CHAPTER I

INTRODUCTION
I.1 GENERAL OUTLINE

Epidemiology

In the Netherlands, about 350 new patients per year are diagnosed with a malignant testicular germ cell tumor. This corresponds with an annual incidence of about 3 per 100,000. Germ cell tumors are the most prevalent type of malignancy in men aged between 20 and 35 years. Two to three per cent of the patients have bilateral tumors. Bilateral tumors usually occur metachronally, and only very rarely synchronously. Malignant germ cell tumors occasionally run in families, but it is not clear whether heredity plays a role.

Etiology

The only proven risk factor for the development of a testicular tumor is cryptorchidism. Twelve per cent of the testicular tumors arise in patients with an undescended testicle. The risk that a tumor will develop in an undescended testicle is 20 to 40 times higher than in a testicle that descends normally. There is also a higher incidence of testicular tumors in men infected with the human immunodeficiency virus (HIV). In addition, the presence of testicular atrophy may influence the development of testicular tumors. It has also been found that the Klinefelter syndrome is associated with mediastinal germ cell tumors and that orchitis forms a possible risk factor.

Dissemination

In principal, the dissemination route of testicular germ cell tumors is no different from that of other malignant tumors. Tumor cells can spread via the lymphatic and circulatory systems. The first lymph node stations of the testes are the lumbar lymph nodes, which are located close to the vertebral column at the level of L2 to L4. From there, tumor cells can spread lymphogenously, via the thoracic duct to the mediastinum and supraclavicular lymph nodes. Haematogenetic dissemination can take place in two ways: directly to the lungs via vascular invasion in the testicle, or indirectly to the lungs via the lumbar lymph nodes, cisterna chyli and the thoracic duct to the subclavian vein. Direct invasion of...
adjacent structures, such as the rete testis, epididymis and the spermatic cord, can also occur. However, malignant germ cell tumors chiefly disseminate via the lymphogenous route.\textsuperscript{10}

Symptomatology

A testicular tumor usually presents as a painless swelling in the testicle. Slight trauma often draws a patient’s attention to the swelling. Other possible symptoms resemble orchitis, epididymitis or testicular torsion. Some patients present without any testicular complaints or abnormalities, but with symptoms of distant metastases. Retroperitoneal lymph node metastases can cause back pain or renal colic by compressing or blocking the ureter. Lung metastases can give rise to dyspnoea, haemoptysis and pleural irritation. In addition, gynaecomastia can form the first clinical symptom of a tumor that is producing human chorionic gonadotrophin (hCG).\textsuperscript{11}

Diagnosis and staging

Differential diagnoses in the case of testicular complaints comprise a malignancy, varicocele, hydrocele, spermatocele, epididymitis, orchitis, testicular torsion and lateral inguinal hernia. It is important to establish whether the scrotal swelling is intratesticular or extratesticular. Intratesticular swellings should be considered malignant until proven otherwise, whereas extratesticular swellings are generally benign. Physical examination includes thorough palpation of the scrotal contents, palpation of the abdomen, supraclavicular lymph nodes and the mammae in case gynaecomastia is present. Ultrasonography of the scrotal contents is the examination of choice to distinguish between an intratesticular and an extratesticular swelling. Laboratory investigations play varying roles. In patients with a seminoma, the serum hCG may be slightly increased and there is usually a higher than normal level of placenta-like alkaline phosphatase (PLAP). In patients with nonseminomatous germ cell tumors, specific serum tumor markers may be present, namely hCG and alpha-fetoprotein (AFP). In all patients with a malignant germ cell tumor, the serum lactate dehydrogenase (LDH) level may be increased. Diagnosis is made on the basis of histological examination of tissue obtained after orchidectomy via an inguinal incision. Orchidectomy is performed if the
testicular swelling is clinically suspicious and the laboratory results are abnormal. If the swelling is clinically suspicious, but the laboratory results are normal, the first step is to perform explorative surgery and take biopsies. The frozen section histology technique is used to establish whether or not the swelling is malignant. If the abnormality appears to be benign, the testicle is generally replaced in the scrotum, whereas if it is malignant, orchidectomy is performed. A patient in whom a germ cell tumor has been diagnosed must undergo further staging examinations. Besides physical examination and laboratory tests, these comprise computed tomography (CT scans) of the abdomen and chest. There are no indications to perform Magnetic Resonance Imaging (MRI). At the University Hospital Groningen, the staging classification according to Peckham is used (Table 1).

