Pergamon

European Journal of Cancer Vol. 31A, No. 3, pp. 289–291, 1995
Elsevier Science Ltd
Printed in Great Britain
0959–8049/95 $9.50+0.00

0959-8049(94)00486-2

Comments and Critique

Non-specialist Units, Clinical Trials and Survival from Testicular Cancer

C. A. Stiller

THE PAST two decades have seen striking improvements in the prognosis for testicular cancer, and by the mid 1980s, 5-year relative survival rates of around 90% were being observed in populations in Europe and North America [1–3]. Population-based survival rates by histological type are rarely reported. In Denmark, the rise in 5-year relative survival from 76% for patients diagnosed during 1973–77 to 91% for those diagnosed during 1983–87 was largely attributable to an increase from 64 to 89% for non-seminomatous tumours, although survival from seminoma also saw a more modest improvement from 88 to 95% [1]. The greatly improved prognosis for testicular cancer is one of the major success stories of clinical oncology [4].

The place of general oncology departments in the treatment of testicular cancer has been controversial for some years. The latest contribution to the debate on this topic is the paper by Norum and colleagues in this issue pp. 293–295 [5]. In their series of 98 patients, treated over an 8-year period at a small centre in a remote part of Norway, survival was similar to that in major centres, and the authors argue that patients with testicular cancer can be treated according to co-operative group protocols in a small general oncology department without any adverse effects on outcome.

Nearly 10 years ago, it was reported that survival rates for men with non-seminomatous testicular tumours treated in a general oncology department had been similar to those obtained in the contemporary national multicentre study [6], but at one large centre participating in that study, survival rates were substantially higher [7]. There results were hard to evaluate as they were not population-based, and the numbers of patients were small.

The earliest population-based analysis of survival from testicular cancer in relation to patterns of organisation of medical care concerned 246 patients included in the Irish Testicular Tumour Registry during 1980–85 [8]. In this series, 41% of patients had seminomas and 59% had non-seminomatous germ-cell tumours. 4-year survival was significantly higher for patients who were treated by a urologist (76%) than for those who were not (64%). Patients had similar survival rates whether or not an oncologist was involved in their management, and so the borderline significant survival advantage for those under combined management by a urologist and an oncologist (75% versus 69%) was largely attributable to the presence of a urologist. There were no management guidelines or trials for testicular cancer in Ireland during the study period, but the survival rate of 53% among the 28 patients who received non-standard chemotherapy or less than the full dose of any of four standard regimes was significantly lower than the 76% survival among the 210 who were regarded as having been adequately treated. No reasons were given for the use of non-standard chemotherapy, but all analyses allowed for tumour stage.

Between 1981 and 1986, over 90% of men in Norway and Sweden outside the Stockholm area who underwent orchiectomy for non-seminomatous testicular germ-cell cancer were entered from 16 hospitals in the Swedish Norwegian Testicular Cancer Project (SWENOTECA) [9]. These included 223 with metastatic disease and, after exclusion of 23 patients because of major protocol violations, a wide range of mainly clinical prognostic factors were analysed for the remaining 200 [10]. The 91 (46%) patients who were treated at one large institution had a similar survival rate to those treated elsewhere. This centre, however, had a higher proportion of patients with large volume or very large volume disease according to the MRC classification, and within this poor prognosis group, the 5-year survival rate of 79% among the 42 patients at the major centre was significantly higher ($P=0.01$) than the 49% survival among the 36 such patients treated elsewhere. This difference remained significant in multivariate analysis in which age, serum levels of alpha-fetoprotein and human chorionic gonadotropin, and interval from orchiectomy to start of chemotherapy were all of independent significance.

