EUROPEAN JOURNAL OF CANCER 43 (2007) 2553–2558

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Testicular cancer: Trends in mortality are well explained by changes in treatment and survival in the southern Netherlands since 1970

R.H.A. Verhoeven[a,b], *J.W.W. Coebergh*[a,c,*], *L.A.L.M. Kiemeney*[b,d], *E.L. Koldewijn*[e,f], *S. Houterman*[a,f]

[a]*Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ), P.O. Box 231, 5600 AE Eindhoven, The Netherlands*
[b]*Department of Epidemiology and Biostatistics, Radboud University Nijmegen Medical Centre, The Netherlands*
[c]*Department of Public Health, Erasmus University Medical Centre Rotterdam, The Netherlands*
[d]*Department of Urology, Radboud University Nijmegen Medical Centre, The Netherlands*
[e]*Department of Urology, Catharina Hospital, Eindhoven, The Netherlands*
[f]*Regional Study Group for Urological Oncology IKZ, Eindhoven, The Netherlands*

ARTICLE INFO

Article history:
Received 22 August 2007
Accepted 24 August 2007
Available online 18 October 2007

Keywords:
Conditional relative survival
Mortality
Relative survival
Testicular cancer
Treatment

ABSTRACT

The aim of this study was to interpret changes in mortality from testicular cancer (TC) against the background of changes in treatment and survival in the south of The Netherlands.

Five-year moving average standardised mortality rates were calculated. Primary treatment and relative survival were analysed according to histology, stage and year of diagnosis.

The mortality rate dropped in the period 1979–1986 and then flattened out. The types of treatment that patients received did not change significantly over time and were according to the guidelines. Ten-year relative survival for seminoma TC patients improved from 81% (67–91%) in 1970–1979 to 95% (88–100%) in 2000–2002; for non-seminoma TC patients these rates were 54% (38–68%) and 92% (85–99%), respectively. Conditional 5-year relative survival for seminoma and non-seminoma TC patients 5 years after diagnosis was 99% and 96%, respectively.

In conclusion, there was an enormous increase in relative survival and a significant decrease in mortality.

1. Introduction

Although testicular cancer (TC) only accounts for 0.8% of all male cancers,[1] it is the most common malignancy amongst men aged 15–44 in developed countries. Of all TCs, 95% are germ cell tumours, which are grouped histologically into seminomas and non-seminomas.[2] The majority of the seminoma TCs are diagnosed amongst men in the age group of 30–45 years, while most of the non-seminoma TC patients are between the ages of 20 and 35 years.[2]

The incidence of TC is increasing throughout Europe, but there are large variations in the incidence rates and in the speed at which incidence increases across the European countries.[3] Relative survival of TC has increased during the last 40 years to an average 5-year rate of 93% in Europe,[4–7] but also with substantial variations across Europe.[6] In addition to stage at diagnosis,[8] age at diagnosis matters, younger

* *Corresponding author:* Address: Eindhoven Cancer Registry, Comprehensive Cancer Centre South (IKZ), P.O. Box 231, 5600 AE Eindhoven, The Netherlands. Tel.: +31 40 2971616; fax: +31 40 2971610.
E-mail address: research@ikz.nl (J.W.W. Coebergh).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.08.022

patients exhibiting better survival than older patients.[8,9] Most of the increase in survival is primarily attributed to the introduction of effective cisplatin-containing chemotherapy for advanced disease in the 1970s.[4,10] Mortality has dropped by about 70% in the USA and Europe since the 1970s, but at a lower pace in Eastern Europe than in the European Union and the USA.[11]

The aim of this study was to detect trends in treatment, survival and mortality of TC in the south of the Netherlands from 1970 to 2004, where the management of TC was decentralised.

2. Patients and methods

2.1. Patients

The Eindhoven Cancer Registry (ECR) has collected data on all patients with newly diagnosed cancer in the southern part of the Netherlands since 1955.[12] Until 1988, only patients diagnosed in the eastern part of the area were registered, but since that year patients diagnosed in the middle and western part of North Brabant are also included. Nowadays, the registry serves a population of 2.4 million inhabitants. The area offers good access to specialised medical care in nine general hospitals and two large radiotherapy institutes. Information on diagnosis, staging and treatment was extracted from the medical records by trained registrars.

