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EDITORIAL

Surveillance in testicular cancer: who, when, what and how?

S.A. Sohaib and J. Husband

Department of Radiology, Royal Marsden Hospital, Sutton, Surrey, UK

Corresponding address: Dr S.A. Sohaib, Department of Diagnostic Radiology, Royal Marsden Hospital, Down Road, Sutton, Surrey SM2 5PT, UK.
Email: aslam.sohaib@rmh.nhs.uk

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Abstract

Surveillance as a management strategy in stage 1 testicular germ cell tumour (GCT) is increasing in popularity due to the recognition of the long-term side effects of treatment. Imaging, in particular computed tomography (CT), plays a central part in the surveillance protocols. There is a tendency towards less frequent use of imaging as supported by recent trials in non-seminomatous GCT but further studies are needed with respect to the assessment of seminoma and to evaluate the role of magnetic resonance imaging (MRI) instead of abdominal CT.

Keywords: *Testis cancer; germ cell tumour; imaging; computed tomography.*

Introduction

Surveillance is increasingly the preferred management strategy in stage I testicular germ cell tumours (GCT).[1] This is due to growing awareness of the long-term complications in patients treated with radiotherapy and chemotherapy.[2] Long-term survivors of testicular cancer have a two-fold risk of cardiovascular disease[3,4] and there is a 10% excess lifetime risk of a second malignancy in patients treated with radiotherapy, chemotherapy or both after 30 years of follow up.[5] Surveillance is designed to identify relapse at the earliest stage and therefore enable earlier treatment. Issues arise as to who, when, what and how to survey.

Most surveillance programs include clinical examination, serum markers and computed tomography (CT) scanning to follow up patients but there is great variation in the frequency of imaging between centres.[1] The potential benefit of repeated scanning must be weighed against the consequent financial and health costs. A thoracic CT gives a radiation dose equivalent to 400 chest radiographs (8 vs 0.02 mSv); for a CT scan of the chest and abdomen the dose is increased to approximately 20 mSv (a dose equivalent to 1000 chest radiographs). This results in a 1:1000 lifetime risk of a second cancer/leukemia in a 25-year-old patient over the subsequent 40 years. In order to reduce this radiation exposure, ultrasound and magnetic resonance imaging have been suggested in surveillance programs. However, ultrasound is not as reliable as CT or MR imaging in the assessment of retroperitoneal nodes. Limited data suggest that MR imaging may be used instead of CT for abdominal disease[6] but there are no data from larger prospective trials to support this view.

Non-seminomatous germ cell tumours

The idea of surveying patients closely and treating at the time of relapse has been popular in patients with non-seminomatous germ cell tumours (GCT). In stage 1 non-seminomatous GCT, approximately 30% of patients will relapse; thus treating all patients risks unnecessary toxicity in over 70% of cases.[7,8] Vascular or lymphatic invasion are the most powerful predictors of relapse; the absence of yolk sac elements and the presence of undifferentiated cells are also independent prognostic variables. Relapse rates approach 50% in high risk patients compared to a relapse rate of approximately 20% in those without high risk factors. In the prospective TE04 trial, 45% of those that relapsed did not have raised markers at the time of discovery of recurrent disease.[7]

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Sixty-one percent of relapses occurred in the para-aortic nodes and 10% in the mediastinal or supraclavicular nodes. Ninety-five percent of those who did relapse were in the good prognostic group and overall survival free from GCT was 99%. As relapse is most frequent in the first year after diagnosis (up to 80%) the number of scans should be greatest during this time. Surveillance is performed rigorously with clinical follow-up, serum marker analysis and serial imaging of the thorax and abdomen.

The value of chest CT over chest radiography has been studied in a series of 168 stage I non-seminomatous GCT patients on surveillance who underwent chest X-ray rather than chest CT.[9] Nineteen percent (42 patients) of these patients relapsed; of which 8/42 relapsed with chest disease. Seven out of eight of these latter patients had evidence of disease elsewhere which was identified on abdominal CT. The one patient in this series who had only chest disease at relapse was clearly diagnosed by chest radiography. This led the authors to conclude that chest imaging with CT would not have changed the prognosis of those who relapsed in the chest in their study.

