A Scottish national audit of current patterns of management for patients with testicular non-seminomatous germ-cell tumours

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Summary A detailed casenote review was performed on all 65 patients registered with testicular non-seminomatous germ cell tumours (NSGCT) during 1989 under the Scottish Cancer Registration Scheme. Details of management at presentation and 2 years following diagnosis were recorded and analysed. In a small number of patients an unacceptable delay in diagnosis was noted. Variation was found in the frequency and type of investigations performed on patients placed on surveillance, types of chemotherapy regimens used and numbers of patients entered into trials. Three per cent of patients had a biopsy of the contralateral testis and 27% of patients defaulted from clinic attendance. Considerable variation in the management of testicular NSGCT in Scotland has been identified. The introduction of management guidelines should result in a more consistent approach to the care of these patients. Support, both financial and psychological, may reduce the unacceptable rate of default.

Keywords: audit; non-seminomatous germ cell tumour; management; Scotland; patient compliance

Testicular germ cell tumours are now the commonest cancer in men aged under 40 in Scotland (Sharp et al., 1993a). The age-standardised incidence rate of testicular NSGCT in Scotland for 1988–90 was 2.3:100 000, and has risen from 1.8:100 000 for 1975–77 (Sharp et al., 1993b). Effective chemotherapy has transformed what was invariably a fatal disease, once it had metastasised, to one which is usually curable (Ellis and Sikora, 1987). Cure rates may be related to the ability to give effective treatment and it has been suggested that results are better when there is a particular expertise in the treatment of the disease (Harding et al., 1993).

Orchidectomy followed by intensive surveillance, which is expensive in clinic and medical time, is now considered the accepted management for most patients with stage I teratoma (Peckham et al., 1982; Horwich, 1993). Patients with poor prognostic histological features, and where the disease has spread beyond the testis, require cytotoxic chemotherapy. Cure rates as high as 90% can now be expected for good prognosis metastatic disease (Horwich, 1989). There are now well-documented prognostic factors that can predict for poorer survival. The role of more intensive chemotherapy regimens for these patients has been the subject of much debate and is currently being assessed by an MRC Trial (Kaye et al., 1989).

The importance of complete surgical excision of residual masses after chemotherapy is now accepted and surgeons experienced in this field may be more likely to perform adequate resections (Ewing et al., 1987; Hendry et al., 1987; Whillis et al., 1991).

Most clinicians continue to follow up intensively patients who have been treated for metastatic NSGCT. The rationale for this is that second-line chemotherapy may be curative if the disease is caught early at the time of relapse. Undoubtedly, some patients may be cured by second-line chemotherapy, but for others salvage therapy should be viewed as palliative (Whillis et al., 1991) and opinions vary as to optimal follow-up for these patients.

The aim of this study was to assess variation in investigations at the time of diagnosis and subsequently in the management of patients with both early- and late-stage testicular NSGCT.

Methods

Details of all testicular NSGCT cases diagnosed between 1 January 1989 and 31 December 1989 were obtained from the Scottish Cancer Registration Scheme. Completeness of registration and validity of diagnosis was checked by cross-referring to oncology centre records and is reported in the accompanying paper (Clarke et al., 1995). A casenote review was performed on all new cancer registrations for testicular NSGCT during 1989. Information was extracted on referral dates, speciality of clinicians involved, staging and pretreatment investigations, histology, prognosis (MRC prognostic group; Mead et al., 1992), treatment and post-treatment follow-up for a 2 year period, patient compliance and any relapse details. Information was recorded onto an agreed proforma and the data anonymised.

Visits and procedures were considered to be part of a formal surveillance policy once an 'active' decision had been documented to pursue such a policy. This was also the definition for post-treatment follow-up, with both being measured for 2 full calendar years from the date of the decision.