All testis cancer patients diagnosed between 1970 and 2004 were included in the study. The tumours are grouped according to histological origin, as described in the third revision of the International Classification of Diseases for Oncology (ICD-O)[13]: seminomas (ICD-O codes: 9060–9064), non-seminomas (ICD-O codes: 9065–9085, 9100–1902, 9105) or other. The stage grouping of the TNM-classifications of TC has changed over time in such a way that it became impossible to compare the different stage groups over time. We have therefore chosen to categorise the extent of the disease as: localised (any T, N = 0 and M = 0), lymph node metastasis (any T, N > 0 and M = 0), distant metastasis (any T, any N and M > 0) and unknown. Patients with stage unknown were left out of the stage-specific analysis. Stage was recorded reliably from 1980 onwards, so only patients diagnosed since then were included in the stage-specific analyses.

2.2. Treatment

Five major subgroups were considered for primary treatment: surgery only, surgery and radiotherapy, surgery and systemic therapy, unknown and other/none. The specific type of therapy was not registered, therefore it was not possible to identify whether a patient received cisplatin-containing chemotherapy or another type of chemotherapy.

A fisher-exact test was used to test whether there was an overall change in administered treatment over time. This was done according to histology and stage.

2.3. Relative survival

Data on vital status (available until 1st January 2005) were obtained from the hospital records and the mortality register of the Central Bureau for Genealogy (an institution that registers all deaths in the Netherlands via the municipal population registries). Data on vital status were only available for patients diagnosed in or before 2002.

Relative survival is an estimation of the disease-specific survival. It is calculated as the absolute survival amongst cancer patients divided by the expected survival for the general population with the same sex and age structure.[14] Relative survival was computed with the traditional cohort-analysis for periods with complete 5 and 10-year follow-up. Period analysis was used to estimate the relative survival for the most recent periods with incomplete 5 or 10-year follow-up.[15] Survival analyses were carried out according to histology and stage.

Conditional survival was computed with period analysis for patients diagnosed between 1970 and 2002, and was performed according to histology. Five-year relative survival was computed for every additional year survived, conditional on being alive at that moment. Since patients who have already survived for some years are older than at diagnosis, conditional relative survival rates were also adjusted for survival in the general population with the same age distribution as patients at that time. A conditional 5-year relative survival at year x is the 5-year relative survival for patients who are still alive x years after diagnosis of TC.

2.4. Mortality

Mortality data were obtained from Statistics Netherlands for the period 1970–2005. Five-year moving average European standardised mortality rates per 100,000 person–years were calculated and compared to the Dutch testicular cancer mortality.[16] In addition, trend estimated annual percentage of change analysis was performed for different time periods. For the period 1970–1988 the Dutch mortality rates were only available as crude mortality rates.

3. Results

3.1. Treatment

In total, 966 patients were included for treatment analysis (54% seminoma and 46% non-seminoma).

The overall treatment of the localised seminoma TC patients changed significantly ($p < 0.0001$) over time (Fig. 1a), the surgery alone treatment was lower in the period 1990–1999 than in the other two periods. While the percentage of patients who received surgery and radiotherapy was higher in the period 1990–1999 (93%) in contrast to the periods 1980–1989 (82%) and 2000–2004 (85%). The treatment in the group of seminoma TC patients with lymph node metastasis changed significantly ($p < 0.001$), the percentage of patients who received surgery and radiotherapy decreased from 58% in the 1980s to 32% in the period 2000–2004, while the percentage of patients who received surgery and systemic therapy increased from 33% to 64% in the same period. The distant metastases seminoma TC patients exhibited no significant differences in treatment over time, the number of patients in this group was small ($n = 22$).

In the non-seminoma treatment group there was a significant difference ($p < 0.0001$) in the treatment of patients with

localised disease over time (Fig. 1b). The percentages of localised non-seminoma TC patients who received only surgery and who received surgery and systemic therapy fluctuated over time. The treatment of non-seminoma TC patients with lymph node metastasis changed significantly over time ($p < 0.0001$). Patients more frequently received surgery and systemic therapy in the period 2000–2004 (96%) than in the period 1980–1989 (68%). The changes of treatment of non-seminoma TC patients with distant metastases ($p < 0.01$) are contributable to an increase in the other/none category. Most of the patients in the other/none treatment group received systemic therapy with or without other treatments.

3.2. *Survival*

During a mean follow-up of 10 years, 167 patients died (87 seminoma and 68 non-seminoma).

