Appendix: Historical Overview of Testicular Cancer Treatment at the UMCG
Previously, in the introduction of this thesis, an overview was presented about today’s epidemiology, etiology, pathology, metastatic pattern, symptomatology, diagnostics, staging and (combined) treatment of testicular cancer and its prognosis. In this historical overview a short history of the treatment of testicular cancer is given as it was performed at the Department of Surgical Oncology from the sixties of the last century till now and how the testicular cancer treatment shifted to a multimodality treatment in which today over eight medical disciplines (surgeons, urologists, medical oncologists, radiation oncologists, pathologists, radiologists, nuclear medicine physicians, geneticist, psychologists) and basic researchers are involved.

Testicular cancer was one of the first tumor types for which in 1971 in the Netherlands a national study group, ‘Commissie voor Testis Tumoren’ was established. The intention was to uniform the treatment and to give advice when necessary. Few years later (1978) the national guideline ‘Protocol Testistumoren’ was developed with the support of the Dutch Cancer Society (Koningin Wilhelmina Fonds, de Nederlandse Organisatie voor de Kankerbestrijding (KWF-NOK)). The goal of this guideline was to achieve uniformity in the histopathological classification of seminomatous and nonseminomatous testicular germ cell tumors, to stimulate staging according to the TNM-classification, to describe operative procedures for inguinal orchiectomy and bilateral retroperitoneal lymph node dissection, to give radiation guidelines, as well as to advice on the follow-up after treatment. Moreover the idea was to start a registration of patients with a malignant testicular tumor.

Since the early sixties testicular cancer is one of the clinical treatment and research topics within the Department of Surgical Oncology of the former ‘Algemeen Provinciaal, Stads- en Academisch Ziekenhuis (APSAZ)’, later called Academisch Ziekenhuis Groningen (AZG) and today University Medical Center Groningen (UMCG). Since that time all patients with a suspicious testicular tumor underwent an inguinal orchiectomy. In those days, a centralized histopathology review was performed at the Antoni van Leeuwenhoekziekenhuis in Amsterdam. After a definitive histological diagnosis, patients were staged with an intravenous pyelogram, bipedal lymphography, chest X-ray and tomography of the lungs. In case of suspected retroperitoneal metastatic disease, a supraclavicular lymph node biopsy was performed. When supraclavicular nodal disease was encountered, the patient was considered to have distant lymphogenous disease and surgically ‘incurable’. Patients were initially staged according to the system of Skinner and Scardino (Table 1a), after 1979 according to the Royal Marsden classification.
developed by Peckham (Table 1b)\(^3{,}^4\). In 1997 was the International Germ Cell Consensus Classification (IGCCCG) introduced, a prognostic factor-based staging system for metastatic germ cell cancers, classifying the nonseminomatous tumors in good, intermediate, and poor prognosis\(^5\).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the scrotum, negative nodes and no other evidence of disease</td>
</tr>
<tr>
<td>IIA</td>
<td>Metastases fewer than 6 retroperitoneal lymph nodes, with no nodes &gt;2 cm in diameter</td>
</tr>
<tr>
<td>IIB</td>
<td>Metastases to 6 or more retroperitoneal lymph nodes or any metastasis &gt;2 cm in diameter or extra-capsular spread</td>
</tr>
<tr>
<td>IIC</td>
<td>Bulky abdominal disease detected grossly on abdominal examination before operation, usually associated with significant ureteral deviation and/or obstruction</td>
</tr>
<tr>
<td>III</td>
<td>Metastases above the diaphragm or to the viscera</td>
</tr>
</tbody>
</table>

Table 1a. Staging system by Skinner and Scardino

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor confined to the testis</td>
</tr>
<tr>
<td>II</td>
<td>Metastases confined to abdominal lymph nodes</td>
</tr>
<tr>
<td>IIA</td>
<td>Metastases &lt;2 cm</td>
</tr>
<tr>
<td>IIB</td>
<td>Metastases 2-5 cm</td>
</tr>
<tr>
<td>IIC</td>
<td>Metastases &gt;5 cm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of supradiaphragmatic and infradiaphragmatic lymph nodes. Abdominal status as for Stage II</td>
</tr>
<tr>
<td>IV</td>
<td>Extra lymphatic metastases. Abdominal status as for Stage II, 0 for negative nodes.</td>
</tr>
<tr>
<td>IV</td>
<td>Lung status:</td>
</tr>
<tr>
<td></td>
<td>• L1: ≤3 metastases, ≤2 cm in diameter</td>
</tr>
<tr>
<td></td>
<td>• L2: multiple, ≤2 cm in diameter</td>
</tr>
<tr>
<td></td>
<td>• L3: multiple, &gt;2 cm in diameter</td>
</tr>
</tbody>
</table>

Table 1b. Staging for testicular tumors by Peckham

In the early days patients with a nonseminomatous tumor were treated by the Department of Surgical Oncology and with a seminomatous tumor by the Department of Radiation Oncology. Today however treatment has shifted to a multimodality treatment in which the Departments of Surgical Oncology, Urology, Medical Oncology and Radiation Oncology are involved and patients with seminomas as well as nonseminomas are discussed in the weekly Multidisciplinary Cancer Conferences (MCCs).

