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Original Paper

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

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This paper describes the temporal pattern of germ cell testicular cancer in Scotland between 1960 and 1990. The effect of age on the prognosis of patients with non-seminomatous germ cell tumours (NSGCT) has been assessed by studying all patients presenting in the West of Scotland between 1975 and 1989. Between 1960 and 1990, the number of testicular germ cell tumours registered has increased more than 2-fold; mortality rates have declined equally dramatically. Univariate and multivariate analysis of the data obtained on 440 patients with NSGCT showed age was not a prognostic factor influencing survival. 52 were patients over 40 years at presentation; their 5 years survival was 71% compared with 79% in the younger patients (n = 388). This small survival difference is probably explained by the higher proportion of older patients treated before 1980. Treatment for this older group should be approached with the same curative intent as for younger patients and the same expectation of success.

Key words: testicular germ cell cancer, incidence, prognosis, age
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INTRODUCTION

SEVERAL STUDIES have shown that the incidence of germ cell testicular cancer is increasing [1–3]. The aetiology of this cancer is largely unknown and there is little explanation for the changing incidence. This paper updates the temporal pattern changes of germ cell testicular cancer in Scotland.

We also update the effect of treatment advances on the mortality from germ cell testicular cancer by comparing the temporal trends in incidence and mortality. This is a reliable method of assessing the population impact of improvements in treatment, as distinct from the more common reports, from single [4] or multicentre studies [5], whose patients are selected by referral patterns. Scotland (population 5 million) has the incidence and mortality data to make this method possible.

The second aim of this paper is to look specifically at age as a prognostic factor in non-seminomatous germ cell tumours (NSGCT). Increasing age is an adverse feature for a number of cancers curable with chemotherapy [6–8], although the effect of age on the prognosis of patients with NSGCT is not clear. Some studies, most notably the second MRC study [5], indicate that age is a significant independent prognostic factor for survival, but the importance of age was considerably reduced if deaths from NSGCT alone were considered. Therefore, age was not included in the prognostic index proposed by the authors to define groups of patients in need of more aggressive treatment. Other studies have not shown increasing age to be an independent predictor of worse survival in NSGCT [9, 10].

The results of an observational study, on men with NSGCT diagnosed between 1975 and 1989, are presented, comparing the survival of a minority of older men, with those 40 years and younger.

PATIENTS AND METHODS

Mortality data were taken from the annual reports of the Registrar General for Scotland from 1960 to 1990 [11]. These

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give the population of Scotland, and the number of deaths, in 5 year age bands. Incidence data were available from the Scottish Health Services Common Services Agency, collected via five population based regional registers in Glasgow, Edinburgh, Dundee, Aberdeen and Inverness.

The data are shown with rates that have been age-standardised to the World Standard Population [12]. In view of the low annual incidence of testicular germ cell tumours, a 3 year moving average rate was calculated increasing the stability of the rate. The age-specific data for years 1960, 1961 and 1962 were aggregated and then age-standardised. This average, age-standardised rate per 100 000 person-years was taken as the rate for 1961. Data from 1961 to 1963 gave the 1962 rate and the process repeated until a rate was obtained for 1989.

The population of the West of Scotland Health Board areas (2.74 million) was used to study the effect of age on prognosis of non-seminomatous germ cell tumours in greater detail. All patients living in this area who had non-seminomatous germ cell tumour diagnosed between January 1975 and December 1989 were included, and permission was obtained to study their clinical records. The West of Scotland Cancer Registry was used to identify patients, as were independent listings in the University Department of Medical Oncology (Glasgow) and the Glasgow Institute of Radiotherapy and Oncology. Data taken from the records included age, site and volume of disease and tumour marker concentrations. The data were used to classify patients as having localised (stage 1) or metastatic disease of good or poor prognosis, according to current MRC criteria [5].