For seminoma TC, 10-year relative survival improved from 81% (95% Confidence Interval 67–91%) in 1970–1979 to 94% (83–100%) in the period 1980–1989 while remaining relatively stable in the next decade (Fig. 2a). For non-seminoma TC patients these rates increased from 54% (38–68%) in 1970–1979 to 87% (76–93%) in the period 1980–1989 and to 92% (85–99%) in the 1990s (Fig. 2b). The greatest improvement in survival took place in the second half of the 1970s and the early 1980s.

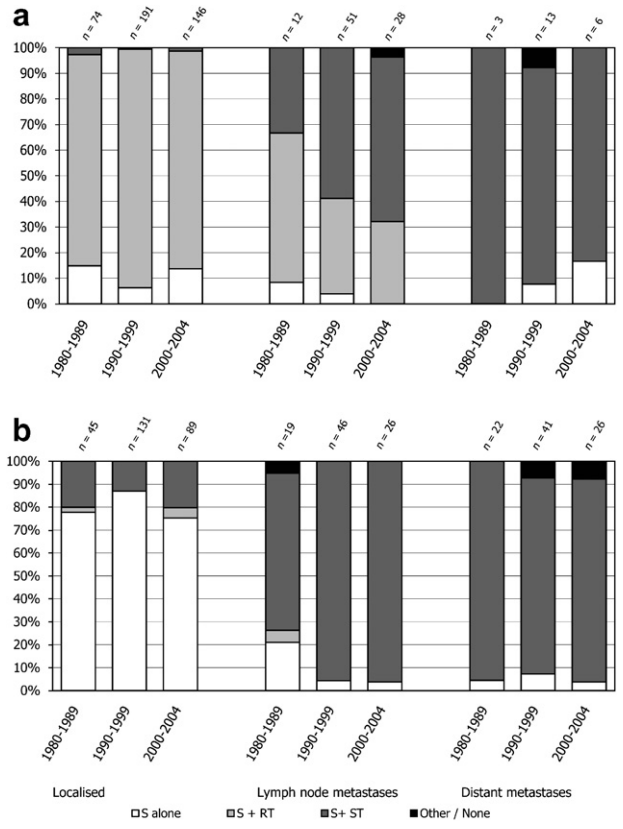

Fig. 1 – Primary treatment of seminoma (a) and non-seminoma (b) testicular cancer according to histology, stage and time. (S, surgery; RT, radiotherapy; ST, systemic therapy).

Ten-year relative survival in the period 1990–2002 was high for patients with both localised seminoma (92%; 86–96%) and localised non-seminoma TC (97%; 92–99%) (Fig. 3). The 10-year relative survival of seminoma TC patients with lymph node metastasis was slightly lower than that of the localised seminoma TC patients (88% versus 92%). Non-seminoma TC patients with lymph node metastasis also had a slightly worse 10-year survival than localised non-seminoma TC patients (93% versus 97%). Three-year survival for the seminoma TC patients with distant metastases was 63%. For the non-seminoma TC patients with distant metastasis 10-year survival was 75%.

Relative survival of patients with TC younger than 50 years was slightly higher than that for those $\geqslant 50$. Only the 1-year relative survival was significantly different: 99% (98–100%) versus 93% (84–98%).

Fig. 4 shows the relative survival curve at diagnosis for both histologies, as well as the conditional 5-year relative survival rate for each additional year survived. For non-seminoma TC patients the conditional 5-year relative survival was 96% after 5 years and for seminoma TC patients it was 98%. Ten years after diagnosis this was 98% and 100%, respectively.

3.3. *Mortality*

After a slight increase in mortality from 0.8 to 1.0 in the period 1970–1978 (Fig. 5), the 5-year moving average mortality rate decreased from around 1.0 per 100,000 person–years in 1979 to 0.4 in 1986, the average annual change being –12%