The transabdominal bilateral retroperitoneal lymph node dissection for nonseminomatous germ cell tumors of the testis was introduced in the APSAZ by Oldhoff in 1963\(^6\). The dissection extends from the renal vessels cranially to the external iliac arteries caudally. The transabdominal approach was given preference over the thoraco-abdominal procedure because the transabdominal approach provided sufficient access and the opportunity to remove lymph nodes adequately on both sides. Between 1963-1968, stage I and II patients underwent this procedure as the only treatment after orchiectomy. In clinical stage I patients, no tumor was encountered in the removed retroperitoneal nodes in 80% of the patients and in the remaining 20% of these patients the retroperitoneal lymph node dissection was considered not only as diagnostic but also as a therapeutic procedure. Clinical stage II patients underwent an exploratory laparotomy and, when possible, a bilateral retroperitoneal lymph node dissection\(^7\). If (sporadically) patients presented with inguinal nodal disease also an inguinal lymph node dissection was performed. In contrast to this pure surgical treatment at the same time testicular cancer patients in other centers in the Netherlands were generally treated with radiation of the retroperitoneal nodal area and/or mediastinum\(^7,^8\).

In Groningen the treatment of nonseminomatous testicular cancer changed in 1968 after the successful reports in literature of adjuvant chemotherapy with actinomycine-D\(^6\). In case of histopathologic documentation of retroperitoneal disease after transabdominal bilateral retroperitoneal lymph node dissection, adjuvant chemotherapy was administered consisting of 1 mg actinomycine-D per day in an 8 hours continuous intravenous infusion during 5 days, every 6 weeks over a period of 2-years, sometimes combined with radiation treatment. In those days this chemotherapy was given by the surgical oncologists themselves. When the retroperitoneal disease was primarily considered irresectable, patients were treated with an induction course consisting of 3-courses of actinomycine-D followed by a second laparotomy and, if possible, resection of the residual retroperitoneal disease, followed again by adjuvant actinomycine-D treatment\(^8\). The 3-years survival for stage I disease was 90% and for stage IIA and IIB 70%. Survival for stage IIC and stage III was disappointing with 3-years survival of only 25\(^%\)\(^8-^{10}\).
At the end of the seventies there were three new developments in the treatment of testicular cancer: 1) the testicular tumor markers, alpha-fetoprotein (AFP), betachoriongonadotropin (B-HCG), and lactate dehydrogenase (LDH) were introduced in the diagnosis of testicular cancer and later on in the staging and evaluation of testicular cancer treatment; 2) Computed Tomography (CT) of the abdomen and chest was introduced in the staging of testicular cancer and quickly replaced the previous described staging methods, intravenous pyelogram, bipedal lymphography and tomography of the lungs; 3) discovery of cisplatin and the introduction of the cisplatin based combination chemotherapy by Einhorn with cisplatin, vinblastin and bleomycin (PVB) for disseminated testicular cancer [6].

Prolonged remissions were achieved in 70% of the disseminated testicular cancer patients treated with PVB [7]. In the Netherlands, including Groningen, shortly after the same survival figures were published [8].

With the introduction of PVB in Groningen, the treatment of testicular cancer became a team approach of pathologist, surgical oncologist, medical oncologist, radiologist and anesthesiologist. All new and treated patients with a nonseminomatous tumor were discussed within the weekly MCC. The medical oncologists had to ‘learn’ how to deliver ‘safely’ the cisplatin based combination chemotherapy [9]. The radiologist had to learn how to ‘assess’ the post chemotherapy retroperitoneal CT scans in particular with respect to tumor response. The surgical oncologists faced the resection of fibrosed and/or necrotic residual disease. The anesthesiologist had to learn how to deal with the side effects of bleomycin to the pulmonary tissue during general anesthesia [10]. The pathologist had to evaluate the resected tumor tissue, e.g. necrosis, fibrosis, mature teratoma and/or viable germ cell cancer. Two research questions were extensively studied 1) tumor maturation due to chemotherapy and 2) immune histochemical analysis of tumor marker production by different histological components of nonseminomatous germ cell tumors [11].

The cisplatin based combination chemotherapy treatment of metastatic nonseminomatous testicular cancer suddenly brought together a range of medical specialists and researchers from different medical disciplines and the testicular research line expanded successfully within the ‘Facultaire Onderzoeksprogramma Oncologie’ of the Medical Faculty of the Groningen University.

