Germ cell cancer: prognostic factors, treatment results and risk for second cancer.

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English summary

Germ cell cancer (GCC) affects mainly males aged 15‑40 years. Since the introduction of cisplatin-based chemotherapy in 1974, treatment of GCC has improved markedly, and patients have a long expected lifetime; approximately 95% survive the disease for > 5 years. GCC has therefore been considered a model of curable cancer, and significant research has been conducted on treatment regimens, prognostic factors and late side-effects. This PhD thesis, based on data from the nationwide Danish Testicular Cancer (DaTeCa) database, contributes significant new data. The database includes information on approximately 5500 Danish patients with GCC diagnosed in 1984‑2007.

Identification of the pre-stage of GCC, germ cell neoplasia in situ (GCNIS), prompted introduction of a Danish screening programme for GCNIS in the contralateral testicle of GCC patients in the early 1980s to prevent the development of bilateral GCC. Patients with unilateral GCC are offered a biopsy of the contralateral testicle at the time of orchiectomy. If GCNIS is found, scrotal radiotherapy is applied to prevent the progression of GCNIS to invasive GCC. The incidence of contralateral GCNIS is approximately 5%, and previous studies have shown a low incidence of false-negative biopsies. We analysed data on 4130 patients screened for contralateral GCNIS (screened cohort) and compared them with 462 patients in whom GCC was diagnosed before the screening programme was implemented (unscreened cohort) (manuscript I). We found no difference in risk for bilateral (metachronous) GCC. A limitation of this study was the small size of the unscreened cohort. Nevertheless, these results raised the question of whether the screening programme should continue in its current form.

In order to compare the results of different regimens administered in different institutions, a common prognostic classification was established in 1997 for patients with disseminated disease treated with cisplatin-based chemotherapy. Approximately 6000 patients were classified into three prognostic groups with the corresponding survival probabilities. Only a

fraction of the patients who were classified, however, had been treated with today's standard: bleomycin, etoposide and cisplatin (BEP). We identified 1889 patients treated with first-line BEP (manuscript II) and found better survival after modern chemotherapy; we also identified possible new prognostic factors for relapse or death, which should be validated in larger cohorts of patients in an international collaborative study.

An excellent treatment outcome comes at a price. Patients with GCC are at increased risk for late effects of treatment, including second malignant neoplasms (SMNs). Previous studies on SMNs and mortality have been limited by short follow-up, missing details on treatment or use of older treatment regimens. The aim of this study was to define treatment-specific risks for SMN and death in comparison with a control group from the age-matched background population. We assigned 5194 patients to four treatment groups: surveillance, radiotherapy, BEP or more than one line of treatment (MTOL) (manuscript III). We found increased risks for SMNs after BEP, radiotherapy, and MTOL but not after surveillance. SMNs were the cause of excess deaths after BEP, radiotherapy and MTOL. We also found excess mortality due to infections after BEP, the majority due to HIV. The risk for SMN after treatment for GCC should be taken into account, and future studies should focus on genetic disposition to late effects, including SMNs.