Pearson's *chi*-squared test was used to compare the distribution of prognostic factors in those patients over 40 years old and their younger counterparts. Actuarial survival curves were based on Kaplan–Meier estimates [13]. Deaths that were not caused by non-seminomatous germ cell tumours or its treatment were considered censoring events. The Cox proportional hazard model was used to identify factors affecting survival [14].

RESULTS

Incidence and mortality data

The incidence of testicular germ cell cancer has risen in all age groups between 1961 and 1990. The number of registrations has increased from around 60 to 150 per annum; the incidence rate has risen approximately 1.4-fold, rising from 2 to 3 per 100 000 in the early 1960s to 5–6 per 100 000 in the late 1980s (Figure 1). Over 70% of all cases occur in men under 40 years old and it is in this age group that the increase in incidence is most prominent, rising from 4 to 10 per 100 000 between 1961 and 1988 (Figure 2). The rise in incidence in testicular germ cell tumours is much less marked in men over 40 years; the rate having increased 40% from 2.35 to 3.35 per 100 000 between 1961 and 1989 (Figure 3).

Initially, there was a small rise in overall mortality; the rates then stabilisd at around 1.1 cases per 100 000 until the late 1970s, when a steady decrease in the mortality rate became apparent (Figure 1). This trend is most prominent in the younger age group, although a similar pattern is seen in those over 40 (Figures 2 and 3).

Age as a prognostic factor

Within the West of Scotland Health Board area, 454 men were diagnosed as having NSGCTs between 1975 and 1989. 14 men were excluded from the subsequent analysis; 12 whose records were not available, 1 whose date of diagnosis was not known, and 1 who was referred to a specialist unit outside Scotland. 52

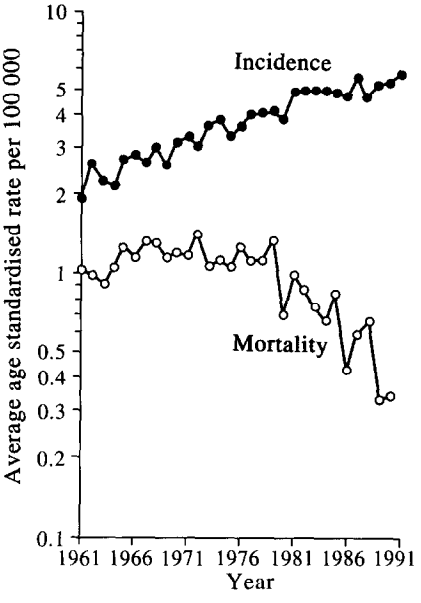

Figure 1. Incidence and mortality of testicular cancer in Scotland (all ages). Age-standardised rates per 100 000; 1960 to 1990.

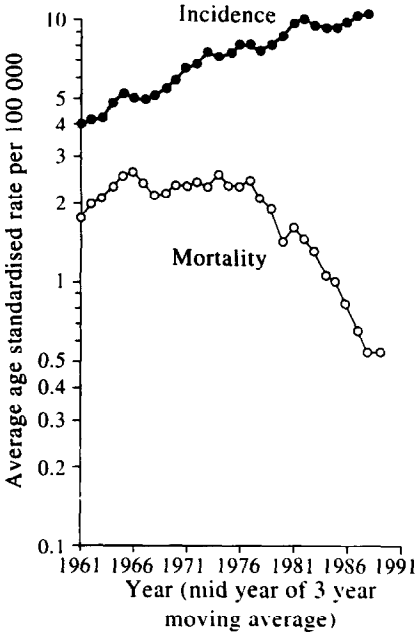

Figure 2. Age-standardised incidence and mortality rates per 100 000 in Scotland (age 15–40 years); 1961 to 1989.

of the remaining patients were over 40 years old, with a median age of 45 years and a maximum of 67 years.