Results

Study group

Sixty-five new cases of testicular NSGCT were registered in Scotland in 1989. Nearly three-quarters of these were aged 34 and under, and only one patient (a paediatric patient treated at a children's hospital who will not be considered further) was not referred to a specialist oncology centre. Two patients (aged 23 and 29) were excluded from the casenote review because of previous primary testicular tumours. Management

was therefore not representative of newly diagnosed testicular NSGCT. The numbers of patients registered at each of the five centres A–E respectively were four, four, six, 19 and 29.

In only 39 of 62 cases (62.9%) was the place of initial presentation documented in casenotes. The majority (35 cases, 89.7%) presented to their general practitioner, two to casualty, one to a psychiatric hospital where he had been treated for depression and one to a general surgeon. Date of presentation was not reliably documented so the waiting time for primary referral could not be measured.

Most patients were initially referred to urological (62.9%) or general surgeons (35.5%). Secondary referrals were either to medical oncologists (38.7%), radiation oncologists (48.4%) or urological surgeons (12.9%).

The median wait for a secondary referral was 13 days, range 1–112 days. In four cases the delay was over 8 weeks (71 days, 78 days, 108 days, 112 days). The reasons for these delays were difficult to interpret but in two cases they may have been related to urological waiting lists and the other two patients were misdiagnosed at presentation by general surgeons as having benign disease.

Details of procedures performed at the time of presentation are documented in Table I. All patients had a histological diagnosis of either NSGCT or mixed NSGCT and seminoma.

Staging according to the Marsden system (Peckham et al., 1979) was assigned by the reviewers in all but two cases. Thirty-five (56.5%) were stage I, 11 (17.7%) stage II, one (1.6%) stage III and 13 were stage IV (21.0%). The proportion of patients by stage at presentation varies between centres but this variation is not statistically significant. The statistical test may be unreliable however due to the small numbers involved ($\chi^2 = 19.63$, d.f. = 12, $0.05 < P < 0.10$).

Management of stage I disease

Of 35 patients with stage I disease six (17.1%) received chemotherapy, one (2.9%) received radiotherapy and 28 (80.0%) were placed on surveillance. The six cases receiving chemotherapy were considered to be at high risk of relapse because of known poor risk histological features. Three of these were registered on the MRC high risk stage I trial. The single case that received radiotherapy was initially diagnosed as a seminoma.

A surveillance policy was pursued in 28 patients. One died in a road traffic accident during the first year and seven cases relapsed (25.0%). Seven of the remainder (35.0%) had defaults documented in their notes. A patient was considered to have defaulted if he had missed at least one appointment.

Patients on surveillance excluding defaulters were seen between eight and 15 times (median 12) during the first year

and three and seven times (median six) during the second year. At each visit tumour markers alphafetoprotein (AFP) and human chorionic gonadotrophin (HCG) were performed, plus a chest radiograph if a computerised tomography (CT) scan had not been booked around the time of the visit. CT scans of the thorax and abdomen were performed on zero to six occasions (median four) in the first year, and zero to three times (median two) in the second year (Table II). Ultrasound was not a procedure recorded but some reviewers noted it had been included in the surveillance programme in a small number of cases.

Seven (25%) stage I cases relapsed on surveillance, all within 6 months of diagnosis (median 17 weeks, range 7–22 weeks).

Treatment of patients with metastatic disease

Thirty-four patients were treated for metastatic disease, of which seven were relapsed stage I cases. All cases received chemotherapy. Four chemotherapy regimens were used for patients with good prognosis disease, with 10 of 20 such patients treated within a clinical trial setting. Six regimens were used for patients with poor prognostic disease with seven of the 12 treated within a trial setting. A single regimen was used for the two patients with an unknown prognosis.

During primary therapy only one patient received radiotherapy. This patient received ten courses of combination chemotherapy followed by whole brain radiotherapy (4048 cGy in 22 daily fractions over 33 days).

At the end of primary therapy 18 cases (52.9%) had a complete regression (CR), eleven (32.4%) had partial regression (PR), one had progressive disease, in three cases the status was inevaluable (markers normal, no or equivocal CT scans) and in a further case there was no information.

