Testicular germ cell tumours. New insights in epidemiology, genetic susceptibility and outcome.
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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2002

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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The management of patients with testicular germ cell tumours has changed substantially since the late 1970s, largely because of the ability of cisplatin-based polychemotherapy to cure patients with metastatic disease and also due to the development of new strategies in tumour-reductive surgery and radiotherapy. Today, more than 90 percent of patients with newly diagnosed testicular germ cell tumours (seminoma or nonseminoma) are cured with available treatment modalities. Further progress in the management of testicular germ cell tumours could result from an improved understanding of the epidemiology, biology and genetics of this uncommon malignancy.

The present thesis describes several epidemiological aspects of testicular germ cell tumours and focuses on the role of a genetic susceptibility of this malignant tumour. In addition, the thesis addresses some relevant topics in the current management of patients with stage I as well as metastatic nonseminomatous testicular germ cell tumours (NSTGCT) and reviews the long-term outcome of patients with metastatic NSTGCT treated at the Groningen University Hospital (GUH) in the past two decades.

The first section of Chapter I contains general information about testicular germ cell tumours. Several epidemiological and aetiologic aspects, with particular attention to observations suggesting a genetic predisposition to testicular germ cell tumours, are discussed. Furthermore, the histological classification of the World Health Organisation, clinical presentation, diagnosis and the value of serum tumour markers are described. Brief descriptions are given of the pattern of metastatic spread and accurate staging methods, and an overview of various prognostic classification systems including the classification system according to the International Germ Cell Cancer Collaborative Group (IGCCCG) is presented. Moreover, the treatment and prognosis of patients with stage I and metastatic testicular germ cell tumours are discussed.

In the second section of Chapter I the aims and outline of the present thesis are described.

Geographic variations in testicular cancer incidence may be caused by differences in environmental factors, genetic factors, or both. Thus, information on geographic patterns of occurrence may lead to more insight into the aetiology of testicular cancer, which is still poorly understood. The aim of the study described in Chapter 2 was to analyse geographic patterns of age-adjusted testicular cancer incidence rates (IRs) in 12 provinces in The Netherlands in the period 1989-1995. Moreover, the age-adjusted IR of testicular cancer by degree of urbanisation was evaluated. Cancer incidence data were retrieved from the files of the nation-wide population-based Netherlands Cancer Registry.

The overall annual age-adjusted IR of testicular cancer in The Netherlands in the
has changed cisplatin-based therapy. Today, germ cell tumours is due to the therapy. Further result from an uncommon germ cell prent tumour. In addition, Groningen showed the highest age-specific IRs in all relevant younger age groups (15-29, 30-44, and 45-59 years), illustrating the consistency of data. The province Friesland, also situated in the northern part of the country, showed the second highest IR of testicular cancer with 5.3 cases per 100,000 men per year (IRR 1.2, 95% CI 1.0-1.5, not significant). This mainly resulted from the high IR of seminoma in Friesland.

Analysis of age-adjusted IRs of testicular cancer by degree of urbanisation in The Netherlands showed no urban-rural differences at analysis of all histological types combined, or at separate analyses of seminomas and nonseminomas. It was concluded that geographic clustering of testicular cancer seems to be present in the rural northern part of The Netherlands areas with a stable founder population. People in this founder population are likely to share a relatively high frequency of genes from common ancestors including genes possibly related to testicular cancer. Although this finding does not exclude the involvement of shared environmental factors in the aetiology of testicular cancer, it may also lend support to a genetic susceptibility to testicular cancer development. We hypothesised that testicular cancer cases in stable founder populations seem particularly suitable for searching testicular cancer susceptibility genes because such genes are likely to show increased frequencies among affected men in founder populations.

The occurrence of bilateral testicular cancer (BTC) may also point to a role of genetic factors in the aetiology of testicular cancer. However, development of second contralateral testicular tumours is also influenced by systemic chemotherapy for the first tumour. Chapter 3 describes the prevalence and prognosis of BTC in a large single-centre population of 445 patients between 1967-1997 with initial stage I disease, in which no systemic treatment was given after first orchidectomy. The majority of stage I patients entered a surveillance study with an intensive follow-up since 1982. We therefore hypothesised that after 1982, BTC was diagnosed at an earlier stage of disease. The prevalence of BTC was 4.7% in a cohort of 170 stage I patients treated between 1967-1981, and 2.9% in a cohort of 275 stage I patients treated between 1982-1997 (not significant). In the period 1967-1981, six patients had stage I second tumours and two patients had stage III second tumours. The former six patients are alive with no evidence of disease and the two patients with metastatic tumours died of disease or of treatment. In the period 1982-1997, all 8 patients had stage I second tumours and all are alive with no evidence of disease. The overall prevalence of BTC in stage I patients was 3.6% and has slightly decreased over the past three decades. Patients developing a malignant tumour in both testes may be considered at high risk of having a genetic predisposition to the
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disease. Furthermore, intensive follow-up, improvement of radiodiagnostic CT techniques, availability of serum tumour markers, and patient education seem to have resulted in earlier diagnosis and lower stage of contralateral testicular tumours, contributing to improved prognosis.