Histology was similar in the two age groups (Table 1). There was no significant difference in prognostic category at diagnosis or referral pattern, although the increase in the number of young men over time is notable (Table 2). Relapse rates for stage 1 patients were similar in the two groups; 6 men in the older age group (28.6%) and 40 (26.1%) in the younger group. 316 patients were eligible for treatment of advanced disease, although 10 died before this was administered. Of the 306 patients who received treatment, 35 were over the age of 40 years. This represents 67% of this group and compares with 70% of the younger patients treated for advanced disease.

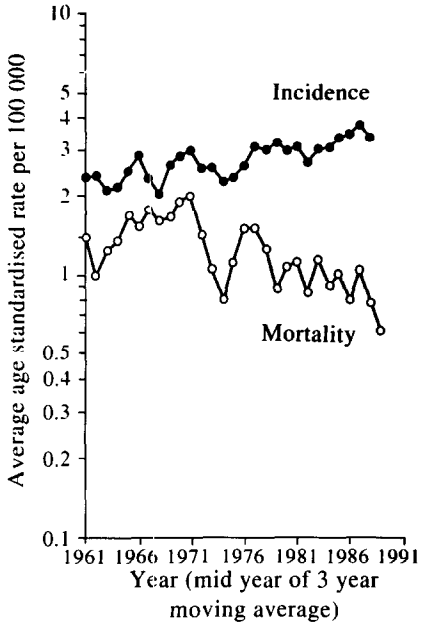

Figure 3. Age-standardised incidence and mortality rates per 100 000 in Scotland (aged over 40 years); 1961 to 1989.

Table 1. Distribution of histological diagnoses at presentation

	Age > 40 (n = 52)	Age ≤ 40 (n = 388)
MT differentiated	4 (7.7%)	18 (4.6%)
MT intermediate	15 (28.8%)	142 (36.6%)
MT undifferentiated	27 (51.9%)	184 (47.4%)
MT NOS	2 (3.8%)	13 (3.3%)
No definite pathology	4 (7.7%)	31 (8.0%)
Other pathology		
+ seminoma	10	62
+ MT trophoblastic	3	42
+ Yolk sac	16	77

MT, malignant teratoma.

Stage I disease was increasingly managed according to the MRC protocols. A range of chemotherapy regimens were employed in the treatment of advanced disease, the most common of which were BEP (bleomycin, etoposide, cisplatin) (25%), PVB (cisplatin, vinblastine, bleomycin) (24%), EP (etoposide, cisplatin) (12%), BOP/VIP (bleomycin, vincristine, cisplatin/etoposide, ifosfamide, cisplatin) (10%), BEP/PVB (7%). No significant differences were found in the chemotherapy regimens given to the two age groups, although numbers were small (Table 3). Both patient groups received a median of four treatment cycles (the range was 1–12 for those over 40 years old, and 1–17 for the younger age group).

In the group studied, 100 men died, 90 from NSGCT. Treatment was considered to have contributed to 6 of these deaths. Among older men, 17 (33%) died; 14 from the underlying malignancy or its treatment. 83 (21.4%) deaths occurred amongst the younger patients, 76 of which were tumour-related.

Table 2. Distribution of prognostic factors at the time of diagnosis

	Age > 40 (n = 52)	Age ≤ 40 (n = 388)	
Small volume	42 (80.8%)	281 (72.4%)	
Large volume	4 (7.7%)	61 (15.7%)	$\chi^2 = 2.44$
Very large volume	6 (11.5%)	46 (11.9%)	$P = 0.28$
MRC prognostic category			
stage 1	21 (40.0%)	153 (39.4%)	
Metastatic good prognosis	25 (48.0%)	169 (43.6%)	$\chi^2 = 1.02$
Metastatic poor prognosis	6 (11.5%)	66 (17.0%)	$P = 0.6$
Year of diagnosis			
1975–1979	20 (38.5%)	90 (23.2%)	
1980–1984	13 (25.0%)	141 (36.3%)	$\chi^2 = 6.2$
1985–1989	19 (36.5%)	157 (40.5%)	$P = 0.05$
Treatment centre			
unit 1	23 (44.2%)	212 (54.6%)	$\chi^2 = 2.0$
Others	29 (55.8%)	176 (45.4%)	$P = 0.16$