Table 1. Staging for testicular tumors according to Peckham

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Tumor limited to the testis</td>
</tr>
<tr>
<td>II</td>
<td>Infra-diaphragmatic lymph node involvement</td>
</tr>
<tr>
<td>II A</td>
<td>Metastases &lt; 2 cm in diameter</td>
</tr>
<tr>
<td>II B</td>
<td>Metastases 2-5 cm in diameter</td>
</tr>
<tr>
<td>II C</td>
<td>Metastases &gt; 5 cm in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Supra- and infra-diaphragmatic lymph node involvement; Abdominal status A, B, C as for Stage II; No extralymphatic metastases</td>
</tr>
<tr>
<td>IV</td>
<td>Extra lymphatic metastases; Abdominal status A, B, C as for Stage II; 0 for negative nodes; Lung status:</td>
</tr>
<tr>
<td></td>
<td>( L_1 ) ( \leq 3 ) metastases; ( \leq 2 ) cm in diameter</td>
</tr>
<tr>
<td></td>
<td>( L_2 ) multiple metastases; ( \leq 2 ) cm in diameter</td>
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<tr>
<td></td>
<td>( L_3 ) multiple metastases; &gt; 2 cm in diameter</td>
</tr>
<tr>
<td></td>
<td>Liver status:</td>
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<td></td>
<td>( H^* ) liver involvement</td>
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</tbody>
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Histology

Testicular germ cell tumors can be divided into seminomas (± 55%) and nonseminomas (± 45%). Nonseminomas can be further divided into a number of subgroups. Various classifications have been developed over the years. At the University Hospital Groningen, the classification of the World Health Organisation (WHO) is used (Table 2).14

Table 2. Histological classification of testicular tumors, World Health Organisation

A. Tumors of one histological type
   1. Seminoma
   2. Spermatocytic seminoma
   3. Embryonal carcinoma
   4. Yolk sac tumor
   5. Polyembryoma
   6. Choriocarcinoma
   7. Teratoma
      a. Mature teratoma
      b. Immature teratoma
      c. With malignant transformation

B. Tumors of more than one histological type
   1. Embryonal carcinoma and teratoma (teratocarcinoma)
   2. Choriocarcinoma and any other types
   3. Other combinations

A nonseminoma can consist of one component, but there is usually a combination of components, whether or not including seminoma. Embryonal carcinoma is the most poorly differentiated tumor component; no specific differentiation direction is recognisable. Yolk sac tumor and choriocarcinoma resemble fetal membranes and placental tissue, respectively. Teratoma can contain a mixture of tissues, such as epithelium, cartilage, muscle or nerve tissue. When these tissues have a more or less normal structure, with good recognition of the differentiation
Introduction

direction, the tumor is referred to as mature teratoma. When these tissues are not fully evolved, the tumor is referred to as immature teratoma. As testicular tumors often contain different components, it is very important to examine various areas of the tumor histologically. Staging of the primary tumor is performed according to the guidelines of the Union Internationale Contre le Cancer (UICC). In Table 3 clinical-macroscopic staging and histological staging are described.  