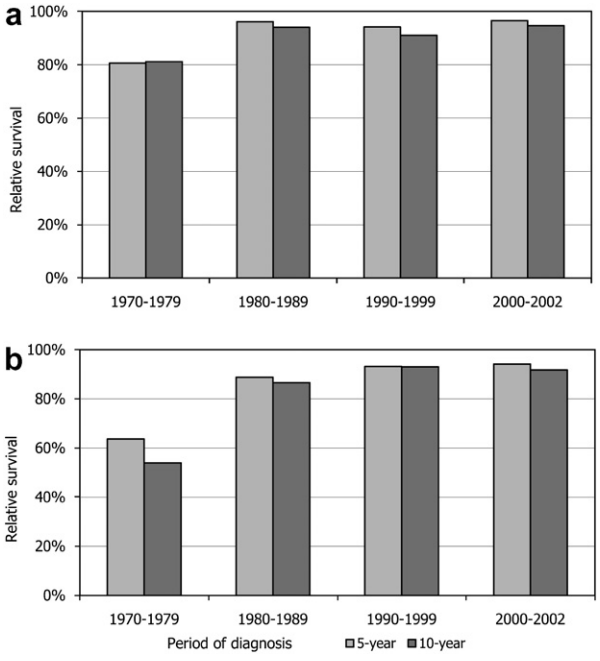

Fig. 2 – Five- and 10-year relative survival of patients with seminoma (a) and non-seminoma (b) testicular cancer in the south of the Netherlands. The 10-year survival of the period 1990–1999 and the 5- and 10-year relative survival of the period 2000–2002 were calculated by means of period analysis.

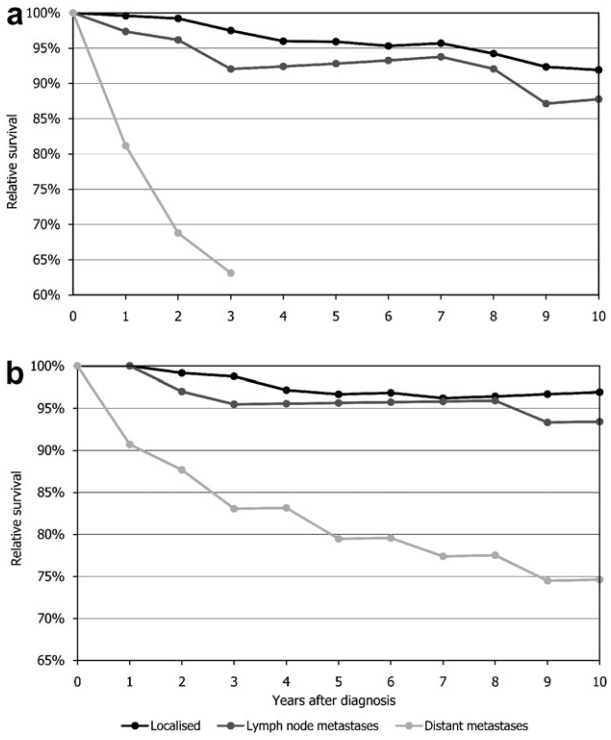

Fig. 3 – Relative 10-year survival curve according to stage for seminoma (a) and non-seminoma (b) testicular cancer patients diagnosed in the south of the Netherlands during 1990–2002.

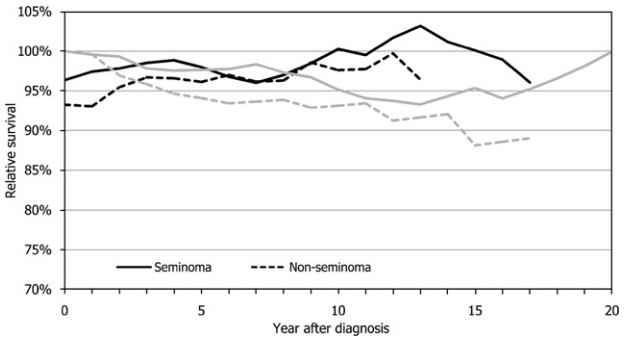

Fig. 4 – Actuarial and conditional survival for patients with seminoma and nonseminoma testicular cancer. Black lines are conditional 5-year survival rates; grey lines are relative survival rates at diagnosis.

($p = 0.07$). In the latest period, 1987–2005, the mortality rate fluctuated between 0.2 and 0.5, being similar to the trend for the entire Netherlands.

4. Discussion

This study shows a marked increase in survival of TC, especially for non-seminoma TC, in the south of the Netherlands since the mid-1970s accompanied by a significant decrease in mortality. These changes started in the late 1970s and continued to change until the end of the 1980s. Since 1990 the survival and mortality have remained relatively steady.