Table 3. Treatment received for metastatic disease

	Age > 40 (n = 35)	Age ≤ 40 (n = 271)
Platinum chemotherapy	23 (65.7%)	211 (77.9%)
Other chemotherapy	2 (5.7%)	12 (4.4%)
Radiotherapy	10 (28.6%)	42 (15.8%)
Surgery	0	6 (2.2%)

Platinum chemotherapy versus other treatment
$\chi^2 = 2.9$ 1DF $P = 0.09$

Univariate analysis showed that the 5 year period of diagnosis, tumour extent, treatment unit but not age, influenced survival. A multivariate Cox's model (Table 4) confirmed their independent influence and the non significant impact of age.

Kaplan–Meier estimation curves (Figure 4) give an overall 5 year survival of 71% for those over 40 years old which compares with 79% in the younger age group. If deaths from teratoma alone are considered, the comparison is similar, with 5 year survivals of 73% (SE 0.06, 95% CI 61–85%) and 81% (SE 0.02, 95% CI 77–85%), respectively.

DISCUSSION

Our results confirm a steady increase in incidence in testicular germ cell tumours that is of similar magnitude to that reported in other countries [1, 2, 15]. In common with other reports, our study shows the largest increases in younger men, making this cancer the most common malignancy in men aged 25–35 years. The Scottish incidence rate has been shown to be high in comparison with other rates recorded worldwide [16].

Few clear risk factors for testicular germ cell tumours have been identified. The presence of an undescended testicle is one known predisposing factor [17]. Other speculative risk factors include maternal hormone levels during pregnancy [18], which

Table 4. Multivariate analysis assessing which prognostic variables are important in determining survival

Variable	Categories	No. of patients	Relative death rate (and 95% CI)	*P* value
Age	≤ 40 years	388	1	0.80
	> 40 years	52	1.38 (0.77–2.49)	
MRC prognostic groups	Good	174	1	< 0.001
	Intermediate	194	4.76 (2.46–9.16)	
	Poor	72	26.6 (13.1–54.3)	
Year of diagnosis	1975–1979	110	1	< 0.001
	1980–1984	154	0.43 (0.27–0.69)	
	1985–1989	176	0.16 (0.08–0.31)	
Treatment centre	unit 1	235	0.36 (0.23–0.58)	< 0.001
	Others	205	1	

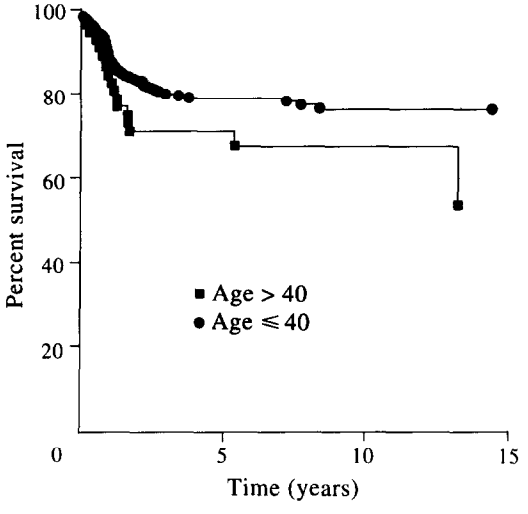

Figure 4. Kaplan–Meier estimation curve showing the survival of the two different age groups.

may contribute to the well documented social class association, genetic factors [19], and vasectomy [20]. Interest in postnatal environmental factors has been stimulated by recent studies linking falling sperm count with the rising incidence of testis cancer [21], and a high incidence of testicular cancer in those who had served in Vietnam [22].

