL STAGE I AND STAGE IIA DISEASE (CS I & CS IIA)

↓

Radiotherapy (CS I & CS IIA) or Surveillance (only CS I)

Follow up

NOT CS I OR CS IIA disease or relapse

↓

Protocol for treatment of advanced seminomatous testicular cancer or relapse

1. INTRODUCTION

Pure seminoma constitutes approximately 60% of all germ cell tumours. Seminoma is rare before puberty and the peak incidence occurs between thirty and forty years of age. Over the last 20 years the incidence of testicular germ cell tumours has increased. Data from the Swedish and Norwegian cancer registries predict an increase in seminoma from about 90 cases annually in Sweden (1983-1987) to about 140 (1998-2002) and from about 75 cases annually in Norway (1983-1987) to about 130 (1998-2002) (1). Thus, the incidence of seminoma both in Sweden and Norway seems to be increasing.

At the time of diagnosis, approximately 80% of the patients will be in clinical stage I or IIA (CS I or CS IIA).

Little is known about etiological risk factors for developing testicular tumours. Ten percent of the patients have had a previous history of cryptorchidism. Some epidemiological studies show a significantly increased percentage of pure seminoma as compared to germ cell tumours of other histologies in men with undescended testis.

A rising incidence for cryptorchidism has also been observed and that may indicate a further increase in testicular tumour incidence.

Due to an extreme radiosensitivity, seminoma has for decades been documented to be a curable malignancy by radiotherapy in early stages. The development of effective chemotherapy has also improved the curability for advanced disease, and the total cure rate is now above 95%.

More recently, several centers have reported on the success of surveillance in stage I seminoma. Although the main treatment will be radiation therapy, patients will be given the opportunity to choose between these two options.

The CS I & CS IIA seminoma protocol is estimated to have a patient accrual time of 3 years including more than 300 patients.

2. OBJECTIVES (CS I and CS IIA)

2.1 To register all patients with seminomatous testicular cancer within the multicenter setting of the SWENOTECA in order to maintain or increase the quality assurance of staging and therapy, thereby maintaining and possibly improving the good results in the treatment of seminomatous germ cell tumour in CS I or CS IIA with a lower radiation dose.

2.2 To evaluate recurrence rate and survival in patients undergoing post-orchidectomy radiotherapy.

2.3 To evaluate recurrence rate and long-term outcome of patients on surveillance.

2.4 To standardize the staging procedure, treatment and follow up in patients with seminomatous germ cell tumour in clinical stage I or IIA (CS I or CS IIA).

2.5 To evaluate late side effects after adjuvant radiotherapy of the retroperitoneum (e.g., neurologic and hormonal long term effects, carcinogenic effects).

2.6 To evaluate the effect of surgery and adjuvant para-aortic and ipsilateral iliacal radiation on gonadal function as reflected in changes of serum LH/FSH, testosterone and SHBG (sex hormone binding globulin).

2.7 To evaluate the value of the serum markers β-HCG, LDH placental alkaline phosphatase (PlAP**)** in the staging procedure and follow up, and as prognostic markers.

3. PRINCIPLES OF INVESTIGATION

3.1 *Clinical diagnosis*

Induration and enlargement of the testicular parenchyma are the classical clinical signs of a testicular tumour. In approximately one tenth of cases, presenting symptoms are essentially non-testicular. Ultrasound in the clinical work-up of testicular tumours has provided a major improvement of the diagnostic procedure (2).

Transscrotal needle aspiration or biopsy from the tumour must be avoided, due to the possibility of tumour cell contamination and implantation in the biopsy area.

3.2 *Histology*

Histopathological diagnosis is performed according to classical histopathological criteria. Immunohistochemical studies of seminomas are rarely indicated, but may be helpful in complex cases, especially those that are overgrown by lymphocytes and resemble lymphoma.

Most seminomas contain very little keratin, or the immunoreactive epitopes of keratins are not readily detectable in paraffin-embedded tissue. This fact is most useful for distinguishing seminomas from embryonal carcinoma cells.

Several variants of seminoma have been described. Today such subclassifications are considered to be of no practical value. For example, the term anaplastic seminoma was previously used for tumours showing cytologic pleomorphism and high mitotic activity. However, the survival of patients with these tumours is not different from those with classic seminoma and does not influence management (3-5); therefore, the value of this concept has been challenged and to some extent abandoned.

Spermatocytic seminoma is a distinct tumour of uncertain histogenesis and occurs in elderly patients. The benign character and good prognosis of the spermatocytic variant of seminoma should be acknowledged. No adjuvant radiotherapy in this subgroup is warranted (5*) and this seminoma entity is not included in the current protocol.*

3.3 *Biochemical tumour markers*

The importance of alphafoetoprotein (AFP) and the β-chain of human chorionic gonadotrophin, β-HCG, as tumour markers have been established for non-seminomatous testicular cancer (1). On the other hand, we lack sensitive and specific tumour markers for seminoma.

The detection of elevated levels of AFP concomitantly with a histological diagnosis of seminoma, implies that the tissue specimens should be reevaluated with respect to yolk sac elements in the tumour and the patient treated accordingly. A few patients, however, have their "normal" AFP level slightly above the usual limit (= 1.5 upper limit). One should be aware that reparative and infectious/viral processes of the liver may induce a moderate increase in AFP. Therefore, if the elevated level of AFP is modest, at least one confirmatory test should be performed if no yolk sac elements are found, before starting treating the patient as having a non-seminoma.

Depending on tumour volume, 20-50% of patients with seminoma have elevated levels of β-HCG (6). An increase in β-HCG to 200 should be considered consistent with a pure seminoma. In case of higher values the tissue specimen should be thoroughly reevaluated with respect to non-seminomatous components.

Causes of false positive β-HCG results include cross-reactivity of the antibody with luteinizing hormone (LH) and treatment-induced hypogonadism (5).

Lactate dehydrogenase (LDH) is a widely distributed enzyme of glycolytic metabolism and is released by many tissue types following cell damage. Total serum LDH levels are elevated in about 80% of patients with metastatic seminomatous testicular cancer (7).

Placental alkaline phosphatase (PlAP) has been reported to have the highest sensitivity to detect metastatic disease, with a relatively high specificity, and also the best method (as compared to β-HCG and LDH) to indicate a relapse (8). Serum PlAP has also been reported to be initially increased in about 50% of patients with seminoma, the mean magnitude of elevation being several times the normal value (9).

No significant correlation between PlAP and LDH or between PlAP and β-HCG has been found (9). Therefore, a combination of these three markers should be of value, with a reported positive identification rate of more than 80% (8, 9). Whether the patients are smokers or non-smokers should be taken into consideration when evaluating a PlAP value, as this marker has been found to be useful only in non-smokers (10). Of this reason too, serum PlAP assay should not stand alone as a marker for seminoma.

3.4 *Diagnostic radiography*

Chest x-ray and CT-scan of the abdomen and pelvis are mandatory in the staging procedure of testicular cancer. Computerised tomography (CT-scan) of the chest will be done because a CT-scan of the chest also may be useful as a reference examination. Ultrasound of the abdomen is optional in cases of an inconclusive CT-scan. In such cases magnetic resonance imaging, MRI, may also be used.

3.5 *Fertility measures and hormonal analyses*

Before radiation therapy sperm count and sperm cryopreservation are recommended and should be discussed with the patient. Cryopreservation is however optional, depending on the patient's choice.

In addition, before orchiectomy and before start of radiation therapy or surveillance, LH/ FSH, testosterone and SHBG should be analysed for evaluation of current and later sexual function/dysfunction. The hormone analyses should preferentially be done in the morning or at least before noon (due to their circadian stage dependent variations).

4. PRINCIPLES OF TREATMENT (CS I and CS IIA)

4.1 *Introduction*

The standard treatment of early stage seminoma is radiotherapy to the retroperitoneal lymph nodes. This treatment is very effective and based on the knowledge that seminoma cells are extremely radiosensitive and on their predictive nodal pattern of metastatic spread. Of newly diagnosed patients with seminoma, approximately 70% are in stage I according to clinical staging procedures. Of these, about 85% have true stage I disease, while the remaining 15-20% have not yet detectable metastases, mainly in the paraaortic lymph nodes (11).

