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Rare cancers and specialist centres

Testicular germ cell tumours are the most common cancers in young men. The past 20 years has witnessed a revolution in their treatment, and over 90% of all patients may now expect to become long term survivors free of disease. The first phase of this success occurred in the 1960s. At this time treatment of early stage tumours improved substantially in association with improvements in the surgical treatment of retroperitoneal lymph nodes and radiotherapy to the para-aortic lymph nodes. Advocates of these two treatment options debated their merits for early stage tumours but when data were comparable the survival rates were the same.[1-3] The second phase began in 1975 with progress in cytotoxic chemotherapy, which in 10 years has taken the cure rate of patients with both malignant teratoma and seminoma with extralymphatic metastatic disease from 8% to close to 90%.

This dramatic success has led to an increasing debate whether such patients still need to be referred to specialist centres or whether they should be treated in local units. Though at any time when the results in these units are analysed they lag behind the major centres by a few years, the difference is now smaller (p 669).[4,5] Some questions have to be resolved: what is the best chemotherapy for patients with the most extensive advanced metastatic malignant teratoma? And how much treatment is necessary for early stage teratoma and seminoma? For these patients with early disease the dispute over the relative merits of radiotherapy and surgery to the retroperitoneal lymph nodes has become outdated by advances in staging procedures and the dramatic effects of cytotoxic chemotherapy. The critical question for these patients is whether prophylactic treatment of the retroperitoneum is justified—as was the routine treatment up until four years ago.

Despite the successes of chemotherapy few centres cure more than two thirds of patients with really advanced malignant teratoma with a large volume of tumour and high concentrations of tumour markers (though these now constitute less than one fifth of cases). Two principal issues remain under debate as possible means of improving these results—namely, whether the use of a larger number of higher dosage of drugs might increase the cure rate and whether encouragement of early diagnosis might reduce the incidence of these patients at poor risk.

There are four treatment regimens containing cisplatin which have produced 75-85% long term (greater than two years) disease free survival in patients with metastatic testicular teratoma.[6-10] Each research group produced only 55-65% cure rates with similar regimens when they first reported their results.[11-15] All produce close to 100% survival in patients with a good prognosis—small volume metastatic disease—but salvage less than two thirds of patients with poor prognostic features.

Recently this improvement of results occurring in pioneering groups with accumulated experience has been further documented in a retrospective multicentre prognostic factor analysis undertaken by the Medical Research Council Working Party on Testicular Tumours.[16] This report showed that results improved by 20%—from 69% to 89%—over six years and that this improvement was considerably more than the minor difference in the results achievable with the different regimens reviewed (though the analysis did not take into consideration differences in referral pattern or amount of drug given).

Originally the main argument in favour of the more complicated multiple drug regimens[6-9] (such as that of Newlands *et al*[8,13] over the three drug regimens[6,7,10-12,15] was the high cure rate achieved by complex chemotherapy alone in patients with poor prognostic factors and those rare patients with metastases in the brain and liver. A recent report of cure of brain metastases using the Einhorn three drug regimen (bleomycin, vinblastine, and cisplatin) together with radiotherapy has thrown doubt on this observation, particularly as patients given the more complicated regimens may take up to three to six months longer to complete treatment. This issue is far from resolved, however, and is the subject of a new study being developed through the Medical Research Council Working Party on Testicular Tumours.

The improvement of results with experience provides one of the strongest justifications for encouraging referral of patients with these rare tumours to centres with a specialist interest in their management. The nursing and junior medical staff in such centres are continually treating patients of this kind and have experience in the minutiae of management and the complications that may occur. For the future, however, given the distress caused to patients by long distance travel while they are suffering from side effects of cytotoxic chemotherapy, it may be necessary to balance distress and benefits by arranging for some of the chemotherapy to be given locally. The general strategy of management, the timing of surgery, and the changes in drug scheduling—the factors which are important in determining the success[10]—would need, however, to be controlled centrally for all the patients to benefit from the latest idea in this rapidly evolving topic. The improved results and the successes of the specialist childhood cancer centres[17] suggest

a model that might be developed to establish a network of recognised centres for treating testicular tumours. The recent launching of a Medical Research Council study of surveillance in stage I tumours and a trial of two bleomycin schedules for patients with small volume metastatic disease should help in the establishment of this network.