In a population-based series of 440 men in the West of Scotland who had a malignant non-seminomatous testicular germ-cell tumour diagnosed during 1975–89, 235 (53%) were treated at a single very large unit, 194 (44%) at four other tertiary referral units and only 11 (3%) elsewhere [11]. Significantly fewer patients with Stage I and more with poor-prognosis metastatic disease were referred to the largest unit. Almost all (97%) of the men in that unit were treated according to national protocols, compared with 61% elsewhere. In a univariate analysis, 5-year period of diagnosis, tumour extent, treatment unit and delay in diagnosis all influenced survival. In multivariate analysis, the

Correspondence to C. A. Stiller at the University of Oxford, Department of Paediatrics, Childhood Cancer Research Group, 57 Woodstock Road, Oxford OX2 6HJ, U.K.
Received 17 Nov. 1994, accepted 21 Nov. 1994.

first three of these factors were important for survival, each being independently highly significant ($P<0.001$). After allowance was made for period of diagnosis and extent of disease, the mortality rate ratio at the four smaller units compared with the largest was 2.65 (95% confidence interval 1.65–4.28, $P<0.001$). When the analysis was restricted to patients who received protocol treatment, the result was essentially unchanged, with a mortality rate ratio of 2.82 (95% confidence interval 1.53–5.19, $P<0.001$). It was concluded that there was a survival advantage for centralised treatment over and above any advantage attributable to protocol treatment.

Between 1982 and 1988, survival of 133 patients with metastatic testicular germ-cell tumours in a series of trials at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, was higher than among 172 comparable patients included in five population-based cancer registries in other parts of the United States during 1978–84 [12]. Most patients in both series received platinum chemotherapy, although some in the registry series may not have been treated according to standard protocols. For patients with minimal or moderate disease in the Indiana University classification, the difference in survival was highly significant (95% versus 73% at 3 years, $P<0.001$), while for advanced disease it was only marginally so (52% versus 40% at 3 years, $P=0.056$). In general, American men with testicular cancer had apparently not benefited as much from major advances in treatment as those treated at one large centre. Great caution, however, should be exercised in interpreting these findings for three reasons. First, it is not known how typical the trial series was of the population of patients in the MSKCC catchment area. Second, the registry patients were diagnosed on average 4 years earlier than those at MSKCC and, although survival of MSKCC patients did not vary significantly with diagnosis year during 1979–88, there was said to be a slight trend towards better survival in more recent years. Third, 31 patients were excluded from the registry series but only one from the MSKCC because the extent of disease could not be precisely determined from available records. When the registry cases were reclassified by worst possible stage, 18 of those previously excluded could be included; the survival difference between the two series was reduced for the minimal to moderate group (95% versus 79%, $P=0.017$) and largely disappeared for the advanced group (52% versus 47%, $P=0.177$).

The present report from Norway gives results for a consecutive series of 47 men with seminomas and 51 with non-seminomatous tumours diagnosed during 1985–93 [5]. All patients received standardised treatment in accordance with SWENOTECA protocols. 5-year actuarial relative survival was 98% for both histological subgroups. There were two deaths from progressive disease, both in patients who initially presented as Stage IV. 10 other patients relapsed but were still alive at latest follow-up. Impressive as these results are, it should be remembered that cure is now routine for patients diagnosed with small volume disease, and that, for those with large volume disease, the survival rate is based on a relatively small number of patients and must have a correspondingly large standard error.

Recently, there has been rapid growth in the literature on centralised treatment, entry to trials and survival for cancer patients [13]. Many studies of different types of cancer have concluded that patients who are treated at specialist centres or at major units seeing large numbers of patients have higher survival rates. A survival advantage has also often been found for patients treated according to standard protocols, usually within trials. Few studies, however, have investigated the effect of size or type of centre on the survival specifically of patients who were in clinical trials or treated on protocols.

In the United States, data were analysed from trials conducted by the Eastern Cooperative Oncology Group (ECOG) during 1976–81 for several cancer sites [14]. There was no evidence that survival of patients with myeloma, leukaemia, lymphoma, melanoma, gynaecological or genitourinary tract cancer, gastrointestinal tract cancer or breast cancer differed between those who were treated at major centres that were members of ECOG and those who were entered in the same trials from community hospitals. Patients entered in trials for lung cancer or head and neck cancer from community hospitals had a mortality rate ratio of about 1.2 compared with those at ECOG member centres but the differences were non-significant. Similarly, no difference in survival was found between patients at major centres and other hospitals who were treated according to radiotherapy protocols of the Radiation Therapy Oncology Group during 1976–85 for prostate cancer, head and neck cancer, glioma or brain metastases [15].

