Testicular germ cell tumors

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CHAPTER VII

SUMMARY

Over the past twenty years, the role of surgery has been influenced considerably by many new developments in the diagnosis and treatment of patients with malignant testicular germ cell tumors. This thesis describes a number of aspects of the present role of surgery in the treatment of patients with malignant testicular germ cell tumors in the light of five studies. The majority of patients were treated for a nonseminomatous testicular germ cell tumor (NSTGCT).

In the general part of the Introduction, brief descriptions are given of the epidemiology and etiology of malignant testicular tumors. Dissemination, symptomatology and diagnosis are discussed. Overviews are presented of the staging classification according to Peckham and the histological classification of the World Health Organisation; a description is also given of primary tumor staging according to the guidelines of the Union Internationale Contre le Cancer. The second part of the Introduction deals extensively with historical and recent developments in the diagnosis and treatment of patients with malignant testicular germ cell tumors. Particular attention is paid to the changing role of surgery. Over the years, the value of surgery has shifted from being primarily therapeutic to being more diagnostic in an adjuvant setting; developments such as the discovery and application of very effective cisplatin-based polychemotherapy and serum tumor markers, and improvements in clinical staging through computed tomography (CT scanning) are responsible. In addition, surgery plays a facilitating role in monitoring the effect of treatment with polychemotherapy.
The research questions which formed the basis of this thesis are formulated at the end of the Introduction and addressed in the five chapters that follow.

Chapter II describes 154 patients with clinical stage I NSTGCT who were treated according to the wait-and-see policy between 1982 and 1992. These patients were followed-up prospectively over a ten-year period by means of solely awaiting the progress of events. This means that if there were no demonstrable metastases after orchidectomy, further management over the subsequent years was confined to frequent outpatient check-ups. At each follow-up visit, a patient underwent physical examination and the serum tumor markers human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) were determined. In addition, chest X-rays and CT scanning of the abdomen and chest were conducted according to a fixed schedule.
Records were kept of the number of patients who developed metastases, the interval between orchidectomy and the diagnosis of metastases and how the metastases were detected. Using multivariate logistic regression analyses, a

search was made for unfavourable prognostic factors for the development of metastases. During a median follow-up of seven (range 2-12) years, 42 patients developed metastases (27.3%). All the cases of disseminated disease were detected within two years of orchidectomy, while more than 90% of them were even detected within the first year. The vast majority were detected by increased levels of serum hCG and/or AFP and by CT scanning. None of them were detected via the chest X-ray. Development of metastases appeared to be related to the presence of vascular invasion of the primary tumor, an embryonal carcinoma component in the primary tumor, an increased hCG level prior to orchidectomy and the absence of mature teratoma in the primary tumor. Vascular invasion proved to be the only independent risk factor for the development of metastases (P=.001). After treatment with cisplatin-based polychemotherapy, the survival rate in the total group of 154 patients was 98.7%. Two patients died of progressive disease, but it should be mentioned that one of them refused to be treated with polychemotherapy and opted instead for homeopathic treatment.
It can be concluded that it is justified to apply a wait-and-see policy to patients with clinical stage I NSTGCT. This also applies to the possible development of metastases in patients with unfavourable prognostic factors. Owing to the fact that all metastatic disease developed within two years of orchidectomy, it does not appear to be necessary to continue follow-up for 10 years. In the light of reports in the literature on patients who developed metastases after two years, it is considered advisable to continue follow-up for five years. Furthermore, it does not seem to be worthwhile to take chest X-rays, because none of the metastatic disease was detected in this manner. These findings have led to the formulation of a new wait-and-see follow-up schedule for patients with clinical stage I NSTGCT.