The role of pelvic CT has also been called into question. In one series of patients with testicular GCT, pelvic lymphadenopathy was seen in 16 of 167 patients (9.6%). The presence of bulky para-aortic lymphadenopathy was the only significant predictor for pelvic disease and was present in 11 of 16 patients. In the absence of this or other risk factors for pelvic disease (previous scrotal or inguinal surgery, maldescent, tunica vaginalis invasion, retro-peritoneal lymph node dissection), routine pelvic CT for patients on surveillance for stage I disease may constitute unnecessary irradiation.[10]

Protocols vary between centres but most will scan patients between two and six times during the first year. As yet no consensus on optimal management has been reached but it is seen that those centres that scan more frequently do not detect relapse at a significantly earlier stage than others. Indeed in one study of 46 patients, all relapses detected after the 3-month CT were picked up by clinical suspicion, raised tumour markers or chest X-ray.[11] Furthermore results of the MRC TE08 study, a prospective randomized trial of two versus five CT scans in patients with stage 1 non-seminomatous GCT, showed that there was no difference in the outcome in patients in the five scan schedule compared to the two scan schedule.[12]

Is there a role for fluorodeoxyglucose (FDG)-positron emission tomography (PET) in identifying patients for surveillance? Early studies suggested that FDG-PET may improve surveillance by predicting patients likely to relapse. A Danish pilot study on stage I non-seminomatous GCT showed that FDG-PET could identify 70% of patients who subsequently relapsed with metastatic non-seminomatous GCT.[13] Similar results were obtained in a small German study comparing FDG-PET and retroperitoneal lymph node dissection.[14] The negative predictive value of the Danish study was 92% which would suggest that adjuvant treatment could be avoided in most patients with stage I non-seminomatous GCT and a negative FDG-PET. This hypothesis, i.e. the use of FDG-PET to predict relapse in patients with clinical stage I non-seminomatous GCT, has been investigated by the Medical Research Council (MRC) in the UK in the TE22 study.[15] The study showed that although FDG-PET identified a proportion of patients with disease not detected by CT, the relapse rate amongst FDG-PET negative patients remained high. The study results therefore suggest that FDG-PET scanning is not able to identify patients at sufficiently low risk of relapse to replace other treatment options in this setting.[15]

Seminoma

In seminoma, the wide-scale adoption of surveillance was limited until recently due to the lack of a reliable tumour marker. A predominantly intra-abdominal site of relapse meant that regular cross-sectional imaging was needed. However, surveillance has recently been popularised after publication of a new predictive model for relapse in stage I seminoma. A multivariate analysis of patients from Canadian, UK and Danish centres has identified tumour size (>4 cm) and invasion of the rete testis as significant predictors of relapse. In the absence of both these factors, patients have no more than a 12% risk of relapse, suggesting that there is a group of patients with a particularly low risk of relapse where surveillance might be an attractive option. Relapses are rare after 2 years but have been reported to occur up to 6 years after initial diagnosis.[16,17] The majority of relapses are in the para-aortic nodes followed by mediastinal nodes, supraclavicular nodes and lung metastases.[17,18] Only 30% of seminoma relapses are serum marker positive. No studies have addressed the optimal scanning or follow up frequency with widely differing policies.[1] The policy at our hospital is for 6 monthly abdominal CT scans and chest X-ray for the first 2 years and the pelvis is only imaged if there has been previous pelvic surgery. Annual abdominal CT and chest X-ray are then performed until 5 years after the initial diagnosis.

Summary

Surveillance as a management strategy in stage 1 testicular GCT is gaining increasing popularity due to the recognition of the long-term side effects of treatment. The patients *who* are being surveyed are those likely to be at low risk of relapse, i.e. very good prognosis patients. Surveillance protocols are most intensive *when* the risk of relapse is highest, i.e. in the first 2 years with decreased monitoring thereafter. *What* these protocols survey are sites of likely relapse, i.e. the retroperitoneum

and chest typically. *How* the sites of relapse are imaged is with a combination of chest radiography and abdominal CT. There is a tendency towards less frequent use of imaging as supported by recent trials in non-seminomatous GCT but further studies are needed with respect to the assessment of seminoma and to evaluate the role of MR imaging instead of abdominal CT.