Schröffordt Koops and Sleijfer successfully introduced the ‘wait and see’ policy in the APSAZ for stage I disease and exploratory laparotomies were no longer performed [12,13]. In case of a recurrence, effective chemotherapy was available [14]. Treatment of disseminated nonseminomatous tumors consisted of cisplatin, vinblastin and bleomycin (PVB) and since the mid-eighties of bleomycin, etoposide and cisplatin (BEP). More recently the systemic treatment is based on so called ‘IGCCCG prognostic factors’ and individualized for example in patients with pulmonary disease, administering 4 cycles EP instead of 3 cycles BEP [15]. After systemic chemotherapy there might be a biochemical complete response, with or without residual retroperitoneal and/or lung disease evaluated on abdominal/cHEST CT. All residual retroperitoneal/lung disease needs to be resected [16-20]. Further treatment is depending on the histopathology of the resected specimen. In case of necrosis or mature teratoma no further therapy is indicated, while second line chemotherapy might be indicated when viable germ cell cancer is encountered.

Also the treatment of seminomatous tumors of the testis changed and improved during the last two decades, mainly due to CT radiation planning, less radiation doses and the introduction of systemic chemotherapy for stage III and IV disease. More recently treatment for stage I disease has changed: wait and see policy is implemented, one course of carboplatin or still radiation. Orchiectomy is only the surgical part of the treatment for patients with a seminoma of the testis. Further treatment, radiation or systemic treatment, is based on the disease stage and the advisement of the multidisciplinary cancer conference (MCC).

In Groningen, the modified retroperitoneal lymph node dissection was introduced: only resection of residual retroperitoneal disease with the ultimate goal to reduce the morbidity of retrograde ejaculation [21-23]. For an adequate vascular access to continuously deliver PVB, in the early eighties patients received an AV-fistula between the radial artery and the cephalic vein [24]. The complication rate of this surgical procedure was high and therefore the Venous Access Port (VAP) was successfully introduced in the mid-eighties [25].

In Europe, there are European Society of Medical Oncology (ESMO) guidelines with regard to the treatment of disseminated nonseminomatous tumors but these do not fully correspond with the guidelines of the National Comprehensive Cancer Network (NCCN) [26-27]. In contrast to the small differences in systemic treatment, differences are very large with respect to the surgical removal of residual retroperitoneal tumor mass(es). At the UMCG only the macroscopic residual abnormalities are removed, while in the USA complete or modified (template) retroperitoneal lymph node dissections are still performed [28-30]. One of the advantages of the UMCG strategy was the less sexual disorder [31-32].

At the UMCG, resection of residual retroperitoneal disease is centralized, in contrast to other centers in the West where the referring general surgeon or urologist generally performs the adjuvant surgery. The role of surgery in the treatment of disseminated testicular cancer was well defined at the end of the nineties, as well as all surgical research questions seemed to be answered. Therefore the research within the Department of Surgical Oncology, in close collaboration with the Department of Medical Oncology shifted towards the Department of Genetics and the Department of Psychosocial Oncology on subjects such as genetic
susceptibility, tumor biology, endocrine aspects, sexuality, quality of life, survivorship issues and long-term toxicity in testicular cancer. The last decade Gietema of the Department of Medical Oncology has especially focused on long-term effects of testicular cancer treatment within national and international collaborative groups.

With the extensive achieved experience in laparoscopic surgery, this minimal invasive operative technique was introduced by Hoekstra a decade ago in the treatment of testicular cancer at the UMCG. In most centers laparoscopy is used as a minimal invasive staging procedure, e.g. nerve preserving uni- or bilateral retroperitoneal lymph node dissection (RPLND), for stage I NSTGCTs. At the UMCG the surgical staging, RPLND or exploratory laparotomy, was already abandoned in the mid-eighties when the CT staging became available. The technique of laparoscopy was for the first time used at the UMCG in the resection of residual retroperitoneal tumor mass (RRRTM) in 2004. Since then performing laparoscopic resections of RRRTMs in testicular cancer patients has become a routine procedure at the UMCG for the surgical oncologists.

Although the technique of laparoscopic resection of RRRTMs is safe, this minimally invasive procedure, with a nice oncological and cosmetic outcome, is still not widely accepted in the Netherlands, Europe and the United States. Are there still new surgical treatment options in the treatment of testicular cancer? With the availability of the Da Vinci Robot at the UMCG in 2018, the technique of robotic (assisted) resection of residual retroperitoneal tumor masses with the goal to resect residual retroperitoneal tumor masses with the same cosmetic result but less morbidity, e.g. preserving sexual function.

References