Fig. 5 – Five-year moving average testicular cancer European standardised mortality rates per 100,000 person–years (ECR, Eindhoven Cancer Registry). *For the period 1970–1988, non-standardised rates were used to calculate the 5-year moving average.

4.1. *Treatment*

Allmost all (99.9%) of the patients who received surgery underwent an orchidectomy, while only 22 lymph node dissections were registered, 17 of which were carried out in the period 2000–2004. The fact that this number of lymph node dissections is lower than expected is because we only registered primary treatment within 6 months of diagnosis. Most secondary lymph node dissections were probably performed more than 6 months after diagnosis.

National and international guidelines[17–20] recommend surgery and radiotherapy for patients with localised seminomas. In our study, 82% of these patients received this combined treatment in the 1980s increasing to 93% in the period 1990–1999 and decreased to 85% in the period 2000–2004. Seminoma TC patients with lymph node metastasis were advised to undergo surgery and radiotherapy or systemic therapy depending on the size of the lymph node metastases. Ninety-five percent of these patients received one of these treatment combinations. The number of patients who underwent surgery and systemic therapy appears to be increasing. Eighty-six percent of the seminoma TC patients with distant metastasis underwent surgery and systemic therapy as indicated in the guidelines.

Surgery only or surgery and systemic therapy has been advised for patients with localised non-seminomas, and 98% received either one of these two treatment combinations. Surgery with systemic therapy is the preferred treatment for non-seminoma TC patients with lymph node and distant metastasis, 90% and 89% of these patients received this combined treatment, respectively.

In total there were 9 patients in the other/none treatment category, 1 of whom received no therapy; the other 8 patients underwent systemic treatment with or without other treatments.

The beneficial effect of centralisation of treatment of TC patients with distant metastases, which has been described repeatedly, arises from the complexities of staging, supportive care during aggressive systemic treatment and dedicated surveillance.[21] However, in our region clinical management of TC has remained relatively decentralised, only 60% of patients with distant metastastic tumours have been treated in larger hospitals, with little change over time. In the 1990s survival from TC in the south of the Netherlands was similar

to that of the Northwest region of the country, where treatment is concentrated in three major cancer centres.[22]

4.2. Survival

Relative survival of patients with seminomas and non-seminomas increased substantially over time to a 5-year survival of 97% for seminomas and 94% for non-seminomas in the period 2000–2002, similar to the North west region of the Netherlands (98% and 95%, respectively[22]), England and Wales (5-year survival of TC improved from 70% in 1971–1975 to 95% in 1991–1993[4]) and Sweden (5-year survival of seminoma and non-seminoma TC improved from about 87% and 47% in the mid 1960s to 97% and 96% in the mid 1990s, respectively[5]).

Survival analyses according to stage and histology showed better survival for localised disease and lymph node metastasis compared to distant metastasis of both seminoma and non-seminoma TC, similar to the results for most of the countries in the EUROCARE study, which covered the diagnostic period 1987–1992.[8]

American TC patients younger than 50 years exhibited significantly better survival for almost all histological and stage subgroups than TC patients of 50 years and older,[9] as in the EUROCARE study.[8] We also found higher survival rates for patients below the age of 50, but only 1-year survival was significantly different.

A group of patients can be considered cured when the conditional 5-year relative survival approaches 100%. Survival for this group of patients is then similar to that for the general population with the same age structure. Under these conditions seminoma TC patients are cured after 3 years and non-seminoma TC patients after 9 years.

4.3. Mortality

Mortality dropped from around 1 per 100,000 person–years to 0.3 in 2005, with the greatest decrease in the period 1979–1986. This pattern of steep decrease is similar to what was found for male populations of the United States and the European Union and is generally (in the absence of any other reasonable explanation) attributed to better systemic therapy.[4,23,24] The fluctuations in the period 1986–2005 are most likely due to random variation around a general trend of mortality and a rising incidence, mainly for localised TC, in the south of the Netherlands.[25]

5. Conclusion

Although the treatment combinations prescribed for these patients did not vary over time and the treatments administered followed national and international guidelines, there was a substantial improvement in TC survival over time, resulting in a marked decrease in mortality since the 1970s, which has been sustained in the last 15 years despite a marked increase in incidence.