Chapter III evaluates the additional value of a new serum tumor marker, TRA-1-60, for the follow-up of patients in the wait-and-see group. TRA is the abbreviation for Terato Related Antigen.
In 1991, Marrink developed a serum immunoenzymometric assay for the detection of TRA-1-60 reactive antigen. This antigen is released into the serum of patients who have an embryonal carcinoma component in the primary tumor. As embryonal carcinoma, with a frequency of 70%, is by far the most common histological component of NSTGCT, TRA-1-60 formed a promising potential tumor marker. The upper normal reference value and the serum half-life of TRA-1-60 were determined and a possible relationship was investigated between an increased serum TRA-1-60 level at the time of orchidectomy and the

development of metastases. To establish the normal serum level, TRA-1-60 was measured in 100 healthy men in the same age group as the patients with an NSTGCT. The upper normal reference value was found to be 230 U/ml. The serum half-life time of TRA-1-60 was determined from the sera of five patients without metastases who had an initial value of >850 U/ml in combination with strongly increased hCG and/or AFP levels prior to orchidectomy. After orchidectomy, their serum tumor marker levels were determined two or three times per week until the hCG and/or AFP levels had normalised. As the tumor markers hCG and AFP in these patients normalised according to their known half-lives: two days for hCG and six days for AFP, it could be assumed that TRA-1-60 would also normalise according to its own half-life. The half-life of TRA-1-60 was found to be 9.5 days. Sensitivity, specificity and positive and negative predictive values of the three tumor markers, hCG, AFP and TRA-1-60, were calculated and proved to be comparable. In the 42 patients with clinical stage I NSTGCT who developed metastases during follow-up, the TRA-1-60 levels were evaluated one month prior to the detection of metastases by CT scanning and at the time that metastases were confirmed by CT scanning. One month prior to detection, 21 out of the 42 patients (50.0%) were found to have elevated TRA-1-60 levels. In 10 of them, it was the only tumor marker that was elevated. At the time that metastases were confirmed by CT scanning, 24 patients had increased TRA-1-60 levels, while in nine of them it was the only elevated tumor marker. Disease free survival was significantly poorer in patients with a TRA-1-60 level of >500 U/ml at the time of orchidectomy (P=.015).
It can be concluded that TRA-1-60 has definite additional value to hCG and AFP. Monitoring a combination of these three tumor markers can be expected to improve the early detection of metastases.

Chapter IV describes 132 patients with disseminated testicular cancer who were treated with polychemotherapy via a Venous Access Port (VAP) between 1983 and 1994. Perioperative and late complications related to VAP implantation were recorded and multivariate analyses were performed to detect any factors that could predict the occurrence of complications. In the literature, various complications of VAP implantation have been described, but contrary to our investigation, none of the studies were performed on a homogeneous group of patients.
The median age of the patients was 28 (range 16-55) years. Perioperative complications occurred in five patients (3.7%); two patients had a pneumothorax, two had severe blood loss and one had a mediastinal bleeding. The VAPs

remained in situ for a median of 413 (range 7-1607) days. In 31 patients (23.0%), 42 late complications were recorded (31.0%). The total number of late complications corresponded with 0.76 complication episodes per 1000 patient days. These late complications comprised: system obstruction in 13 patients (9.6%), thrombosis in 11 patients (8.1%), infection in six patients (4.4%), catheter defect in six patients (4.4%), extravasation in four patients (3.0%) and local skin necrosis in two patients (1.5%). Significantly more complications occurred in patients who had received intravenous chemotherapy prior to VAP implantation ($P<.001$). This difference was demonstrated with both multivariate and univariate analysis. In addition, univariate analysis showed that more complications occurred with VAP implantation under local anesthesia than under general anesthesia. In order to make a valid comparison of the results of this study with those in the literature, the complication incidence of various other authors was calculated and expressed as the number of episodes per 1000 patient days. In this way it was found that broadly speaking, our results agreed with those reported in the literature, but it appeared that the VAPs implanted into the University Hospital Groningen patients remained in situ for a relatively longer period than those at other clinics. This was because it was standard policy at the University Hospital Groningen to leave the VAP in situ for up to one year after the completion of chemotherapy, so that if further chemotherapy was required to treat additional residual disease it could be administered via the same VAP. However, as the risk of late catheter defects appeared to increase, it is worthwhile to consider removal at an earlier stage.
It can be concluded that the implantation and use of a VAP forms a safe means of administering polychemotherapy. The only independent risk factor for the development of late complications was a history of polychemotherapy administration prior to VAP implantation.