4.2 *Radiotherapy of the regional lymphatics vs. surveillance*

With the experience of cis-platinum containing chemotherapy regimens assuring high cure rates for advanced testicular cancer, a surveillance policy has been discussed. The main reason for a surveillance policy would be to spare patients already cured by orchiectomy from acute and late toxicity of radiotherapy.

In the near future, risk factors for occult metastatic disease of CS I seminoma will be better defined. Further evaluation of such factors will probably then make surveillance a more frequent chosen strategy. Until then, prophylactic irradiation will be the most frequent option within the SWENOTECA group for management of patients with CS I seminoma. However, patients will be given the possibility of choosing surveillance after orchiectomy after written and oral information.

4.3 *Radiotherapy*

The major reason for maintaining radiotherapy as standard treatment is the excellent results in terms of recurrence and survival. When compiling ten series including 1765 patients, there were only two in-field recurrences. These two particular patients were treated with a total dose of 15 and 21 Gy, respectively, while the majority of patients received a total dose between 25 and 40 Gy given in 13 to 20 fractions (11). Several studies indicate that a total dose of 25 Gy fractionated over three weeks will eradicate microscopic spread (12-14).

Adding the results from 14 series published from the last decade reporting on 2376 patients with stage I seminoma, the total relapse rate was 4,5% and 2,3% died from seminoma (11). Many of these patients were, however, staged and treated before the CT-scan era, and cis-platinum based chemotherapy was not available for all with recurrent disease. For patients examined with modern imaging techniques, the total relapse rate is probably 2-3% and the overall cure rate will most likely be very close to100%.

4.4 *Acute and late toxicity*

The acute toxicity due to the irradiation is minor, although a significant number of patients do suffer from nausea and a few from vomiting, usually a couple of hours after the daily treatments. These side-effects are, however, usually overcome by modern antiemetics.
An increased incidence of peptic ulceration occurring during the first six months after radiotherapy has been reported. Those afflicted usually have a previous history of peptic disease. Although the etiological connection to radiotherapy is unknown, this is a possible side-effect to keep in mind (15, 16).

Other gastrointestinal complications such as diarrhoea or bowel obstruction are dose-dependent and very rare with a dose of less than 30 Gy (17).

A diversity of explanations have been proposed to understand the impaired sperm production found in testicular cancer patients; e.g. congenital testicular dysfunction, disrupted blood-testis barrier leading to autoimmune mediated injury, and increased temperature and pressure effects of the primary tumour in the scrotum (18). Since most of seminoma patients are in the reproductive age, the additional damage to the remaining testis by the radiotherapy has to be kept as low as possible.

The remaining testis receives from 1-3% of the total dose from scattered radiation; i.e., a dose between 0.3-0.8 Gy when the total dose is 27 Gy. Doses less than 0.5 Gy usually cause a transient oligozoospermia, while higher doses cause azoospermia. If the dose is less than1.5 Gy, a recovery is seen to above 80% in the majority of cases within 2 years (19). That is, fertility should not be endangered by the radiotherapy in patients with normal sperm count before treatment. The scattered dose to the remaining testicle can be further minimized by using a shield, which should be recommended on a general basis. The radiation dose to the remaining testis should be measured at least once during treatment and should be less than 1% of the midplane dose.

Some radiotherapy centers offer sperm analysis and cryopreservation of sperm, which also are recommended on a general basis in the present protocol, being first discussed with the patient.

Data regarding second malignancies others than of contralateral testicular tumours are conflicting. An increased relative risk of leukaemia has been reported, three observed cases versus 0.85 expected. No excess risk was found for other malignancies (20).

In contrast, a Scottish study found an excess risk of less than two, of developing urinary and gastrointestinal tumours after a latency period of more than 15 years. However, no increased risk of leukaemia was observed (21).

One large Cancer Registry Study including 17 730 cases of testicular cancer (including NSGCT) collected between 1945 and 1984 representing 113 215 person-years at risk, showed a 20% overall excess of second cancers. In that study, no increased incidence was found regarding bladder or gastrointestinal tumours, but increased risks of melanoma, connective tissue tumours, non-Hodgkin's lymphoma and leukaemia were reported (22).

The finding of an increased incidence of cancers 15-20 years after irradiation for stage I seminoma, has initiated an interest in finding alternative treatment regimens.

One course of carboplatin, the first realistic alternative to radiotherapy, is currently being tested in several centers (23), including a MRC trial (22). Reported data from treatment centers using a single course of carboplatin as adjuvant therapy with no relapses in 114 patients are of considerable interest in providing an alternative to radiation therapy (24). Mature results from these trials and others are awaited.

One should be aware that one case of acute promyelocytic leukaemia after treatment for seminoma with carboplatin has been reported (21). However, it is not known whether patients with seminoma have a tendency to develop second malignancies regardless of any treatment for the primary disease (25).

So far with the present experience and taking the pros and cons into account, adjuvant radiotherapy is still considered the treatment of choice in stage I (and stage IIA) seminoma.

4.5 *Target volume and dose*

The lymph nodes primarily engaged in metastatic disease are those bilaterally in the paraaortic region and ipsilaterally in the iliac region. The standard target volume has therefore always included these two areas (5).

Prior inguinal or scrotal surgery, or an advanced primary tumour invading the tunica albuginea, have previously been a reason to include inguinal-femoral nodes and sometimes the involved half of scrotum into the target volume. The risk for recurrence in these areas is, however, very low and since any recurrence within this location is easy to detect at an early stage, it is no longer considered necessary to include these regions into the target volume (16).

The need for including the iliac nodes has also been questioned. A prospective randomized trial, run by the Medical Research Council, will hopefully answer this question. The MRC group has reported a 3% relapse rate in the pelvis and a mortality of 0.25% (1 of 400 patients died).

On the basis of these results the SWENOTECA group has therefore decided to include the ipsilateral iliac nodes in the recommended target volume, and thereby most likely avoid relapses in the pelvis.

Using modern staging, several studies have revealed that a total dose of 25 Gy given over three weeks is highly effective. Total doses of more than 30 Gy did play a role when the staging technique was less sensitive.

In the literature 1.8-2.0 Gy per fraction is recommended. According to a questionnaire answered by the SWENOTECA members the most commonly used dose was 1.8 Gy per fraction and day,
5 times weekly.

Given the guidelines above and using this fractionation the SWENOTECA group has agreed on a total dose of 25,2 Gy (1.8 Gy x 14) over a period of three weeks for CS I and 27.0 Gy (1.8 Gy x 15) for CS IIA.

Treatment should be started within 6 weeks after orchiectomy.

For radiotherapy technique see further 9.

4.6 ***Surveillance*** *(only Clinical Stage I)*

Adjuvant retroperitoneal radiotherapy after orchiectomy remains the treament of choice in most centers today. However, the success of surveillance in stage I non-seminomatous germ cell testis tumours (26, 27) and the establishment of curative chemotherapy for advanced disease, have led to re-examination of the standard treatment approach. Surveillance of stage I seminoma is growing in prominence as a means to treat these patients (28), although there have been few reports of long-term follow-up of surveillance alone for patients with stage I testicular seminoma (29, 30).

Starting in the early eighties three large groups have reported on a surveillance policy for stage I seminoma. With 506 patients recruited and a median follow-up of 30-33 months a relapse-rate of 6-18% was observed. Relapsing patients were treated with radiotherapy and/or chemotherapy and they are all living free of disease (31).

Surveillance studies generally have shown that 15-20% of patients relapse (32), and even higher relapse rates have been reported (33). The majority of relapses are in para-aortic lymph nodes. However, the available data from the surveillance and adjuvant radiotherapy series suggest that almost 100% of patients with stage I testicular seminoma are cured, whichever approach is chosen (26).

