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EDITORIAL

Testicular germ cell tumours – still many challenges

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The Swedish and Norwegian Testicular Cancer Group, SWENOTECA, has recently published a series of papers documenting survival of testicular cancer from a geographically complete population. The cancer specific five-year survival for all seminomas was 99.6%, and for non-seminomas 100% in stage I, and 91% in patients with metastases [1–3]. The cancer specific survival for all non-seminomas in Norway and Sweden is 97–98%, which is at top international level. Similar results have also been documented in other Nordic countries [4–6]. Of non-seminomatous patients with metastases considered tumour-free after primary treatment, 77% were cured by three or four standard BEP courses, while 18% needed addition of ifosfamide to obtain tumour control. Only 5% were referred to high dose therapy with stem cell support. In this issue of Acta Oncologica, Haugnes et al. give more information on the patients treated with high dose therapy [7]. An overall survival of 72% among those failing standard primary therapy is very encouraging. The high dose regimens also yielded 58% overall survival in relapsing patients, in line with previous studies [8,9]. The SWENOTECA's risk adapted strategy gives the majority of patients a chance to avoid potentially life-threatening side effects from high dose therapy (5% mortality) despite that they initially may present with poor prognostic factors. The results of previous randomised studies in poor prognosis patients and in the salvage setting, have not satisfactorily settled the case whether high dose therapy is a valuable treatment option, as discussed by Haugnes et al. [10,11]. The recent findings continue to indicate that high dose therapy remains a viable option in carefully selected subgroups [7,9].

A number of studies have addressed the relation between the increasing frequency of testicular cancer and other components of the testicular dysgenesis syndrome (chryptorchism, hypospady, poor semen quality), as originally proposed by Skakkebæk [12]. A focus has been on the influence of possible hormone disruptors or other environmental factors in utero or in early life [13,14]. Often a birth cohort effect has been concluded from epidemiological studies, but no causal factor has yet been discovered [15]. Immigration studies clearly document that first generation immigrants keep a similar risk profile as the country of birth, while the second generation adapts to the country of residence, further indicating an influence of external factors [16,17]. The challenge now is to identify possible preventable external factors.

The large geographical variance in incidence of testicular germ cell cancers has for a long time puzzled those interested in testicular cancer epidemiology and clinic [18]. There is a well known axis from the Baltic countries in East, through Finland and Sweden to Norway and Denmark where the incidence is highest in the world together with parts of Northern Germany and Switzerland (Figure 1) [6,19,20]. In this issue, Kvammen et al. demonstrate that there is variation within the counties in Norway, but less pronounced than previously reported from Denmark [21,22]. The aim of this new study was to demonstrate a possible difference in incidence related to county of birth and diagnosis. As the relative difference was similar by both criteria, the jury is still out whether an external, possibly lifestyle factor, can also influence the development of testicular cancer. There may be an element of western axis also within Norway as both Rogaland, and Møre and Romsdal are western coastal counties, similar to an east-west axis previously documented in Denmark, although it

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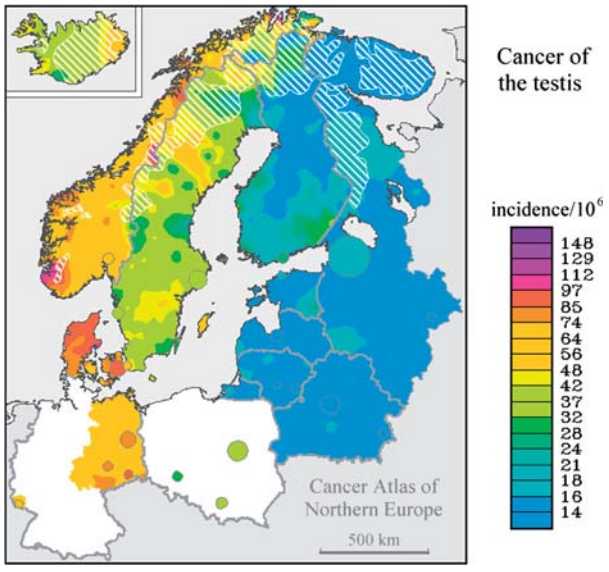

Figure 1. Incidence of testicular cancer in the Nordic countries. With permission from the Finnish Cancer Registry [20].

is much more clearly demonstrated between countries (Figure 1) [20].

In recent years there has been a strong focus on late side effects and rehabilitation of cancer survivors [23–27]. Impaired cognitive function as a potential side effect of chemotherapy has gained considerable interest among health professionals and patients. It has popularly been referred to as "chemo-brain" [28–30]. In adults this phenomenon has most extensively been studied in women treated for breast cancer. The cognitive changes are subtle and complex with a number of confounding factors, including hormonal changes, fatigue, and psychological aspects [30–32]. A few studies have addressed cognitive function in men treated for testicular cancer [33–38]. Some report self-reported cognitive complaints to be rather common irrespective of cancer treatment, or to increase following chemotherapy [35,38]. However, self-reported cognitive problems were not related to a decline in neuropsychological performance, but rather with emotional distress and fatigue. Skoogh et al. in this issue present the results of a study performed in 960 Swedish testicular cancer survivors, three to 26 years following their cancer treatment [39]. The study focuses on activities and behaviour in everyday life that may depend on cognitive function, assessed by a study-specific questionnaire that included 59 questions reflecting six specific cognitive domains [attention, memory, visual-spatial ability, language, speed ("slow thinking") and executive function ("activating")], and six questions assessing affected well-being if having difficulties within each of these domains.

Compared with men who only had orchiectomy, they found that men treated with five or more cycles experienced compromised language, with significant findings in five of seven language questions ("at least once a week", relative risk 2.0–3.3), primarily in men with low education. Significant findings in the other domains were not found, except in a minority of the questions (3 of 26) reflecting memory. As the relative risks pertain to problems experienced at least once a week, and most domains were not affected, the overall cognitive problems may be considered rather subtle. However, testicular cancer patients treated with five or more cycles reported more affected well-being if having difficulties within four of the studied domains. Testicular cancer survivors treated with five or more cycles are in general more susceptible to late effects [40–42]. Today, the majority of metastatic patients are cured by three to four BEP cycles, and for these men the results of the current study are reassuring, as no significant findings were found following up to four cycles.

Chemotherapy associated cognitive changes are in some patient groups supported by the documentation of changes in both white and grey matter by dedicated magnetic resonance imaging (MRI) examination [43,44]. The mechanisms behind cognitive changes are largely unknown, and there are still many unanswered questions. It is likely that the varying genetic background plays a role in the inter-individual susceptibility of such effects [45]. Some genetic candidates have been proposed for neurotoxicity and hearing loss [46–48]. In rats impaired memory after chemotherapy was prevented by simultaneous administration of an antioxidant (N-acetyl cysteine) [49]. Thus cognitive effects may possibly be prevented in the future, but much research is needed before preventive drugs can be administered concurrently with curative chemotherapy in human beings.

In the early 1980s, following the successful publications on major progress in testicular cancer patients in Denmark, one of the researchers said: "The problem with testicular cancer is now solved" [50–52]. Clinicians have later been through a period with the introduction of new diagnostic tools and a more refined and personalised approach. In addition to the topics discussed above, the new genetic analyses, currently used as research tools, certainly will provide new insight which we as clinicians must adapt into practical clinical settings [53–57].

Thus there are still many questions to be solved, but we all should be encouraged by the progress made during the past 30 years.

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