Table 3. Tumor staging according to the UICC

<table>
<thead>
<tr>
<th>Macroscopic staging</th>
<th>Histological staging</th>
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<td>T₀</td>
<td>pT₀</td>
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<td>T₁</td>
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<td>T₄ₕ</td>
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<td>TX</td>
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I.2 TREATMENT AND FOLLOW-UP

Historical developments

The role of surgery in the treatment of patients with testicular tumors has changed considerably over the years. Until the end of the previous century, treatment for these patients comprised orchidectomy alone.\textsuperscript{16,17} However, physicians had been aware for some time that patients might have metastases in the retroperitoneum. In 1887, Kocher was the first to describe the resection of a retroperitoneal mass from a patient with a testicular tumor.\textsuperscript{18} He removed a tumor mass that was ‘as large as a man’s head’ from the retroperitoneum. However, the patient developed local recurrence five months later. The first transabdominal retroperitoneal lymph node dissection was performed by Roberts in 1902; however, the patient died of peritonitis.\textsuperscript{19} Lumbar retroperitoneal lymph node dissection was described for the first time by Chevassu\textsuperscript{20} and Howard\textsuperscript{21} in 1910. Coley was opposed to performing retroperitoneal lymph node dissection, because at that time (1915) the surgical mortality rate was 10\% to 15\%, which he considered too high to be acceptable. An additional argument was that in 50\% of the patients with testicular tumors, no tumor-bearing lymphatic tissue was found during surgery. Coley therefore injected patients who had a malignant testicular tumor with ‘Coley’s fluid’.\textsuperscript{17} The fluid comprised a mixture of Bacillus prodigiosus toxin and a filtrate of haemolytic streptococcus. The encouraging results of this therapy were very likely due to hyperthermia caused by the toxins.\textsuperscript{22} In this period, radiotherapy was also applied for the first time. In 1916, Béclère was probably the first to use radium on a retroperitoneal metastasis from a testicular tumor.\textsuperscript{23} Orbaan, a Dutch physician, was the first to publish the results of treating metastases from ovarian and testicular tumors with radiotherapy.\textsuperscript{24}

In 1923, Hinman described the results of patients with a testicular tumor who he had treated with a so-called ‘radical operation’, by this he meant retroperitoneal lymph node dissection (RPLND).\textsuperscript{25} He concluded that his results signified an improvement of 100\% in comparison with treatment comprising orchidectomy alone. At that time, orchidectomy alone cured only 15\% of the patients, while the ‘radical operation’ was said to have cured 30\%. Until the end of the 1930s, RPLND was the standard treatment after orchidectomy, irrespective of whether a patient had a seminoma or a nonseminomatous tumor. In the subsequent period, physicians somewhat lost interest in RPLND because of the good results of
Introduction

radiotherapy, particularly in patients with a seminoma.\textsuperscript{26} It was not until 1948 that Lewis propagated treating seminomas differently from nonseminomas.\textsuperscript{27} He concluded that patients with a seminoma should be treated with orchidectomy and radiotherapy, while patients with a nonseminomatous testicular tumor should be treated with orchidectomy, RPLND and radiotherapy.

A little later, the discussion in the literature became chiefly focused on the surgical approach to RPLND. Cooper et al. introduced a thoraco-abdominal approach to ipsilateral RPLND.\textsuperscript{28} Variations of the technique were then described by Vallet\textsuperscript{29} and Lewis.\textsuperscript{30} In 1953, Leadbetter published his results, on the basis of which he concluded that besides ipsilateral lymph node dissection, contralateral lymph node dissection should also be performed.\textsuperscript{31} Following the work of Roberts in 1902,\textsuperscript{19} Mallis et al.\textsuperscript{32} and Stehlin et al.\textsuperscript{33} described a transabdominal approach to bilateral retroperitoneal lymph node dissection in 1958 and 1959, respectively.