The main advantage of surveillance is that 80% of patients can be spared slightly toxic overtreatment. The main disadvantage is the need for frequent long-term follow-up, which is stressful to the patient. Good patient compliance, mandatory to an observation period policy, may be difficult on a long-term basis.

Surveillance protocols demand close follow-up with repeated clinical controls, chest x-rays, CT-scans or ultrasound of the abdomen and pelvis during at least 5 years. Furthermore, surveillance in seminoma, compared to non-seminomatous testicular cancer, is more difficult to perform because of the lack of reliable tumour markers. In seminoma, it is also known that late relapses may occur and therefore a prolonged follow-up might be necessary. The current experience regarding surveillance policy is that it is safe, provided the patient is co-operative.

There are several questions not yet answered concerning surveillance. First of all, quality of life aspects regarding the fear of relapse during surveillance versus side effects of radiotherapy have to be investigated.

During surveillance there might also be a risk for extended metastatic spread, causing the need of more toxic treatment. Finally the cost-benefit aspects have not yet been fully considered.

5A. CLINICAL STAGING: MODIFIED AFTER THE ROYAL MARSDEN HOSPITAL STAGING SYSTEM

CS I No evidence of metastases

CS Mk+ β-HCG persistently elevated (not declining according to its half-time), but no metastatic disease demonstrated

CS II **Metastatic disease restricted to abdominal nodes**

- A Maximal transverse diameter <2 cm
- B Maximal transverse diameter 2-5 cm
- C Maximal transverse diameter >5-10 cm
- D Maximal transverse diameter > 10 cm

CS III Supradiaphragmatic node involvement

For abdominal lymph nodes:
- 0 No metastases
- A-D According to CS II

CS IV Extra-lymphatic metastases

Lung substage:
- L1 ≤3 metastases, no metastases >2 cm
- L2 >3 - ≤20 metastases, no metastases >2 cm
- L3 ≤20 metastases, >2 cm
- L4 >20 metastases

For abdominal lymph nodes:
- 0 No metastases
- A-D According to CS II

- H+ Liver metastases
- Br+ Brain metastases
- Bo+ Bone metastases

Grouping according to Medical Research Council:

Small volume disease: CS Mk+, II_{A-B}, $III_{0-A-B, L1-2}$

Large volume disease: CS II_{C-D}, III_{C-D}, $IV_{C-D, L1-L2}$

Very large volume disease: CS $IV_{0-D, L3-L4}$; extralymphatic extrapulmonal metastases (bone, liver, brain)

5B. TNM PATHOLOGICAL AND CLINICAL CLASSIFICATION

T - Primary Tumour

The extent of the primary tumour is classified after radical orchiectomy; see pT.

pT - Primary Tumour

pTX Primary tumour cannot be assessed (if no radical orchiectomy has been performed, TX is used).
pT0 No evidence of primary tumour (e.g. histologic scar in testis).
pTis Intratubular germ cell neoplasia (carcinoma in situ).

pT1 Tumour limited to testis and epididymis without vascular/lymphatic invasion; tumour may invade tunica albuginea but not tunica vaginalis.
pT2 Tumour limited to testis and epididymis with vascular/lymphatic invasion, or tumour extending through tunica albuginea with involvement of tunica vaginalis.
pT3 Tumour invades spermatic cord with or without vascular/lymphatic invasion.
pT4 Tumour invades scrotum with or without vascular/lymphatic invasion.

N - Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 Metastasis with a lymph node mass 2 cm or less in greatest dimension or multiple lymph nodes none more than 2 cm in greatest dimension.
N2 Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension.
N3 Metastasis with a lymph node mass more than 5 cm in greatest dimension.

M - Distant Metastasis

MX Distant metastasis cannot be assessed.
M0 No distant metastasis.
M1 Distant metastasis.
  M1a Non-regional lymph node or pulmonary metastasis.
  M1b Distant metastasis other than to non-regional lymph nodes and lungs.

6. SURGICAL PROCEDURES

6.1 *Management of patients with testicular tumours*

Exploration of the testis should be performed on the basis of clinical and ultrasound investigations. The size of the tumour should be measured by ultrasound.

There is no place for transscrotal fine needle aspiration or biopsy from the tumour. Exploration is always warranted in cases of doubt on clinical grounds.

A blood sample must be taken for determination of tumour markers and level of hormones (LH/ FSH, testosterone, SHBG) before the exploration of the testis. In case of neglect, a sample has to be collected as soon as possible postoperatively.

6.2 *Exploration of the testis*

An incision identical to that performed in patients with inguinal hernia is done. The anterior wall of the inguinal canal is divided and the ductus deferens and spermatic vessels are dissected free at the internal opening of the inguinal canal. A vessel clamp is put on the spermatic cord close to the peritoneal fold.

The testis and epididymis are pushed out of the scrotum, dissected free from its surrounding fascia and put into a bowl. The inguinal field is covered with cloths and the tunica vaginalis is opened. A solid tumour surrounded by testicular parenchyma is highly suggestive of a malignant process. In cases of doubt, the tunica albuginea should be incised as well, the testis divided and a specimen sent for frozen section examination while the spermatic cord is clamped.

A suspicion of malignancy makes orchiectomy warranted.

When orchiectomy is the option, the testis is covered with cloths, the instruments used for incision of the tumour are removed and gloves are changed.

The inguinal field is uncovered, the ductus deferens and vessels are ligated and divided separately close to the peritoneal fold.

The testis, epididymis and spermatic cord are subjected to urgent histopathological examination, always including assessment of tumour infiltration in lymphatics and blood vessels. When infiltration is difficult to assess on routine H/E-sections, a variety of immunohistological techniques are available to improve the evaluation.

The testis is replaced into the scrotum only if both macro- and frozen section examinations reveal a benign lesion.

6.3. *Biopsy of the contralateral testis*

The testis is held firmly and a transscrotal incision is made laterally on the tunica vaginalis, long enough to see it clearly. After incising the parietal layer, make a small incision in the tunica albuginea to allow testicular tubules to bulge out. Snip off a tuft of tubules cleanly with fine, sharp scissors. Plunge scissors and biopsy at once into a specimen pot containing **Bouin's solution**. Close the incision in the tunica and skin separately with interrupted 4-0 absorbable sutures.

7. CRITERIA FOR INCLUSION (CS I and CS IIA)

7.1 ***Histologically confirmed seminomatous germ cell tumour of the testis.***
Slides of the tumour must be available for review by a panel of pathologists.

7.2 ***Clinical stage I or IIA disease with negative markers.***

- 7.2.1 No evidence of metastatic disease more than clinical stage IIA.
- 7.2.2 Normal CT-scan and X-ray of the chest.
- 7.2.3 Normal CT-scan of abdomen and pelvis or lymph nodes less than 2cm.
- 7.2.4 Normal tumour markers after orchiectomy.
- 7.2.5 No increase in β-HCG, LDH, PlAP or AFP at start of radiotherapy, i.e., tumour markers should be repeated before start of radiation therapy.

7.3 ***No horseshoe-kidney or other anomalities/conditions regarded as (relative) contra-indications to adjuvant radiotherapy.***

8. PRE-IRRADIATION ASSESSMENTS

8.1 Assay of serum AFP, β-HCG, LDH, and PlAP (if significantly elevated preorchiectomy)

8.2 CT-scan and X-ray of the chest

8.3 CT -scan of abdomen and pelvis (with i.v. contrast)

8.4 Serum creatinine

8.5 Haemoglobin, white blood cell count and platelet count

8.6 Liver enzymes (ALAT, ASAT, γ-GT, ALP)

8.7 LH/FSH, testosterone, SHBG

8.8 Sperm count and sperm banking are offered (optional).

8.9 Blood pressure measurement

9. RADIOTHERAPY

9.1 *Patient position and fixation*

The patient is placed in the supine position. Fixation should be used according to local practice for reproducible positioning of the patient during the whole treatment process.