The reduction in mortality seen during the time period studied is a result of improvement in treatment. The major advance has been the use of chemotherapy for disseminated disease, particularly the introduction of cisplatin in the mid 1970s. Initial cisplatin-containing combinations produced long term control in 60% [23]. Figure 1 shows the impact on mortality data for Scotland when the results became more widely known. Refinement of these chemotherapy regimens have further improved survival rates [4] which is reflected in the continued fall in the Scottish mortality rate for testicular cancers during the 1980s.

Increasing age is an adverse feature for a number of other malignancies currently curable with chemotherapy. In Wilms' tumour, increasing age at diagnosis is associated with a high relapse rate and reduced survival [7]. Most malignancies associated with childhood have a much poorer prognosis when they occur in adult patients [8]. Age has been identified as a significant prognostic factor in adult lymphomas, both Hodgkin's and Non-Hodgkin's disease, where an age greater than about 50 years at diagnosis is associated with a lower survival rate [24]. In these tumours it has never been satisfactorily determined whether the effect of age on prognosis reflects inherent differences in the tumour and/or host response, or whether it results from inadequate chemotherapy delivery or poor chemotherapy tolerance.

There is little objective evidence for the best treatment of the older patient with cancer as most clinical trials exclude them by setting upper age limits. The concern that they may not withstand intensive tretament often leads to empirical dose reductions being made to reduce toxicity, which may lead to less effective treatment [25]. In NSGCTs our study was unable to assess total drug doses or dose intensity in relation to age, but there was no difference between the number of treatment courses received by the two groups.

The second MRC study [5] defined three prognostic categories of NSGCT based on four clinical variables that were of independent prognostic importance. The two age groups in our study were reasonably balanced across the three prognostic categories. We previously suggested that specialist unit treatment confers an independent survival advantage [26]; studies in ovarian cancer [27] and childhood malignancies [28] also imply a treatment centre effect. A similar proportion of patients in both age groups were treated in such a specialist centre (unit 1).

The use of cisplatin chemotherapy was becoming increasingly widespread in the early years of this study, but only during the time period 1985–1989 was its use universal in metastatic disease. As a result of this difference in treatment, survival of the earlier cohorts of patients was significantly worse (Table 4). A higher proportion of the over 40 year old age group presented in the first 5 years of the study (Table 2), and received radical radiotherapy treatment, which might account for the smaller

percentage in this age group who received cisplatin-based chemotherapy (Table 3).

There was no statistically significant difference in survival between those over 40 years old and their younger counterparts. The small survival difference may be accounted for by the greater proportion of older patients treated in the early years of the study, when the use of cisplatin combination chemotherapy was not universal.

Treatment for older patients with NSGCTs should, therefore, be approached with the same curative intent as for younger patients, in the expectation of a similar level of success.