Recent developments

At the University Hospital Groningen, bilateral RPLNDs were introduced in 1963. The transabdominal approach was used and dissection was limited to the retroperitoneal lymph nodes caudal to the renal vessels. In patients with nonseminomatous testicular germ cell tumors (NSTGCT), Wobbes described the results of treatment over the period 1963 to 1977.\textsuperscript{10} During that period, retroperitoneal lymph node dissection was considered to be the standard diagnostic and therapeutic intervention in patients with clinical stage I NSTGCT. Metastases were found in the retroperitoneal lymph nodes in 25\% to 35\% of the patients. The majority of these patients were subsequently treated with actinomycin-D chemotherapy, because of its cytostatic effect.\textsuperscript{34} If, during surgery, it was found that RPLND was not possible because the metastases were too extensive, the patient received actinomycin-D and a second attempt was made at a later date. In patients with distant metastases, chemotherapy has been playing a major role since the beginning of the 1950s. At first, treatment usually comprised a single drug, sometimes in combination with actinomycin-D. In 1960, Li described the results obtained with a combination of chlorambucil, methotrexate and actinomycin-D.\textsuperscript{35} The advantage of combination therapy is the synergistic effect, because different drugs are active against different parts of the cellular process. In addition, a nonseminomatous tumor can contain one or more components, with different levels of chemo-sensitivity.
At the beginning of the 1970s, the first results were described of treatment with vinblastine and bleomycin.\textsuperscript{36-38} Response rates varied from 32\% with monotherapy, to 90\% with combination therapy. The first real breakthrough in the treatment of patients with disseminated NSTGCT occurred in 1977. In that year the results were published of treatment with cisplatin in combination with vinblastine and bleomycin (PVB).\textsuperscript{39} This combination appeared to be so effective that it was decided to change the treatment policy of these patients into PVB followed by the possible resection of residual retroperitoneal and/or pulmonary metastases. PVB polychemotherapy was introduced at the University Hospital Groningen in 1977.\textsuperscript{40} The combination was applied as the standard treatment for many years. In view of the high level of toxicity, various modifications were investigated, which led to a new standard: the combination of bleomycin, etoposide and cisplatin (BEP).\textsuperscript{41}

In the 1970s, CT scanning was introduced which enabled more accurate clinical staging than had been possible previously with lymphangiography and lung tomography.\textsuperscript{42,43} In the early stages, CT scanning of the retroperitoneal region was not considered to be totally reliable. Therefore, explorative laparotomy was performed to be completely certain about the presence or absence of retroperitoneal lymph node metastases. However, it soon became apparent that explorative laparotomy did not have any consequences on the clinical stage established on the basis of the CT findings. During an interim analysis it was decided to perform laparotomy only in cases in whom CT scanning could not give a definite answer about retroperitoneal lymph node metastases. The role of MRI in determining the effect of the treatment for patients with disseminated NSTGCT was also examined. Hogeboom found that MRI did not have any advantages over CT scanning.\textsuperscript{44} Since then, newer MRI equipment has become available (with breath holding techniques), so the value of MRI compared to CT scanning of the retroperitoneum will have to be re-evaluated.

Another important development in relation with diagnosis and staging is the possibility of measuring tumor marker levels (hCG and AFP) in a patient’s serum. The response to treatment can be monitored by means of hCG and AFP, but it is important to measure the serum levels of these markers prior to orchidectomy to record the original levels.\textsuperscript{45,46} Owing to the fact that at least 20\% of NSTGCT do not produce tumor markers, attempts have been made to find new tumor markers over the past few years. In 1991, a serum immuno-enzymometric assay was developed at the Immunochemistry Laboratory of the
Introduction

University Hospital Groningen for the detection of TRA-1-60 reactive antigen. This antigen is found in patients whose primary tumor contains embryonal carcinoma. TRA-1-60 is a very promising potential tumor marker, because embryonal carcinoma is the most common histological component of NSTGCT.

In patients with clinical stage I NSTGCT, the cure rate after RPLND was about 80% to 90%. However, nearly all of the patients developed retrograde ejaculation, because the sympathetic ganglia and the hypogastric plexus had been damaged. As this group of patients chiefly comprises young men, this is a very serious complication. In addition, in 65% to 75% of the cases, RPLND only had diagnostic value, without any therapeutic consequences, because no metastatic viable cancer was found during histological examination.