Familial occurrence of testicular cancer also suggests a genetic predisposition to the disease. A genetic susceptibility may also be reflected by high rates of urogenital developmental anomalies and BTC in families prone to testicular cancer. In Chapter 4, the proportion of familial testicular cancer was analysed retrospectively in a single-centre population of 693 testicular cancer patients treated between 1977-97 and the relative risk (RR) for first-degree relatives of patients was estimated. In addition, the existence of urogenital developmental anomalies and bilateral testicular neoplasms in familial testicular cancer patients was evaluated.

Twenty-four of 693 patients (3.5%) had a first-degree relative with testicular cancer. These 24 cases belonged to 17 families; in seven of these 17 families both affected first-degree family members were part of the study population of 693 patients. Consequently, the 693 studied patients belonged to a total of 686 families. Thus, the actual proportion of familial testicular cancer was 2.5% (17 of 686 families). The familial cases consisted of 11 brother pairs, including two pairs of identical twins and one pair which also had two affected cousins, and six father-son pairs (in total 36 cases, 12 treated elsewhere). Estimates of the RR to first-degree relatives showed a 9- to 13-fold increased RR to brothers (P<0.001) and a 2-fold increased RR to fathers (not significant) of testicular cancer patients. Among the 36 patients with familial testicular cancer, two (5.6%) had BTC, four (11.1%) had undescended tests, three (8.3%) had inguinal hernia, and one (2.8%) showed renal hypoplasia.

The present data on familial occurrence of testicular cancer may lend additional support to a role of genetic factors in the aetiology of testicular cancer.

Current efforts in testicular cancer research have focused on developing treatment regimens based on prognostic factor analysis in order to provide an accurate risk-adapted management of testicular cancer patients. Since stage of disease affects treatment and prognosis, detailed information on stage distribution of testicular cancer is necessary for planning this research. In Chapter 5 the stage distribution was assessed using various classifications, i.e. the Royal Marsden (RM), Indiana, European Organisation for Research and Treatment of Cancer (EORTC), IGCCCG and the Medical Research Council (MRC), in 517 patients with NSTGCT treated at the GUH between 1977-96.

The number of patients in four consecutive 5-year periods (1977-81, 1982-86, 1987-91, 1992-96) was 119, 141, 141, and 116, respectively. Frequency analyses showed a significant increase of the number of RM stage I, in proportion to stage II-IV, in 1982-86 (55%, OR 2.54), 1987-91 (53%, OR 2.33) and 1992-96 (61%, OR 3.24) compared to the period 1977-81 (33%). A separate analysis of patients with disseminated disease showed a 9- to 13-fold increase of the number of RM stage I in 1992-96 (29% and 56% in 1992-96 compared to 1977-81) with 1977-81 (55%, OR 2.54), 1987-91 (53%, OR 2.33) and 1992-96 (61%, OR 3.24) compared to the period 1977-81 (33%). It was concluded that the stage distribution has not changed. The increasing number of stage I patients was apparently not due to a better identification of stage I.

This finding is of particular importance for the treatment of patients with disseminated disease in this period. Today, the so-called 'primary RT' regimen is used in patients with disseminated disease, and relapsing patients are treated. In the future, the strategy is to include patients with disseminated disease into the relapsing patient group. This will allow retrospective comparisons of current and future treatment strategies. This approach will result in more effective and less toxic treatments. Today, the proportion of patients in the primary RT group is only 29% (1992-96) compared to 55% (1977-81). This finding is of particular importance for the treatment of patients with disseminated disease in this period.
disease showed a proportionate significant decrease of the number of RM stage II in 1992-96 (29%, OR 0.43) compared with 1977-81 (49%). There was also a relative decrease of good-prognosis patients with disseminated disease in 1992-96 compared with 1977-81, using analyses of the Indiana (from 56% to 33%, OR 0.39) and EORTC classification (from 78% to 56%, OR 0.36). Analyses of the IGCCCG and MRC classification showed a significant decrease in the percentage of good-prognosis patients with metastatic disease in 1982-86 compared with the first 5-year period (for IGCCCG, from 54% to 35%, OR 0.46, and for MRC, from 43% to 24%, OR 0.42).

It was concluded that the stage distribution of NSTGCT over the past two decades has changed. The proportion of stage I patients has increased since the early 1980s, apparently resulting from a shift of low-extent disseminated disease to stage I disease. This finding is relevant in reducing the treatment intensity required in a higher proportion of patients and a subsequent reduction of long-term risk from treatment.

Today, the standard treatment for patients with clinical stage I NSTGCT is either primary RPLND or close surveillance with cisplatin-based polychemotherapy for relapsing patients. Both treatment modalities produce an excellent survival outcome approaching 100%. Consequently, selection of the most appropriate treatment strategy is not pre-eminently guided by survival considerations. In Chapter 6 relevant topics in the management of clinical stage I NSTGCT are reviewed to provide information that will allow a rational selection of the most appropriate management option. The choice between the available options, each having its merits and its drawbacks, should be made based on a number of factors including treatment-related morbidity, views and expertise of the physician, patient preferences, the expected degree of patient compliance, and prognostic factor analysis.