9.2 *Definition of volumes*

9.3 *Anatomy of the regional lymph nodes*

The anatomy of the regional lymph nodes can (ideally) be demonstrated using lymphography, but this procedure is being used less and less. Alternatively, CT and US will be used.

The Clinical Target Volume (CTV) includes:
-lymph nodes in the ipsilateral iliac region
-pre-sacral nodes
-bilateral nodes retroperitoneally up to the level between the 10th and 11th thoracic vertebra.

If regional adenopathy is demonstrated, a Gross Tumour Volume (GTV) will have to be defined separately from the CTV for subclinical disease only.

9.4 *Organs at risk*

Kidneys
Contralateral testis
Medulla

9.5 *Field arrangement*

For treatment planning purposes, margins have to be added to the CTV (and GTV, when present). For details, see figure page 17.

A simulator procedure is mandatory.

Treatment is given with two parallel-opposed AP and PA equally weighted fields.

In order to avoid problems with adapting two separate fields it is recommended to use individually moulded shields or multileaf collimators to form the fields. (The penumbra of the beam has to be taken into account when delineating the shielded area).

For patients in reproductive age a lead shield should be used to protect the contralateral testis from scattered radiation.

Urography may be performed to control for renal function and position of kidneys in relation to radiation field (optional)**.**

The treatment portals ("L-field") are defined as:

- The para-aortic lymph node region, from *the upper border* of the 11th thoracic vertebra to the lower margin of the 5th lumbar vertebra and the ipsilateral iliac lymph nodes.

The AP/PA radiation portals must cranially include the transverse processes of the vertebrae**.** On the ipsilateral side it will correspond to a field border extending 1 cm laterally from the transverse process at the level of the kidney (and caudally not extending laterally more than half the width of the vertebral body from the lateral part of the vertebral bodies. On the contralateral side, the field border should not at any level extend laterally more than half the width of the vertebral body from the lateral part of the vertebral bodies.

Caudally the «dog leg» part of the field will extend from the junction between the 5th lumbar vertebra and S1 down to the ipsiliateral anterior inferior iliac spine, and from the level of the upper margin of the contralateral sacroiliacal joint to the lateral top of the obturator foramen.
See figure page 17.

9.6 *Beam quality*

Minimum 6 MV photons can be used with isocentric or SSD technique.

9.7 *Dose prescription*

CS I: 1.8 Gy per fraction 5 days weekly, 14 fractions to a total dose of 25,2 Gy, prescribed in the central axis of the mid-plane.

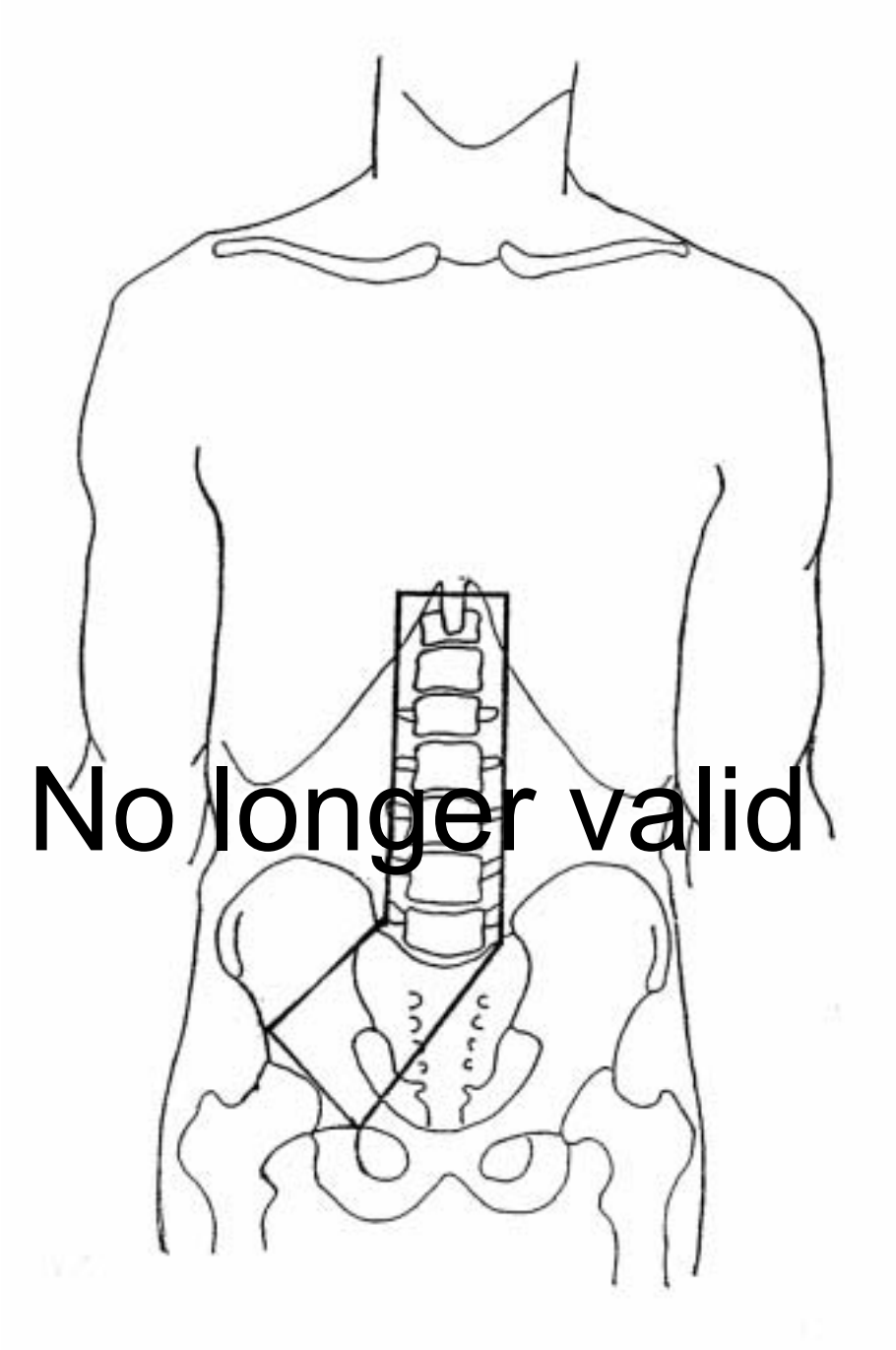
CS IIA: 1.8 Gy per fraction 5 days weekly, 15 fractions to a total dose of 27,0 Gy, prescribed in the central axis of the mid-plane.

9.8 *Quality controls*

a) Simulator film for documentation.
b) Verification film of the fields during treatment.
c) Measurement of the dose to the remaining testis.

9.9 *Reporting doses*

The dose to the planning target volume should be reported; i.e. 25, 2 Gy or other.



10A. FOLLOW-UP Seminoma CS I and CS IIA after radiotherapy

1st Year	**m 3**	clin invest, tm, s-creat, LH/FSH, testosterone, SHBG chest x-ray (optional)
	m 6	clin invest, tm, and s-creat (optional), chest x-ray, abdominal CT/US
	m 9	clin invest, tm
	m 12	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal ultrasound or CT-scan, sperm-count (optional)
2nd Year	**m 16**	clin invest, tm, s-hematol, s-creat, chest x-ray
	m 20	clin invest, tm, s-hematol, s-creat, chest x-ray (optional)
	m 24	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
3rd Year	**m 30**	clin invest, tm, s-hematol, s-creat, chest x-ray
	m 36	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal ultrasound or CT-scan, sperm count, LH/FSH, testosteron, SHBG, blood pressure
4th Year	**m 42**	clin invest, tm, s-hematol, s-creat, chest x-ray
	m 48	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
5th Year	**m 54**	clin invest, tm, s-hematol, s-creat, chest x-ray
	m 60	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG, blood pressure
6th-10th Year	**m 72**	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
	m 84	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
	m 96	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
	m 108	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG
	m 120	clin invest, tm, s-hematol, s-creat, chest x-ray, LH/FSH, testosterone, SHBG, blood pressure

clin invest - clinical investigation
tm - tumour markers (β-HCG, LD, PlAP)
s-creat - serum creatinine
s-hematol - haemoglobin, white blood cell count, platelet count

Notes:
Due to significant circadian variation in serum testosterone, samples for determination of this hormone (as well as the other hormones) should be obtained early in the day.