For childhood acute lymphoblastic leukaemia in Britain during 1971–84, survival was significantly higher for children entered in the MRC trials than for those who were not [16]. There was also a significant trend in survival rates with size of treatment centre, categorised by number of children treated for the disease during the study period. Within the trials, however, there was little evidence of any effect of treatment centre size on survival. Between the individual centres treating the largest number of patients, there was considerable heterogeneity in survival rates; the unusually high survival rate at one centre during the 1970s was thought to be due to what was then an unusually strong emphasis on strict adherence to the protocol [17]. In the Greater Delaware Valley in the United States, survival of children receiving protocol treatment also varied little between types of hospital, and the lowest survival rate was observed for children at non-specialist centres who had non-standard treatment [18].

It has been estimated that it took 3 years from the start of the first study of combination chemotherapy including cisplatinum for testicular cancer before a substantial improvement in survival appeared in Connecticut and other areas in the United States contributing to the population-based Surveillance Epidemiology and End Results Program [19]. During the 11 years starting in 1979 when cisplatinum treatment for germ-cell tumours was introduced in Germany, mortality from testicular cancer in Munich fell much more rapidly than in the rest of the then Federal Republic, particularly in the 15–44 age group [20]. Concern was expressed that patients in other parts of the country, particularly outside the main cities, might not have access to the most modern treatment. Anxiety on this issue is heightened by the possibility that increasing proportions of German testicular cancer patients are being treated outside specialist centres [21].

Larger proportions of ineligible patients and more frequent protocol violations can be an obstacle to participation of small, non-specialist units in clinical trials [22], but this need not be so [14,15]. Of course, access to modern treatment is not a problem if all patients, even those at small units, are treated according to current protocols, as is the case in the series reported here by Norum and associates (pp. 293–295 [5]). It may, however, only be practicable to provide the supportive care necessary for safe administration of the potentially most highly toxic treatment at a few major centres.

The experience reported by Norum and associates

(pp. 293–295 [5]) may not be typical of that at smaller centres. Interestingly, the only two studies in which survival of cancer patients treated according to standardised protocols was better at a very large centre than elsewhere both related to testicular teratoma [9, 10]. The possibility remains that the higher survival rates at the single large centre in each study were attributable to some characteristic of the centre in question other than its size. Platinum chemotherapy is also effective in ovarian cancer, and it is noteworthy that in a national study of 479 women treated in Scotland during 1987, the mortality rate ratio of 1.4 for women not treated at a multidisciplinary combined clinic was significantly higher ($P<0.01$), even after allowance was made for the effect of platinum therapy on survival, although whether this was given as part of a standard protocol was not analysed [23].

The question whether the survival advantage of protocol treatment for cancer patients is further enhanced by treatment at major centres is unresolved, and the answers may differ according to diagnostic group and type of treatment. The best way of attempting to answer it for testicular germ-cell tumours, as for other cancers, is through large-scale population-based studies covering a wide enough geographical area to include several treatment centres of the most specialised type. Cancer registries have an invaluable role to play in such studies.

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Acknowledgements—I am grateful to Mrs E.M. Roberts for secretarial assistance. The Childhood Cancer Research Group is supported by the Department of Health and the Scottish Home and Health Department.

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European Journal of Cancer Vol. 31A, No. 3, pp. 291–292, 1995

0959–8049/95 $9.50 + 0.00

0959-8049(94)00533-8

Should We Still Advocate Referral to Specialist Centres for Teratoma?

M.J. Hughes and S.B. Kaye

WHO SHOULD be treating patients with malignant teratoma? In particular, is there evidence that referral of such cases to a "specialist" centre influences outcome? In many solid tumours the data on this controversial topic are rather sparse, but in malignant teratoma there are two separate large scale population based studies which support the notion that referral does confer