Conflict of interest statement

The authors have no conflicting interests in regard to this submitted article.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**:74–108.
2. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review. *J Urol* 2003;**170**:5–11.
3. Huyghe E, Plante P, Thonneau PF. Testicular cancer variations in time and space in Europe. *Eur Urol* 2007;**51**:621–8.
4. Power DA, Brown RS, Brock CS, Payne HA, Majeed A, Babb P. Trends in testicular carcinoma in England and Wales, 1971–99. *BJU Int* 2001;**87**:361–5.
5. Talback M, Stenbeck M, Rosen M, Barlow L, Glimelius B. Cancer survival in Sweden 1960–1998 – developments across four decades. *Acta Oncol* 2003;**42**:637–59.
6. Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94 – results and commentary. *Ann Oncol* 2003;**14**(Suppl 5):v61–v118.
7. Aareleid T, Sant M, Hedelin GEUROCARE Working Group. Improved survival for patients with testicular cancer in Europe since 1978. *Eur J Cancer* 1998;**34**:2236–40.
8. Sant M, Aareleid T, Artioli ME, et al. Ten-year survival and risk of relapse for testicular cancer: a EUROCARE high resolution study. *Eur J Cancer* 2007;**43**:585–92.
9. Spermon JR, Witjes JA, Kiemeney LA. Difference in stage and morphology-adjusted survival between young and elderly patients with a testicular germ cell tumor. *Urology* 2002;**60**:889–93.
10. Einhorn LH. Curing metastatic testicular cancer. *Proc Natl Acad Sci USA* 2002;**99**:4592–5.
11. Levi F, La Vecchia C, Boyle P, Lucchini F, Negri E. Western and eastern European trends in testicular cancer mortality. *Lancet* 2001;**357**:1853–4.
12. Coebergh JWW, Janssen-Heijnen MLG, Louwman WJ, Voogd AC, editors. *Cancer incidence, care and survival in the South of the Netherlands, 1955–1999: a report of the Eindhoven Cancer Registry with cross border implications*. 1st ed. Eindhoven: Comprehensive Cancer Centre South (IKZ); 2001.
13. Fritz A, Percy C, Jack A, et al. *International classification of Diseases for Oncology*. 3rd ed. Geneva: World Health Organization; 2000.
14. Hakulinen T, Abeywickrama KH. A computer program package for relative survival analysis. *Comput Programs Biomed* 1985;**19**:197–207.
15. Brenner H, Gefeller O, Hakulinen T. Period analysis for 'up-to-date' cancer survival data: theory, empirical evaluation, computational realisation and applications. *Eur J Cancer* 2004;**40**:326–35.
16. <http://www.ikcnet.nl/page.php?id=217> [accessed January 20, 2007].
17. Albers P, Albrecht W, Algaba F, et al. Guidelines on testicular cancer. *Eur Urol* 2005;**48**:885–94.
18. Horwich A, Shipley J, Huddart R. Testicular germ-cell cancer. *Lancet* 2006;**367**:754–65.
19. Dearnaley D, Huddart R, Horwich A. Regular review: managing testicular cancer. *BMJ* 2001;**322**:1583–8.
20. Available from URL: http://www.oncoline.nl/richtlijn/item/pagina.php?id=17244&richtlijn_id=302 [accessed Jun 14, 2006].
21. Collette L, Sylvester RJ, Stenning SP, et alEuropean Organization for Research and Treatment of Cancer Genito-Urinary Tract Cancer Collaborative Group and the Medical Research Council Testicular Cancer Working Party. Impact of the treating institution on survival of patients with "poor-prognosis metastatic nonseminoma. *J Natl Cancer Inst* 1999;**91**:839–46.

22. <http://www.ikcnet.nl/page.php?id=224> [accessed January 20, 2007].
23. Levi F, Lucchini F, Boyle P, Negri E, La Vecchia C. Testicular cancer mortality in Eastern Europe. *Int J Cancer* 2003;**105**:574.
24. Hatton MQ, Paul J, Harding M, MacFarlane G, Robertson AG, Kaye SB. Changes in the incidence and mortality of testicular cancer in Scotland with particular reference to the outcome of older patients treated for non-seminomatous germ cell tumours. *Eur J Cancer* 1995;**31A**:1487–91.
25. Verhoeven RHA, Houterman S, Kiemeney LALM, Koldewijn EL, Coebergh JWW. Testicular cancer: marked birth cohort effects on incidence and trends in stage distribution and mortality in southern Netherlands since 1970. Int J Cancer [in press].