More controversial is whether the patients with the highly curable seminomas or with metastatic malignant teratomas of small volume need to be referred centrally. I believe that there are two arguments, one scientific and one economic, which make it vital that this should continue to be the ideal. In addition to the enormous advances in the use of chemotherapy to treat patients with germ cell tumours of the testis the past 10 years has also witnessed a revolution in the biochemical, histological, and radiological diagnostic staging techniques. Measurement of serum concentrations and immunohistochemical detection of the tumour markers human chorionic gonadotrophin, and α fetoprotein, and more recently estimation of placental alkaline phosphatase activity,[18] have improved the accuracy of histopathological staging by detecting early stages of development of malignant teratoma in patients with seminoma. They have also improved the diagnosis of relapse—and our ability to detect response to treatment early. These developments, together with improvements in radiological staging with the introduction of computed tomography, have enabled the specialist centres to pioneer the way to reduce the amount of treatment for stage I patients. The surveillance studies have shown that 75-80% of patients with stage I malignant teratomas[19-21] and (though the studies are at a much earlier stage) possibly 90% of those with stage I seminomas[22] may need no additional treatment other than observation to allow detection of relapse. In the minority who do relapse tumour treatment may still be given at an early enough stage to guarantee close to total cure.

It would be premature, however, to conclude that this approach is safe in the long term; indeed, some centres may still feel justified in using prophylactic surgical or radiotherapeutic treatment to the retroperitoneum—even though this is unnecessary for 80-90% of patients—in order to save the minority having to suffer the toxicity of cytotoxic chemotherapy. Only by careful follow up of large numbers, however, will the safety of the minimum regimen be established. The same applies to the question of how little chemotherapy is necessary to cure patients with early metastatic disease now that the cure rate is about 100%. The introduction of etoposide in combination, instead of vinblastine, has reduced the toxicity of the drug regimen, though this is still not negligible. With this rapid evolution in treatment strategies and the increasing recognition that it may be possible to cure early stage tumours with fewer courses of chemotherapy the danger is that if these patients do not continue to be treated in specialised centres information will be lost and it will take twice as long to learn whether these innovations are safe.

Cost effectiveness is now the watchword, and with cuts in services can specialisation of this kind be justified? In many centres tumour marker assays are performed in small batches locally at infrequent intervals, so increasing the unit cost. The service would be considerably more cost effective if performed in recognised central laboratories with computerised documentation. Again, delay in diagnosis is an important and potentially reversible factor determining the need for expensive chemotherapy. If Britain had a network of recognised centres for the diagnosis and treatment of testicular tumours this would provide a focus for developing a campaign to encourage early diagnosis.[23] A recent analysis of costs of treatment has shown that savings of up to half a million pounds a year might be possible.[24]

Though I have concentrated predominantly on the treatment of tumours of the testis, much of the discussion applies equally to the other rare malignancies curable by chemotherapy such as rhabdomyosarcoma, neuroblastoma, and bone tumours in children[25] and the acute leukaemias and poor prognosis lymphomas in children and adults.[26,27] As progressive improvement of results is continuing to occur this national resource of experience and information must not be lost by diffusing the care of patients among too many clinicians. Diffusion might also mean that new leads—and, equally important, late toxicities of treatment—might be overlooked.[28] Clearly a policy of supporting specialist centres must recognise patients' wishes, in particular the economic and psychological distress they suffer when being treated at a distance from home.[29] Most important, the staff of peripheral hospitals must not lose contact with their patients; indeed they need to be encouraged to contribute where possible in order that they will see the benefits of central referral.

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