By including the ipsilateral iliac lymph nodes in the radiation field, the need for frequent CT-scans or ultrasound is reduced in the follow-up, thereby reducing diagnostic radiation to the patient as well as reducing costs and the need for manpower.

One should be aware that skeletal metastases may be the first relapse.

10B. FOLLOW-UP **Seminoma CS I. Surveillance.**

1st Year	**m 3**	clin invest, tm, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 6	clin invest, tm, s-creat, chest x-ray, abdominal CT/US
	m 9	clin invest, tm, s-creat, chest x-ray, abdominal CT/US
	m 12	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
2nd Year	**m 15**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 18	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 21	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 24	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
3rd Year	**m 28**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 32	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 36	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US sperm count, LH/FSH, testosterone, SHBG, blood pressure
4th Year	**m 42**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 48	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
5th Year	**m 54**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 60	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US LH/FSH, testosterone, SHBG, blood pressure
6th-10th Year	**m 72**	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 84	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 96	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 108	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 120	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US

clin invest - clinical investigation
tm - tumour markers (β-HCG, LD, PlAP)
s-creat - serum creatinine
s-hematol - haemoglobin, white blood cell count, platelet count
Ultrasound (US) should be performed as often as possible to reduce the X-ray exposition of repeated CT-scans.

Note: One should be aware that skeletal metastases may be the first relapse.

10C. FOLLOW-UP Seminoma CS IIB - CS IV.

1st Year	**m 2**	clin invest, tm, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 4	clin invest, tm, s-creat, chest x-ray, abdominal CT/US
	m 6	clin invest, tm, s-creat, chest x-ray, abdominal CT/US
	m 8	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
	m 10	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)
	m 12	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
2nd Year	**m 15**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 18	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 21	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 24	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
3rd Year	**m 28**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 32	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 36	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US sperm count, LH/FSH, testosterone, SHBG, blood pressure
4th Year	**m 42**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 48	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US
5th Year	**m 54**	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US
	m 60	clin invest, tm, s-hematol, s-creat, chest x-ray, abdominal CT/US LH/FSH, testosterone, SHBG, blood pressure
6th-10th Year	**m 72**	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)
	m 84	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)
	m 96	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)
	m 108	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)
	m 120	clin invest, tm, s-hematol, s-creat, LH/FSH, testosterone, SHBG, chest x-ray, abdominal CT/US (optional)

clin invest - clinical investigation
tm - tumour markers (β-HCG, LD, PlAP)
s-creat - serum creatinine
s-hematol - haemoglobin, white blood cell count, platelet count
Ultrasound (US) should be performed as often as possible to reduce the X-ray exposition of repeated CT-scans.

Note: One should be aware that skeletal metastases may be the first relapse.

11. TREATMENT OF ADVANCED SEMINOMA (CS IIB - CS IV)

11.1 *Present treatment policies*

Generally, the present policies for treatment of advanced seminomatous germ cell tumours are similar to those for the nonseminomatous. For = stage IIB disease cis-platinum based chemotherapy is the accepted standard. In Scandinavia, a combination of cis-platinum and etoposide with the same doses as for non-seminomatous tumours in the BEP regimen is used, but most centers leave out the bleomycin.

11.2 *Treatment results*

Even advanced seminomatous tumours usually have a good prognosis. In a material from MSKCC with 142 patients with advanced seminoma, 86% were alive and had achieved a durable response with a median follow-up of 43 months. In the same material, it was observed that an elevated pretreatment serum concentration of LDH or β-HCG predicted an inferior survival, but that among 33 patients with extragonadal tumours (19 mediastinal, 13 retroperitoneal, 1 unknown primary) 32 (97%) were alive and free of disease. The conclusion was drawn that, irrespective of primary site, advanced seminoma has a favourable response to cis-platinum based chemotherapy and should be considered good risk (34). A study from the Royal Marsden Hospital has also shown excellent treatment results with cis-platinum or carboplatinum based chemotherapy (35).

A subtype of seminoma, "atypical seminoma", may have a more aggressive clinical course and can be associated with the presence of elevated AFP(!) or β–HCG levels in refractory patients (36, 37). The histologic characteristics include an increased mitotic index and nuclear-to-cytoplasmatic ratio, nuclear pleomorfism, indistinct cytoplasmatic membranes, and a distinct immunohistochemical staining pattern. Like classic seminoma, it generally does not express cytokeratin, but unlike classic seminoma it does express type1 precursor to blood-group antigens. It is possible that atypical seminoma represents an early transformation to non-seminomatous histology rather than a true seminoma. In accordance with the SWENOTECA III and IV protocols for NSGCT, *all tumours associated with an elevated AFP level should be treated as NSGCT (see also §3.3, p.7).*

Based on the favourable prognosis for seminoma with existent chemotherapy schedules, regardless of location of the primary tumor, there is no urgent need for an improvement in today's standard therapy.

In contrast to NSGCT, seminomatous tumours are often characterised by a slow clinical regression rate. In a recently published EORTC study, 16 of 17 patients with retroperitoneal masses of 10 cm at presentation had a persistent mass immediately after chemotherapy. Three of these were resected within the following six months and showed complete necrosis. Four dissolved during the first year of follow up, but nine lesions persisted for 1 year without leading to relapse (38). In addition to the fact that tumour markers are normal in approximately half of the patients with advanced disease, this leads to difficulties in early evaluation of treatment response. It can be noted, however, that in the Royal Marsden material from their surveillance protocol between 1979 - 1985 for clinical stage I seminoma, 26 relapses (74%) were revealed by rising serum marker levels (35).

11.3 *First line chemotherapy recommendations*

Patients with stage $\geq$ IIB disease should receive cis-platinum based chemotherapy after orchiectomy.

Four courses of EP (etoposide, 100 mg x m-2 x d-1 x 5 d + cis-platinum, 20 mg x m-2 x d-1 x 5 d) are recommended. Except for the absence of bleomycin this therapy is identical to BEP as

described in the SWENOTECA protocol for NSGCT. Bleomycin has been omitted because of the risk of pulmonary toxicity.
Even with low volume disease 4 cycles of EP is recommended.

However, in the case of highly advanced seminoma; i.e., very large volume disease, SWENOTECA recommends treatment according to the BEP-regimen from start of therapy.

In case of protracted neutropenia or severe neutropenic-related infection, treatment with hematopoietic growth factor should be considered, starting 24 hours after the end of the next course of cytotoxic therapy.

Evaluation of response should be performed after 2 courses of therapy. In case of no or slow reduction in tumour marker (β-HCG or LDH) or no reduction in tumour size (evaluated by CT scan), intensified therapy with addition of ifosfamide should be recommended.

11.4. *Recommended treatment policy and monitoring of treatment effects*

Residual masses often occur after chemotherapy of advanced seminoma. Ninety percent of these masses contain fibrosis only (39, 40). The finding of teratoma is extremely rare. It has been reported that a residual mass with a diameter > 3 cm after chemotherapy contains residual tumour in about 30-40 percent of cases. Surgery was suggested to determine the histology of the tissues for selection of further measures (39). However, observation after chemotherapy followed by radiotherapy when progressive disease is detected by non-invasive methods, has been recommended as well (41). Postchemotherapy surgery in patients with an advanced seminoma is associated with substantially higher per- and postoperative complications as compared to patients with advanced non-seminoma. Thus, current and comparable options in terms of efficacy for management of postchemotherapy masses include observation and radiotherapy. Such postchemotherapy radiotherapy should be given to limited fields and at doses from 36-40 Gy. Currently, routine postchemotherapy surgery is not recommended in patients with seminoma.