Chapter V presents a study on 112 patients who underwent resection of retroperitoneal residual tumor mass (RRTM) after the completion of cisplatin-based polychemotherapy. Attention is focused on establishing the histology of the residual tumor, in order to be able to evaluate the ultimate effect of treatment. RRTM was found to comprise necrosis and/or fibrosis, mature teratoma or viable cancer. The resection of necrosis or fibrosis is not actually necessary and does not have any therapeutic consequences, whereas the resection of mature teratoma is worthwhile to prevent the growth of potentially malignant cells. If a residual tumor mass contains viable cancer, chemotherapy should be continued.
The histology of the RRTM and surgical morbidity were examined. In addition, a search was made for factors that might explain why complications arose. The

median size of the resected RRTM was 4 cm, ranging from 0-18 cm. In ten patients (9.0%) the RRTM contained viable cancer; in 49 patients (44.1%) only necrosis and/or fibrosis were found; in 49 other patients (44.1%) the RRTM contained mature teratoma and in three patients (2.8%) no residual tumor mass was found at laparotomy. A total of 26 complications occurred in 20 patients (18.0%). The most frequent complication was urinary tract infection, which occurred in nine patients (8.1%). One patient died during the induction of anesthesia. Postmortem examination did not reveal any clear indications about the cause of death. There were no significant relationships between the occurrence of complications and the age of the patient, the size of the residual tumor, the operative duration, previous laparotomy or the histological findings. In the light of recent literature data, the discussion centres on the complications that occurred in these patients and compares them to those reported by authors from other clinics; attention is also paid to techniques for predicting the histology of residual tumor.
It can be concluded that surgical resection of RRTM should be considered as the golden standard for evaluating the effect of polychemotherapy treatment. The surgical technique is relatively safe, with a morbidity of 18.0%, which mainly comprises urinary tract infection (8.1%). Knowledge of the potential complications associated with this intervention will help to limit their occurrence.

Chapter VI reveals that after radical treatment with polychemotherapy, residual lesions may not only be found in the retroperitoneum, but also in the lungs. The indication for thoracotomy in patients with NSTGCT is completely different from that in other disseminated malignancies. In general, surgery for the latter group of patients is the only remaining curative option, whereas in patients with NSTGCT the indication for thoracotomy chiefly entails evaluation of the effect of chemotherapy, or prevention of the growing teratoma syndrome. At the University Hospital Groningen, the decision to perform thoracotomy partly depended on the histology of the retroperitoneal residual tumor mass. It was expected that a pulmonary residual tumor mass (PRTM) would have the same histology as the RRTM. If the RRTM contained only necrosis or fibrosis, thoracotomy was not generally considered to be necessary; if it contained mature teratoma, thoracotomy was performed to prevent the growing teratoma syndrome; and if it contained viable cancer, the patient firstly received further polychemotherapy.
The results and complications of resection of residual tumor mass from the lungs

were evaluated in 31 patients with a stage IV NSTGCT; survival was calculated.

In the patients who had previously undergone laparotomy, the histology of the PRTM was compared to that of the RRTM. Between 1979 to 1996, 32 thoracotomies were performed on 31 patients. In nine cases (28.2%) a solitary metastasis was removed and in 23 cases (71.8%) multiple metastases were removed. The median size was 15 mm, ranging from 2-60 mm. There were five perioperative complications in four patients (12.5%): minimal air leakage in two cases, accidental arterial bleeding in two cases and mucous retention in one case that interfered with artificial ventilation. Three serious postoperative complications occurred (9.4%): one patient needed artificial ventilation for five days, one patient had a pneumothorax which required drainage and the third patient developed pneumonia a few days after surgery. There were also 11 less serious postoperative complications (34.4%), which did not lead to prolongation of the period of hospitalisation by more than two days.

Histological examination of the resected PRTM revealed mature teratoma in 16 patients (51.6%), necrosis and/or fibrosis in 11 patients (35.5%) and viable cancer in four patients (12.9%). In 20 out of the 31 patients, laparotomy had been performed prior to thoracotomy to resect RRTM. In 10 out of these 20 patients (50.0%) the histology of the retroperitoneal tumor mass did not match that of the pulmonary tumor mass. During a median follow-up of seven (range 0.2-16.9) years, five patients died from the disease. The five-year survival rate was 86.6%, while the 10-year survival rate was 82.2%.

It can be concluded that all residual tumor masses should be surgically resected from patients who have received chemotherapy for a NSTGCT, irrespective of the histology of the lesion(s) removed first. This policy, with minimal morbidity, can lead to a 10-year survival rate of 82.2%.