References

[1] Huddart RA, Joffe JK. Preferred treatment for stage I seminoma: a survey of Canadian radiation oncologists. Clin Oncol 2006; 18: 693–5.

[2] Horwich A, Shipley J, Huddart R. Testicular germ-cell cancer. Lancet 2006; 367: 754–65.

[3] Huddart RA, Norman A, Shahidi M, Horwich A, Coward D. Cardiovascular disease as a long-term complication of treatment for testicular cancer. J Clin Oncol 2003; 21: 1513–23.

[4] van den Belt-Dusebout AW, Nuver J, de Wit R, *et al.* Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2006; 24: 467–75.

[5] Travis LB, Fosså SD, Schonfeld SJ, *et al.* Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. J Natl Cancer Inst 2005; 97: 1354–65.

[6] Sohaib SA, Huddart R, Dearnaley DP, Horwich A. Sensitivity of MRI in the diagnosis of retroperitoneal disease in testicular germ cell tumours. AJR Am J Roentgenol 2005; 184: suppl): 63.

[7] Read G, Stenning SP, Cullen MH, *et al.* Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol 1992; 10: 1762–8.

[8] Freedman LS, Parkinson MC, Jones WG, *et al.* Histopathology in the prediction of relapse of patients with stage I testicular teratoma treated by orchidectomy alone. Lancet 1987; 2: 294–8.

[9] Harvey ML, Geldart TR, Duell R, Mead GM, Tung K. Routine computerised tomographic scans of the thorax in surveillance of stage I testicular non-seminomatous germ-cell cancer – a necessary risk? Ann Oncol 2002; 13: 237–42.

[10] White PM, Howard GC, Best JJ, *et al.* The role of computed tomographic examination of the pelvis in the management of testicular germ cell tumours. Clin Radiol 1997; 52: 124–9.

[11] Crawford SM, Rustin GJ, Begent RH, Newlands ES, Bagshawe KD. Safety of surveillance in the management of stage I anaplastic germ cell tumours of the testis. Br J Urol 1988; 61: 250–3.

[12] Rustin GJ, Mead GM, Stenning SP, *et al.* Randomized trial of two or five computed tomography scans in the surveillance of patients with stage I nonseminomatous germ cell tumors of the testis: Medical Research Council Trial TE08, ISRCTN56475197 – the National Cancer Research Institute Testis Cancer Clinical Studies Group. J Clin Oncol 2007; 25: 1310–5.

[13] Lassen U, Daugaard G, Eigtved A, *et al.* Whole-body FDG-PET in patients with stage I non-seminomatous germ cell tumours. Eur J Nucl Med 2003; 30: 396–402.

[14] Cremerius U, Wildberger JE, Borchers H, *et al.* Does positron emission tomography using 18-fluoro-2-deoxyglucose improve clinical staging of testicular cancer? – Results of a study in 50 patients. Urology 1999; 54: 900–4.

[15] Huddart R, O'Doherty M, Padhani A, *et al.* A prospective study of ^{18}FDG PET in the prediction of relapse in patients with high risk clinical stage I non-seminomatous germ cell cancer (MRC study TE22). ECCO 13, the European Cancer Conference, Paris, Oct 30–Nov 3, 2005. Eur J Cancer): suppl 3): 227(abstract).

[16] Warde P, Specht L, Horwich A, *et al.* Prognostic factors for relapse in stage I seminoma managed by surveillance: a pooled analysis. J Clin Oncol 2002; 20: 4448–52.

[17] Oldenburg J, Martin JM, Fossa SD. Late relapses of germ cell malignancies: incidence, management, and prognosis. J Clin Oncol 2006; 24: 5503–11.

[18] Dieckmann KP, Albers P, Classen J, *et al.* Late relapse of testicular germ cell neoplasms: a descriptive analysis of 122 cases. J Urol 2005; 173: 824–9.