Based on the documentation in the previous section, and that at present no existing non-invasive technique can reliably differentiate viable malignant tumour from necrotic or fibrotic residues, we recommend that patients with slowly regressing but persisting radiological findings (including masses > 3cm) after primary chemotherapy are closely monitored with an appropriate radiological method (CT, MRI) and serum markers. Consolidating radiotherapy after four courses of chemotherapy is in this situation and at this time not considered indicated. Thus, in the SWENOTECA protocol, the basic option is observation for at least 6 months after chemotherapy.

In conclusion: In the SWENOTECA protocol it is recommended that patients with advanced seminoma who have normal radiographs or a small residual mass (diameter < 3 cm) after chemotherapy are observed without further intervention. Patients with an enlarged residual mass (diameter > 3 cm) are observed for at least 6 months after chemotherapy. In cases when the residual mass is persisting and stable, the choice is between continued observation, irradiation or proceeding with surgery. In cases of surgery, resection of the tumour is preferred; when this is not possible, a biopsy should always be taken. If histopathology reveals residual disease, radiotherapy should be administered. Progressive disease of the initially treated volume should be treated either with surgery, radiotherapy or second line chemotherapy. Thus, the actual treatment option should be left open to be decided based upon an individual case evaluation within the responsible treatment center.

11.5 *Second line chemotherapy*

Four courses of BEP-IF (cis-platinum, 20 mg x m-2 x d-1 x 5 d + etoposide 75 mg x m-2 x d-1 x 5 d + ifosfamid, 1.200 mg x m-2 x d-1 x 5 d + bleomycin 30.000 I.E. x d-1 + 5 + 16). See the

SWENOTECA protocol for NSGCT for further information on procedures for drug administration and criteria for dose reduction.

11.6 ***Third line chemotherapy*** (alternative regimens with platinum resistance)

EMA-CO. POMB-ACE (42). See the SWENOTECA protocol for NSGCT for further information on procedures for drug administration and criteria for dose reduction.

High-dose chemotherapy with stem cell support will be an optional treatment modality. See the SWENOTECA protocol for NSGCT for further information on procedures for drug administration.

12. TREATMENT OF RELAPSE AFTER SURVEILLANCE OR AFTER RADIOTHERAPY

In case of a relapse = 2cm in the retroperitoneum in the surveillance group, the treatment can be either radiation treatment to a L-field to 27.0 Gy to 30.6 Gy, or chemotherapy.

Chemotherapy should be given as follows: 3-4 courses of EP (etoposide, 100 mg x m-2 x d-1 x 5 d + cis-platinum, 20 mg x m-2 x d-1 x 5 d) are recommended. Except for the absence of bleomycin this therapy is identical to BEP as described in the SWENOTECA protocol for NSGCT.

It is today concluded that the dose-limiting effect of prior radiotherapy is not evident in patients who have undergone moderate dose infradiaphragmatic radiotherapy only (43). In particular, there is no evidence for an increased failure rate of salvage treatment in patients relapsing after modern radiotherapy of stage I seminoma.

One should today be aware that combination of radiotherapy and intensive chemotherapy should be avoided whenever possible due to the increased risk of acute and particularly long-term toxicity, including induction of second malignancies (25, 44, 45).

13. CONCLUSION WITH REGARD TO TREATMENT OF ADVANCED SEMINOMA

Cisplatin-based combination chemotherapy represents the treatment of choice in the majority of patients with advanced seminoma. Due to the age and general condition in patients, individualised treatment is often necessary based on an awareness of prognostic factors. The presence of non-pulmonary visceral metastases and an elevated serum LDH represent independent adverse factors for progression-free survival. Postchemotherapy surgery is only necessary occasionally, but should be considered in young patients with a persistent residual mass and should be done with increasing masses. The combination of intensive chemotherapy and large-field radiotherapy should be avoided (46).

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SWENOTECA V, SEMINOM I/IIA
Registreringsblankett IIB-IV

Svenske pasienter	Norske pasienter
Swenoteca sekretariatet	Kontor for klinisk kreftforskning
Tumörregistret	Onkologisk avdeling
Universitetssjukhuset	Haukeland Sykehus
221 85 Lund	5021 Bergen

Sykehus

Avdeling **Lege**

Navn _____

Født (d/m/å) ☐☐.☐☐.19☐☐ **Personnr.** ☐☐☐☐☐

Fylles ut av Kontor for klinisk kreftforskning: **Sykehusnr.** ☐☐☐ **Pasientnr.** ☐☐☐☐

Orchiektomi

☐ nei ☐ ja Dato (d/m/å) ☐☐.☐☐.20☐☐ Malign tumor i testis ☐ nei ☐ ja Kontralat. testisbiopsi ☐ Cis ☐ ikke Cis ☐ ikke utført

Sykehus Pat. avd. PAD nr. ☐☐☐☐☐☐ - ☐☐ år

Orchiektomi Side ☐ hø ☐ ve Størrelse tumor ☐☐☐ x ☐☐☐ mm ☐ Vasc - ☐ Vasc + Spermiogram utført ☐ nei ☐ ja

Hormonanalyse før orchiektomi

FSH ☐☐,☐ LH ☐☐,☐ Testosteron ☐☐,☐ SHBG ☐☐☐,☐

Hormonanalyse før strålebehandling

FSH ☐☐,☐ LH ☐☐,☐ Testosteron ☐☐,☐ SHBG ☐☐☐,☐

BT

Syst. ☐☐☐

Diast. ☐☐☐

Tumormarkører

Øvre normalverdi og enhet (egen lab.) AFP ☐☐ ..... β-HCG ☐☐ ..... LD ☐☐☐ PlAP ☐☐ ☐ Røyker - ☐ Røyker +

Før orchiektomi

Dato (d/m/å)			
☐☐.☐☐.20☐☐	AFP ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	β-HCG ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	LD ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	PlAP ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført

Etter orchiektomi (ved definitiv stadieinndeling)

Dato (d/m/å)			
☐☐.☐☐.20☐☐	AFP ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	β-HCG ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	LD ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført
☐☐.☐☐.20☐☐	PlAP ☐☐☐☐☐,☐	☐ normalt	☐ forhøyet ☐ ikke utført

Tumormarkør(er) indikerer fremdeles tumor ☐ nei ☐ ja

Metastaser

Lymfeknutemetastaser		Største metastase (mm x mm)
Inguinalt	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Iliakalt	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Paraaortalt	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Retrocruralt	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Mediastinalt	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Supraklav	☐ nei ☐ ja	☐☐☐ x ☐☐☐

Ekstralymfatiske metastaser		Største metastase (mm x mm)
Lunge	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Antall lungemetastaser		☐☐
Skjelett	☐ nei ☐ ja	
Lever	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Hjerne	☐ nei ☐ ja	☐☐☐ x ☐☐☐
Annet	☐ nei ☐ ja	Lok.:

Klinisk stadieinndeling ①

☐ CSI ☐ CSIII ☐ CSMk+ ☐ CSII ☐ CSIV

TNM-klassifikasjon ☐ pTX ☐ pT0 ☐ pTis ☐ pT1 ☐ pT2 ☐ pT3 ☐ pT4 ☐ NX ☐ N0 ☐ N1 ☐ N2 ☐ N3 ☐ MX ☐ M0 ☐ M1

Størrelse lymfeknuter ☐ A ☐ B ☐ C ☐ D

Gruppering i følge MRC ② ☐ small volume ☐ large volume ☐ very large volume

Behandling ☐ strålebehandling ☐ surveillance ☐ kjemoterapi

47713

① Klinisk stadieindelning: modifierad efter RMH

CS I	Inga tecken på metastaser
CS Mk+	AFP och/eller β-HCG kvarstående förhöjda (faller ej enl sin halveringstid) men inga metastaser påvisbara
CS II	Metastaser begränsade till abdominella lymfkörtlar
A	maximal transversell diameter <2 cm
B	maximal transversell diameter 2–5 cm
C	maximal transversell diameter >5–10 cm
D	maximal transversell diameter >10 cm