Sixteen patients did not achieve complete remission at the end of therapy. Three patients had no further treatment, the rest having residual masses excised with or without further chemotherapy. Eleven of the 12 patients who had surgery achieved a CR.

Defaults from follow-up were recorded in 35% of patients on active surveillance and 21% of patients with post-treatment follow-up (27% for all clinic attendances). The commonest reasons recorded for defaulting were anxiety, transport difficulties and lack of finance.

There was a marked difference in the number of patients being treated in a trial setting at a time when almost all patients would have been eligible for inclusion within MRC studies. Only two of the five centres entered patients with 69% and 53% of all patients being entered by centres E and D respectively.

Table I Procedures performed at staging and pretreatment

Procedure	Performed (as documented in notes) Yes	No	Not known	Percentage performed
Pre-operative AFP	51	6	5	82
Pre-operative HCG	51	6	5	82
Pre-operative LDH	10	21	31	16
Post-operative AFP	60	0	2	97
Post-operative HCG	60	0	2	97
Post-operative LDH	18	14	30	29
Ultrasound testis	25	29	8	40
Ultrasound abdomen	14	35	13	23
CT thorax	58	1	3	94
CT abdomen	61	0	1	98
CT brain	1	56	5	2
Chest radiograph	52	4	6	84
MRI	3	56	3	5
Bipedal lymphography	6	52	4	10
CSF markers	0	57	5	0
Biopsy contralateral testis	2	58	2	3
Pathology review	30	27	5	48
Sperm count and/or storage	14	36	12	23
Other	6	54	2	10

Table II Frequency of attendance and procedures performed on stage I NSGCT patients on surveillance (excluding defaulters)

| | Number of attendances or procedures | | | | | | | | | | | | | | | | | Total |
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	NK	
Year 1																		
Visits	0	0	0	0	0	0	0	0	1	0	3	0	5	1	2	1	0	13
AFP	0	0	0	0	0	0	0	0	1	1	1	1	5	1	3	0	0	13
HCG	0	0	0	0	0	0	0	0	1	1	1	1	5	1	3	0	0	13
LDH	5	0	0	0	0	0	0	0	0	1	1	0	0	1	0	0	5	13
Chest radiograph	0	0	0	0	1	0	2	3	1	2	3	0	1	0	0	0	0	13
CT thorax	3	0	0	2	3	2	3	0	0	0	0	0	0	0	0	0	0	13
CT abdomen	1	0	2	2	2	2	4	0	0	0	0	0	0	0	0	0	0	13
Year 2																		
Visits	0	0	0	1	2	3	6	1	0	0	0	0	0	0	0	0	0	13
AFP	0	0	0	1	2	3	6	1	0	0	0	0	0	0	0	0	0	13
HCG	0	0	0	1	2	3	6	1	0	0	0	0	0	0	0	0	0	13
LDH	5	0	0	1	1	0	1	0	0	0	0	0	0	0	0	0	5	13
Chest radiograph	0	1	0	2	6	2	2	0	0	0	0	0	0	0	0	0	0	13
CT thorax	3	2	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	13
CT abdomen	3	2	7	1	0	0	0	0	0	0	0	0	0	0	0	0	0	13

NK, not known.

Discussion

Documentation regarding the patient's first presentation was poor (only recorded for 63% of cases), but most presented to their general practitioner and were referred to either a general or urological surgeon. Secondary referral to oncologists or urological surgeons involved a median wait of 13 days (range 1–112 days) with four cases having delays of over 8 weeks. Although the reasons for such delays are not easy to interpret it would appear that in two cases this was related to urology waiting times. In the other two cases this was related to an initial diagnosis of benign disease.

The documentation of staging and pretreatment investigations varied considerably between cases with the frequency of procedures probably being underrecorded.