1. Osterlind O. Diverging trends in incidence and mortality of testicular cancer in Denmark, 1943–1982. *Br J Cancer* 1986, **53**, 501–505.
2. Stone JM, Sandeman TF, Ironside P, Cruikshank DG, Matthews JP. Time trends in accuracy of classification of testicular tumours, with clinical and epidemiological implications. *Br J Cancer* 1992, **66**, 396–401.
3. Boyle P, Kaye SB, Robertson AG. Changes in testicular cancer in Scotland. *Eur J Cancer Clin Oncol* 1987, **23**, 827–830.
4. Graham J, Harding M, Mill L, *et al.* Results of treatment of non-seminomatous germ cell tumours; 122 consecutive cases in the west of Scotland, 1981–1985. *Br J Cancer* 1988, 182–185.
5. Mead GM, Stenning SP, Parkinson MC, *et al.* The second medical research council study of prognostic factors in non-seminomatous germ cell tumours. *J Clin Oncol* 1992, **10**, 85–94.
6. Simon R, Durrleman S, Hoppe RT, *et al.* Prognostic factors for patients with diffuse large cell or immunoblastic non-Hodgkin's lymphoma: experience of the non-Hodgkins lymphoma pathological classification project. *Med Pediatr Oncol* 1990, **18**, 89–96.
7. Breslow N, Sharples K, Beckwith GB, *et al.* Prognostic factors in non metastatic, favourable histology Wilms tumour: results of the Third National Wilms tumour study. *Cancer* 1991, **68**, 2345–2353.
8. Prestidge BR, Donaldson SS. Treatment results among adults with childhood tumours: a 20 year experience. *Int J Radiat Oncol Biol Phys* 1989, **17**, 507–514.
9. Stoter G, Sylvester R, Sleijfer DT, *et al.* Multivariate analysis of prognostic factors in patients with disseminated non-seminomatous testicular cancer; results from a European Organisation for Reseach on Treatment of Cancer Multi-institutional phase II study. *Cancer Res* 1987, **47**, 2714–2718.
10. Hitchins RN, Newlands ES, Smith DB, *et al.* Long-term outcome in patients with germ cell tumour treated with POMB/ACE chemotherapy: comparison of commonly used classification system of good and poor prognosis. *Br J Cancer* 1989, **59**, 236–242.
11. Registrar General for Scotland. Annual reports 1990, HMSO.
12. Doll R, Smith PG. Age standardised incidence rates. In Waterhouse JAH, *et al.*, eds. *Cancer Incidence in Five Continents*. Lyon IARC, 1982, Vol. IV.
13. Kaplan EL, Meier P. Non parametric estimation from incomplete obesrvations. *J Am Stat Assoc* 1958, **53**, 457–481.
14. Cox DR. Regression models and life tables (with discussion). *J.R. Stat. Soc.* 1972, **21**, 187–220.
15. Heimdal K, Fossa SD, Johansen A. Increasing incidence and changing stage distribution of testicular cancer in Norway. *Br J Cancer* 1990, **62**, 277–278.
16. Muir CS, Waterhouse J, Mack T, *et al.* Cancer incidence in five continents (Volume 5). IARC Scientific Publications No 88, Lyon IARC, 1987.
17. Swerdlow AJ, Huttly SRA, Smith PG. Testicular cancer and antecedent disease. *Br J Cancer* 1987, 55, 97–103.
18. Henderson BE, Benton B, Jing J. Risk factors for cancer of the testis in young men. *Int J Cancer* 1979, **23**, 598–602.
19. Forman D, Oliver RTD, Brett AR, *et al.* Familial testicular cancer: a report of the UK family register, estimation of risk and an HLA class 1 sib pair analysis. *Br J Cancer* 1992, **39**, 284–291.
20. Thornhill JA, Conroy RM, Kelly DG, Walsh A, Fennelly JJ, Fitzpatrick JM. An evaluation of predisposing factors for testis cancer in Ireland. *Eur Urol* 1988, **14**, 429–433.
21. Carlsen E, Giwercman A, Keiling N, Skakkebaek NE. Evidence for decreasing quality of semen during past 50 years. *Br Med J* 1992, **305**, 609–613.
22. Tarone RE, Hayes HM, Hoover RH, *et al.* Service in Vietnam and increased risk of testicular cancer. *J Natl Cancer Inst* 1991, **83**, 1497–1499.
23. Einhorn LH. Testicular cancer as a model for a curable neoplasm. *Cancer Res 1980*, **41**, 3275–3280.
24. Walker A, Schoenfield ER, Lowman JT, *et al.* Survival of the older patient as compared with younger patient in Hodgkin's disease. *Cancer* 1990, **65**, 1635–1640.
25. Fentiman IS. Treatment of cancer in the elderly. *Br J Cancer* 1991, **64**, 993–995.
26. Harding MJ, Paul J, Gillis CR, Kaye SB. Management of testicular teratoma: does referral to specialist centre matter. *Lancet* 1993, **431**, 999–1002.
27. Gillis CR, Hole DJ, Still RM, *et al.* Medical audit cancer registration and survival in ovarian cancer. *Lancet* 1991, **I**, 691–696.
28. Stiller CA. Centralisation of treatment and survival rates for cancer. *Arch Dis Child* 1988, **63**, 23–30.