CS III Metastaser i lymfkörtlar ovan diafragma

För abdominella lymfkörtlar gäller:

0	inga metastaser
A-D	enl ovan CS II

CS IV Extralymfatiska metastaser

För lungmetastaser gäller:

L_1	≤3 metastaser, ingen >2cm
L_2	>3 – ≤20 metastaser, ingen >2cm
L_3	≤20 metastaser, >2cm
L_4	>20 metastaser

För abdominella lymfkörtlar gäller:

0	inga metastaser
A–D	enl ovan CS II

② Gruppering enl Medical Research Council

Small volume disease	CS Mk+, $II_{A–B}$, $III_{0-A–B}$, $IV_{0–A–B, L1–L2}$	
Large volume disease	CS $II_{C–D}$, $III_{C–D}$, $IV_{C–D, L1–L2}$	
Very large volume disease	CS $IV_{0–D, L3–L4}$;	extralymfatiska extrapulmonella metastaser (skelett, lever, hjärna)

SWENOTECA V, SEMINOM I/IIA
Behandlingsblankett IIB-IV

Svenske pasienter	Norske pasienter
Swenoteca sekretariatet	Kontor for klinisk kreftforskning
Tumörregistret	Onkologisk avdeling
Universitetssjukhuset	Haukeland Sykehus
221 85 Lund	5021 Bergen

Sykehus

Avdeling **Lege**

Navn _____

Født (d/m/å) __.__.19__ **Personnr.** _____

Fylles ut av Kontor for klinisk kreftforskning: **Sykehusnr.** ___ **Pasientnr.** ____

Primærbehandling

Strålebehandling __,__ Gy ☐ L-felt ☐ paraaortalt ☐ annet — Første beh.dag (d/m/å) __.__.20__ — Siste beh.dag (d/m/å) __.__.20__

Regime 1 - Kjemoterapi (ved metastatisk sykdom) ☐ EP ☐ annet — Første beh.dag (d/m/å) __.__.20__ — Antall kurer __

Vekstfaktor gitt ☐ nei ☐ G-CSF ☐ annet , spes.:

Siste beh.dag (d/m/å) __.__.20__ — **Årsak** ☐ terapisvikt ☐ annen årsak ☐ ferdig program ☐ bivirkninger spes.:

Dosereduksjon har forekommet ☐ nei ☐ ja — Intervallforlengelse har forekommet ☐ nei ☐ ≤1 uke ☐ >1 uke

Regime 2 ☐ BEP-if/PEI ☐ annet — Første beh.dag (d/m/å) __.__.20__ — Antall kurer __

Årsak til Regime 2 ☐ dårlig effekt av EP ☐ vital cancer ved biopsi/RPLND

Vekstfaktor gitt ☐ nei ☐ G-CSF ☐ annet , spes.:

Siste beh.dag (d/m/å) __.__.20__ — **Årsak** ☐ terapisvikt ☐ annen årsak ☐ ferdig program ☐ bivirkninger spes.:

Dosereduksjon har forekommet ☐ nei ☐ ja — Intervallforlengelse har forekommet ☐ nei ☐ ≤1 uke ☐ >1 uke

Effekt av kjemoterapi (på grunnlag av markører og rtg.undersøkelser)

Dato (d/m/å) __.__.20__ ☐ CR ☐ PR ☐ SD ☐ PD ☐ ikke evaluerbart

Toxicitet ①

		Grad						Grad				
Hematologisk	hvite	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	Neurologisk	perifer neuropati	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
	tromb	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4		obstipasjon	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Renal	S-kreat	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	Infeksjon		☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
Pulmonal		☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	Andre		☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Strålebehandling etter kjemoterapi

☐ nei ☐ ja — Første beh.dag (d/m/å) __.__.20__ — Siste beh.dag (d/m/å) __.__.20__ — Dose __,__ Gy

Effekt av strålebehandling etter kjemoterapi

Dato (d/m/å) __.__.20__ ☐ CR ☐ PR ☐ SD ☐ PD ☐ ikke evaluerbart

Diagnostikk av resttumor ☐ cytologi ☐ biopsi

Kirurgi etter kjemoterapi

☐ nei ☐ ja — Dato (d/m/å) __.__.20__ — Pat. avd. — PAD nr. _____ - __ år

Type kirurgi, abdomen ☐ unilat RPLND ☐ bilat RPLND

Excision av resttumor ☐ lunge ☐ annen lok. , spes.: ☐ annen op., spes.:

PAD ☐ nekrose/fibrose ☐ modent teratom ☐ vital cancer

Radikal operasjon ☐ nei ☐ ja — Kirurgisk alvorlig kompl. ☐ nei ☐ ja , spes.:

Fortsatt behandling

☐ ferdig behandlet ☐ høydosekjemoterapi med rescue

☐ radioterapi ☐ annen behandling , spes.:

21154

① Gradering av toxicitet (WHO 1979)

	Grad 0	Grad 1	Grad 2	Grad 3	Grad 4
Hematologisk (vuxna)					
Vita x 10^9/l	≥ 4,0	3,0–3,9	2,0–2,9	1,0–1,9	< 1,0
Trombocyter x 10^9/l	≥ 100	75–99	50–74	25–49	< 25
Urinvägar					
S-Kreatinin	≤ 1,25xN	1,26–2,5xN	2,6–5xN	5–10xN	> l0xN
Lungor	Inga	Milda symtom	Ansträngnings-dyspnoe	Vilodyspnoe	Sängbunden p g a andningsinsuff.
Neurotoxicitet					
Perifer	Ingen	Paresthesier och/ eller nedsatta senreflexer	Svåra parestesier och/eller lätt svaghet	Intolerabla pare-stesier och/eller uttalad svaghet	Förlamning
Obstipation*	Ingen	Mild	Moderat	Uppspänd buk	Uppspänd buk och kräkningar
Infektion	Ingen	Smärre infektion	Moderat infektion	Svår infektion	Svår infektion med blodtrycksfall
Alopeci	Ingen	Minimal hårförlust	Moderat, fläckvis håravfall	Komplett håravfall men reversibelt	Icke reversibelt håravfall

N = Övre normalgränsen
* = Obstipation, inkluderar ej obstipation p g a morfinpreparat

SWENOTECA V, SEMINOM I/IIA
Oppfølgingsblankett IIB-IV

Svenske pasienter	Norske pasienter
Swenoteca sekretariatet	Kontor for klinisk kreftforskning
Tumörregistret	Onkologisk avdeling
Universitetssjukhuset	Haukeland Sykehus
221 85 Lund	5021 Bergen

Sykehus

Avdeling **Lege**

Navn _____

Født (d/m/å) . . 19

Personnr.

Sykehusnr.

Pasientnr.

Fylles ut av Kontor for klinisk kreftforskning:

☐☐☐ **måneders kontroll, dato (d/m/å)** ☐☐.☐☐.20☐☐

Klinisk bedømning

Klinisk undersøkelse	☐ nei	☐ normal	☐ recidiv	☐ uklart funn
Lungerøntgen	☐ nei	☐ normal	☐ recidiv	☐ uklart funn
CT av thorax	☐ nei	☐ normal	☐ recidiv	☐ uklart funn
CT av abdomen og bekken	☐ nei	☐ normal	☐ recidiv	☐ uklart funn
Ultralyd av abd. og bekken	☐ nei	☐ normal	☐ recidiv	☐ uklart funn
Annet	☐ nei	☐ normal	☐ recidiv	☐ uklart funn

	Nivå		
AFP	☐☐☐,☐	☐ normalt	☐ forhøyet
β-HCG	☐☐☐,☐	☐ normalt	☐ forhøyet
LD	☐☐☐,☐	☐ normalt	☐ forhøyet
PlAP	☐☐☐,☐	☐ normalt	☐ forhøyet
FSH	☐☐☐,☐	☐ normalt	☐ forhøyet
LH	☐☐☐,☐	☐ normalt	☐ forhøyet
Testost.	☐☐☐,☐	☐ normalt	☐ lavt ☐ subst.
SHBG	☐☐☐,☐	☐ normalt	☐ lavt ☐ høyt
BT Syst.	☐☐☐,☐		
BT Diast.	☐☐☐,☐		

Performance status i følge Karnofsky[1]

Karnofsky index ☐ 100 ☐ 80 ☐ 60 ☐ 40 ☐ 20 ☐ nedsatt pga annen sykdom

Seinreaksjon av behandling[2]

Retrograd ejakulasjon	Minsket libido	Impotens	Annen
☐ nei ☐ ja	☐ nei ☐ ja	☐ nei ☐ ja	☐ nei ☐ ja , spes.:

STATUS

☐ ingen tegn til sykdom (NED) ☐ recidiv ☐ annen ca. ☐ død av testis ca. ☐ død av annen ca.