Although many clinicians advocate biopsy of the contralateral testis in all patients to exclude carcinoma *in situ* (Hargreaves, 1986), this was only performed in 3% of cases. This highlights the reluctance of surgeons to inflict another invasive procedure on their patients and the controversy surrounding the necessity for biopsy. Investigations performed at presentation for diagnosis and staging are predictable. Lactate dehydrogenase is rarely measured, which illustrates the controversy as to how valuable this is. Although a non-specific marker, high levels are indicative of a poor prognosis and it may be the only marker in seminoma. As a general rule there is no role for abdominal ultrasound now that CT scanning is widely available. MRI has only recently been introduced and it is not clear as to whether it has any advantage over CT in the management of the disease.

Facilities for sperm storage are available in four of the five centres. Centre A is the exceptions sending sample, to centre B for storage. This was not performed in all patients receiving chemotherapy. There may be good but undocumented reasons for this (e.g. previous vasectomy or clinical urgency to commence treatment). Although the majority of patients with normal sperm counts before therapy will regain fertility after chemotherapy, facilities for storage of sperm should be readily accessible for all patients.

There is considerable variation in the frequency of follow-up and investigations performed when patients are managed on an active surveillance policy. Although there will be many reasons for increasing the frequency of investigations in specific patients there should be a minimum number of attendances and investigations which is considered to be good practice. The variation in CT scanning of the abdomen between zero and six times and zero and three times in the first and second year respectively is of concern.

The incidence for defaulting from surveillance and post-treatment follow-up is worryingly high with 35.0% and 21.4% of cases defaulting respectively. Patients on surveillance in another study have been found to be less compliant compared with those having received chemotherapy as they underestimated the need for follow-up (Young *et al.*, 1991). It is therefore important that only those who are reliable are selected for active surveillance. Some assistance in the form of transport or counselling regarding the importance of follow-up may be necessary.

Chemotherapy regimens for both poor and good risk patients with metastatic disease were largely predictable. Four different regimens for good prognosis disease were used, all are well recognised but vary considerably in their toxicity. Such variation should not exist outside clinical trials and it is noteworthy that only 10 of 20 patients were treated in a trial setting. There should be a consensus as to the most appropriate first-line therapy unless patients are entered into a trial. Six regimens were used for patients with poor prognostic disease with seven out of 12 in trials. Only two of the five centres put patients into clinical trials. The three centres which did not participate stated that this was due to lack of clerical support in 1989, but with the recent introduction of the Scottish Cancer Therapy Network (SCTN) this issue has already been addressed.

The importance of complete resection of residual masses after chemotherapy is well documented. In this study a total of 12 operations were undertaken in a single year by three urological surgeons, one cardiothoracic and two general surgeons in three centres. It may be that with this level of workload such surgery should be performed by fewer surgeons.

Referral patterns in general were predictable but unacceptable delays occurred in a small number of cases awaiting surgery. In at least two cases this was due to the patients being diagnosed as having benign disease and to avoid such delays there should be a high index of suspicion that patients with testicular symptoms might have cancer and are treated urgently.

This study has highlighted considerable variation in several different aspects of the management of NSGCT in Scotland. Follow-up policies for patients on surveillance as well as those after chemotherapy varied considerably and guidelines should be laid down as to what is the minimum advisable with regard to clinic appointments and investigations. Defaults from surveillance and follow-up occurred too often and arrangements for transport or other financial support and psychological support should be made available.

Multiple chemotherapy regimens were used for patients with both good and poor prognostic disease. Although there will always be reasons for tailoring chemotherapy to individual patients national guidelines for first- and second-line chemotherapy for patients not entered into a trial protocol

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might result in a more consistent approach to the management of this disease.

The trial entry is poor for a rare tumour at a time when almost all patients would have been eligible for one trial or another. There is a particularly noticeable variation in trial entry between centres. The reasons for this relate to lack of clerical and other support and this should improve following the setting up of the Scottish Cancer Therapy Network.

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