To date, the role of adjuvant chemotherapy as an alternative management option for patients with clinical stage I NSTGCT at high risk of metastatic disease is limited and needs further evaluation. This systemic adjuvant treatment modality would be a realistic alternative if the reliability of prognostic factors to identify clinical stage I patients at high risk of occult metastases could be improved. Reliable risk assessment will facilitate an accurate risk-adapted management of the individual patient, with a subsequent overall reduction of treatment-related morbidity.

The study described in Chapter 7 reviews chronological changes in the long-term outcome of patients with metastatic NSTGCT treated at the GUH in the past two decades. The 10-year survival of prognostic subgroups according to various prognostic classifications was examined in time to evaluate whether cumulative experience has led to an improved outcome of patients with metastatic NSTGCT, and to explore differences in outcome of prognostic subgroups.

Two hundred ninety-nine patients with metastatic NSTGCT who were treated with cisplatin-based polychemotherapy during the period from 1977 to 1996 were retrospectively staged according to RM classification and the following prognostic
classifications: IGCCCG, Indiana, MRC and EORTC. The number of patients treated between 1977-86 and 1987-96 was 146 and 153, respectively. Survival curves were constructed using the Kaplan-Meier method and disease-specific 10-year survival rates of prognostic subgroups treated during the two consecutive 10-year periods were compared using the logrank test.

The median follow-up of surviving patients during the periods 1977-86 and 1987-96 were 14.7 years (range, 0.2-20.6 years) and 7.0 years (range, 0.4-11.4 years), respectively. The actuarial disease-specific 10-year survival rate of patients with metastatic NSTGCT increased from 76% during the period 1977-86 to 88% during the period 1987-96 (RR 0.51, 95% CI 0.29-0.89, P<0.05). The 10-year survival rates of patients with good, intermediate and poor prognosis according to the IGCCCG classification were 95%, 74%, and 37%, respectively, during the period 1977-86 and 94%, 87%, and 66%, respectively, during the period 1987-96. Patients with a poor prognosis according to the IGCCCG classification showed the greatest increase in 10-year survival (RR 0.43, 95% CI 0.18-1.04, P=0.06). Analysis using the RM, Indiana, and EORTC classifications also showed an improved 10-year survival rate of patients with a poor prognosis who were treated during 1987-96 compared with those who were treated during 1977-86.

In conclusion, the 10-year survival rate of patients with metastatic NSTGCT who were treated with cisplatin-based chemotherapy significantly increased from 76% during the period 1977-86 to 88% during the period 1987-96. This improvement during the cisplatin era resulted mainly from an increase in the survival of patients with metastatic disease who had a poor prognosis. These results indicate that the management of NSTGCT is still improving.

Following cisplatin-based polychemotherapy for metastatic NSTGCT, mature teratoma is often found after resection of retroperitoneal residual tumour masses (RRTM). Chapter 8 describes the clinical course and outcome of patients after resection of residual teratoma, with particular emphasis on patients relapsing with either growing mature teratoma or secondary non-germ cell malignancy.

During the period 1979-95, 113 patients underwent a laparotomy for resection of RRTM after chemotherapy for NSTGCT. Only patients with mature teratoma in the RRTM were included in the present study, and data on the patients who experienced a relapse were studied in detail. Mature teratoma was found in 51 patients (45.1%) within RRTM resected after chemotherapy. Nine of these 51 patients (17.6%) relapsed; the relapses resulted from growing mature teratoma in five patients (9.8%), secondary non-germ cell malignancy in three patients (5.9%), and recurrent germ cell malignancy in one patient (2.0%). In eight patients (15.7%), the recurrent disease occurred after a disease free interval of at least two years after completion of cisplatin-based polychemotherapy. The primary treatment for all relapsing patients was surgical resection. All five patients with growing mature teratoma are alive without evidence of disease, as is the patient with recurrent germ cell malignancy. One of the three
patients treated with resection of postchemotherapy residual teratoma experienced complete disease remission in 45.1% of patients with a poor response to chemotherapy, 17.6% of patients with a moderate response, and 9.8% of patients with a good response. Of these, 8 patients (17.6%) have died of disease, 5 patients (11.4%) died of other causes (RRTM), and the remaining 7 patients are alive with disease.

It was concluded that long-term follow-up after resection of postchemotherapy residual teratoma is indicated because a proportion of patients develop growing mature teratoma or a secondary non-germ cell malignancy. The treatment for these recurrences should be aggressive, e.g. complete surgical resection.

In Chapter 9 guidelines for further research are suggested. In addition, the results of an extensive genotyping study of the HLA-region on chromosome 6 p21 in a large number of testicular cancer patients are described. This genotyping study performed at the GUH could not confirm the previously reported association between HLA class II genes and testicular germ cell tumours.