☐ resttumor (inaktiv) ☐ bilat. testis ca. ☐ død av bivirkninger ☐ død av andre årsaker

Ved recidiv

Lymfeknutemetastaser

	Nei	Ja	Ikke evaluerbart	Største metastase (mm x mm)
Inguinalt	☐	☐	☐	☐☐☐ x ☐☐☐
Iliakalt	☐	☐	☐	☐☐☐ x ☐☐☐
Paraaortalt	☐	☐	☐	☐☐☐ x ☐☐☐
Retrocruralt	☐	☐	☐	☐☐☐ x ☐☐☐
Mediastinalt	☐	☐	☐	☐☐☐ x ☐☐☐
Supraklav	☐	☐	☐	☐☐☐ x ☐☐☐
Annet	☐	☐	☐	☐☐☐ x ☐☐☐

Annet, spes.:

Ekstralymfatiske metastaser

	Nei	Ja	Ikke evaluerbart	Største metastase (mm x mm)
Lunge	☐	☐	☐	☐☐☐ x ☐☐☐
Lever	☐	☐	☐	☐☐☐ x ☐☐☐
Hjerne	☐	☐	☐	☐☐☐ x ☐☐☐
Skjelett	☐	☐	☐	
Annet	☐	☐	☐	☐☐☐ x ☐☐☐

Annet, spes.: _____

Recidivdato (d/m/å) ☐☐.☐☐.☐☐☐☐

Symptom eller undersøkelse(r) som først signaliserte recidiv:

Pasienten går videre til

☐ fortsatt oppfølging

☐ kontroll avsluttet

Dødsdato (d/m/å) ☐☐.☐☐.☐☐☐☐

58898

① **Karnofsky index**

100 = Inga besvär

80 = Kan med viss svårighet fungera normalt

60 = Kräver hjälp tidvis med ADL men klarar sig huvudsakligen själv och behöver hjälp ibland

40 = Ofta sjukhusvårdad , kräver assistans med ADL och behöver vård

20 = Kräver sjukhusvård hela tiden

② Utvärderat ett år efter slutförd behandling

Informasjon om behandling av testikkeikreft av typen seminom i stadium I.

Du er nettopp blitt operert for kreft i testikkelen. En mikroskopisk undersøkelse av svulsten har vist at det dreier seg om typen seminom. Utredning med blodprøver og røntgenundersøkelser har ikke påvist spredning. På fagspråket benevnes dette stadium I.

Vi vet imidlertid at hos en del pasienter med testikkellcreft i stadium I, kan det foreligge spredning av kreftceller. Det skjer som oftest til lymfeknutene som ligger langs ryggraden inne i bukhulen. Hvis så er tilfelle, vil kreftcellene kunne formere seg og gi opphav til dattersvulster i lymfeknutene. Man kan hos enkelte pasienter også se spredning til andre organer. I din nåværende situasjonen foreligger det to alternative strategier: Bare oppfølging eller strålebehandling (se nedenfor). Vi mener på bakgrunn av undersøkelser flere steder i verden at disse to oppleggene er likeverdige. Uansett etterbehandling, vil minst 98% helbredes. Du har således en meget god prognose.

Begge behandlingsalternativer har sine fordeler og ulemper som beskrives nedenfor. Vi håper at du på denne bakgrunn settes i stand til å velge ett av alternativene. Vi vil selvfølgelig hjelpe deg ved å besvare de spørsmål du måtte ha.

1: Etterbehandling med strålebehandling mot mulige spredningsveier i bekkenet og på bakre bukvegg.

Man gir her strålebehandling mot de steder i bekkenet og på bakre bukvegg hvor det kan tenkes å foreligge spredning. Denne behandlingen var standardanbefalingen i Norge og Sverige frem til mars 1999.
Strålebehandlingen foregår over tre uker (i alt 14 behandlinger og med 5 behandlinger per uke). En av bivirkningene ved behandlingen er kvalme som vil kunne stilles med moderne kvalmestillende midler.

Det foreligger en viss risiko for at slik behandling på sikt kan føre til en ny kreftform hos noen. Hvor stor denne risikoen er, er vanskelig å anslå da dagens behandling er forskjellig fra den som ble gitt tidligere med hensyn tu den stråledose som blir gitt. Man vet derfor ikke sikkert om de undersøkelser som har påvist økt forekomst av ny kreft gjelder for dem som får behandling i dag.
Strå.lebehandling reduserer risikoen for tilbakefall i det bestrålte området nesten fullstendig (96 - 98%). De få tilbakefall som kommer, vil være lokalisert ovenfor mellomgulvet, noe som gjør at de er lette å oppdage.
Ulempen ved denne behandling er at 80% av pasientene får unødvendig strålebehandling.

2: Bare oppfølging.

Det blir ikke gitt etterbehandling, men du blir i stedet fuigt nøye opp med kontroller hver 3. måned de to første årene, deretter med lengre mellomrom. Ved å la vare å strålebehandle, vil risikoen for tilbakefall av sykdommen vare 15 til 20 %.
Tilbakefallet kan behandles med cellegiftkurer og man regner med at 90% av dem som får tilbakefall vil helbredes.
Ulempen ved denne oppfølging er at det vil bli flere røntgen-kontroller enn om man fikk behandling med stråler.

Den cellegiftkur man benytter ved et eventuelt tilbakefall benevnes EP-kur (eventuelt BEP-kur) og består av 2 eventuelt 3 forskjeilige cellegifter.
EP-kurer gis som en intravenøs infusjon av medikamentene cispiatin og etoposid i fem dager (ved BEP-kurer gis bieomycin i tillegg en gang i uken). Man må ligge inne i ca. en uke under behandlingen. Det vil være aktuelt å gi 4 kurer med 3 ukers mellomrom. De mest plagsomme

bivirkningene er kvalme og brekninger. Disse plagene kan som regel forhindres og alltid begrenses gjennom moderne kvalmebehandling.

All cellegiftbehandling gir akutte bivirkninger som i noen få tilfeller kan vare alvorlige. Det vii komme håravfall 2 til 4 uker etter den første cellegiftbehandiingen og etter hvert vil man miste alt håret. Håret starter normalt å vokse ut igjen noen uker etter siste kur.
Antallet hvite blodlegemer vil falie i de første to ukene etter hver cellegiftbehandling og man kan på grunn av dette vare mer mottakelig for infeksjoner. Blodverdiene vil som oftest bli normale igjen tre uker etter hver kur. Noen pasienter kan kjenne en plagsom tretthet som vedvarer mellom kurene og en måneds tid etter siste kur.

Som du skjønner finnes det forskjellige behandlingsaltemativer når man har testikkelkreft av typen seminom og i det stadiet du har. De ulike alternativene har sine fordeler og ulemper og man kan i dag ikke bestemt si hva man skal foretrekke. Vi ønsker derfor at du nøye leser gjennom denne informasjonen og prøver å finne ut hva som passer deg best. Det er også viktig at du diskuterer dette med din lege. Vi ønsker å la begge behandlingsaltemativer være åpne, og legger stor vekt på eventuelle ønsker og preferanser fra den enkelte pasient.