Owing to the effectiveness of polychemotherapy, the availability of the tumor markers hCG and AFP (which can also be used to detect recurrent disease), the increase in reliability of clinical staging by CT scanning and the disadvantages of RPLND, it was decided at the Groningen clinic to adopt Peckham’s ‘wait-and-see policy’ in patients with stage I NSTGCT in 1982. This meant that after orchidectomy, these patients entered an intensive outpatient follow-up programme. Besides physical examination, serum was obtained regularly to monitor tumor markers and at specific intervals, a chest X-ray was taken and CT scanning of abdomen and chest was performed. In this way, if any metastases developed, they could be detected at a early stage. Although the recurrence rate in patients with a stage I primary tumor was 25%, they could all be treated effectively with cisplatin-based polychemotherapy.

In order to be able to identify patients with an increased risk of disease recurrence, a search was made for unfavourable prognostic factors. The literature mentions various unfavourable prognostic factors, such as the presence of vascular invasion or lymphatic invasion, the histological tumor (pT) stage, the presence of embryonal carcinoma or teratoma in the primary tumor and increased tumor marker levels prior to orchidectomy. Some clinics have suggested adjuvant treatment with chemotherapy or radiotherapy for the subgroup of patients with clinical stage I NSTGCT and one or more of these risk factors. At present, the primary treatment for patients with stage II or more advanced stage disease in Europe, is orchidectomy and combination chemotherapy. Occasionally, patients with stage IIA or IIB NSTGCT undergo orchidectomy followed by nerve-sparing RPLND, if necessary supplemented by chemotherapy. This approach is mainly applied in the USA.
Chapter I

The cytotoxic drugs used to treat patients with disseminated NSTGCT are administered intravenously. To limit the renal toxicity of cisplatin, intravenous prehydration and posthydration are necessary. In practice this means that the patient retains an intravenous needle for 24 hours per day for seven consecutive days. An alternative approach was introduced at the end of the 1970s: the patients were provided with an arteriovenous shunt (A-V shunt) in the wrist to facilitate the administration of the chemotherapy and infusion fluids.\textsuperscript{53,54} This produced widening of the veins because of arterialisation and made them easier to puncture. An additional advantage was that the rapid flow of blood through the vein quickly diluted the cytotoxic drugs and reduced the irritation to the vessel walls. Unfortunately, the life span of the A-V shunts proved to be very short in practice, namely 2-12 months. Moreover, complications, such as thrombosis and infection, occurred fairly frequently.\textsuperscript{54} At the beginning of the 1980s, the Venous Access Port (VAP) became available. This subcutaneous access system could remain in situ longer and was associated with far less morbidity than an A-V shunt. Therefore, the VAP formed a considerable advance for patients with an NSTGCT that had to be treated with cisplatin-based polychemotherapy.

After completion of chemotherapy, the staging examinations are repeated. Fairly often residual tumor is detected. The treatment policy for such residual disease after chemotherapy depends on whether the primary tumor was a seminoma or a nonseminoma. Residual disease in patients with a disseminated seminoma can be treated with surgery,\textsuperscript{55} radiotherapy\textsuperscript{56} or they can enter a wait-and-see programme.\textsuperscript{57-59} At the University Hospital Groningen, the wait-and-see policy is generally employed for these patients.

If the primary tumor was an NSTGCT and the tumor markers have normalised, but residual disease is present or suspected, the patients usually undergo evaluative surgery. Surgery plays a major role in judging the outcome of chemotherapy. The histology of residual lesions is of importance to determine whether any further treatment is necessary. If the residual lesions only contain necrosis or fibrosis, resection does not have any therapeutic consequences; however, if the lesions contain viable cancer, the patient receives additional polychemotherapy. There is a great risk that if the primary tumor contained a teratoma component, the residual lesions will contain mature teratoma. Histologically, mature teratoma gives the impression of being benign, but cytogenetically it is malignant.\textsuperscript{60,61} In addition, it has been found that residual mature teratoma can develop into large, usually cystic tumors that eventually compress the adjacent organs and give rise to serious complications. This
phenomenon is referred to as the "Growing Teratoma Syndrome". A mature residual lesion can also develop into a second non-germ cell malignancy. With the aim of minimizing the risk of the growing teratoma syndrome or a second malignancy, relaparotomy was performed at the University Hospital Groningen, irrespective of the radiological findings, with resection of any palpable abnormalities, between 1978 and 1984. Thoracotomy was only carried out if there was radiological evidence of lung metastases. Partly based on reports in the literature, the policy of re-laparotomy after chemotherapy was discontinued at the end of 1986 in patients without signs of residual lesions on their CT scans and whose primary tumor had not contained a teratoma component. On the basis of prognostic models, attempts have recently been made in the literature to sharpen the indications for RPLND after polychemotherapy. Additionally, trials are underway to investigate whether new diagnostic methods, such as MRI and Positron Emission Tomography (PET scanning) can be used to predict the histology of metastases.

I.3 RESEARCH QUESTIONS

The above shows that over the years, the role of surgery has been influenced considerably by the many new developments in diagnosis and treatment of patients with testicular tumors. Since the publication of Wobbes' thesis in 1981, RPLND as the only curative option for these patients has evolved into adjuvant surgery after chemotherapy. This thesis describes the present role of surgery in the treatment of patients with malignant testicular germ cell tumors. The studies focus chiefly on the surgical treatment and follow-up of patients with NSTGCT.

At present, there is a more than 15 years of experience with the 'wait-and-see policy' in patients with clinical stage I NSTGCT. A study was performed to investigate whether or not this is a reliable policy; the results are described in Chapter II. Details are given about the recurrence rate of patients who entered the wait-and-see programme, the interval between orchidectomy and the development of metastases and the way in which the metastases were detected. A search was then made for unfavourable prognostic factors that could predict the development of metastases. Also was examined whether it is necessary to continue follow-up for ten years after orchidectomy.
Chapter I

The results of a study on the normal values and half-life of a new serum tumor marker, TRA-1-60, are described in Chapter III. AFP and hCG are the standard tumor markers, so it was of interest to determine whether TRA-1-60 has any additional value in the follow-up of patients with clinical stage I NSTGCT. An increased serum TRA-1-60 value at the time of orchidectomy was examined as a potential unfavourable prognostic factor for the development of metastases.

Chapter IV describes the perioperative and late complications of the use of a VAP as an access system for chemotherapy in patients with disseminated testicular cancer. On the basis of a homogeneous group of patients, attempts were made to identify factors that could predict the development of complications.

The importance of determining the histology of metastases after treatment with orchidectomy and polychemotherapy must be weighed against the complications and risks of surgical intervention. In Chapter V the advantages and disadvantages of resecting residual lesions from the retroperitoneum are discussed. Factors that might have predictive value regarding complications were evaluated.

On analogy with Chapter V, Chapter VI examines the advantages and disadvantages of resecting residual lesions from the lungs. An additional question is whether the indication for resecting residual lesions from the lungs should also depend on the histological results of the retroperitoneal lesions.

In summary, this thesis addresses the following research questions:

1. Is the current policy for all patients with a clinical stage I NSTGCT justified, or should it be modified, possibly only for certain subgroups?

2. What is the significance and value of the new serum tumor marker TRA-1-60 in patients with clinical stage I NSTGCT?

3. What perioperative and late complications are associated with placing a subcutaneous access system for polychemotherapy in patients with disseminated testicular germ cell tumors?

4. What are the advantages and disadvantages of surgical resection of
Introduction

residual retroperitoneal lesions after polychemotherapy in patients with disseminated NSTGCT?

5. What are the advantages and disadvantages of surgical resection of residual pulmonary lesions after polychemotherapy in patients with disseminated NSTGCT?

REFERENCES

Chapter I


Chapter I

Introduction


