Routine computerised tomographic scans of the thorax in surveillance of stage I testicular non-seminomatous germ-cell cancer—a necessary risk?

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Background: The standard management approach to stage I testicular non-seminomatous germ-cell tumours (NSGCT) in the UK is a surveillance programme with adjuvant bleomycin, etoposide, cisplatin (BEP) chemotherapy being offered to individuals with high risk disease. Conventionally, computed tomography (CT) scanning of the thorax has formed part of the surveillance programme. This paper evaluates the contribution of routine thoracic CT imaging in the management of this disease.

Patients and methods: We retrospectively reviewed the case notes of 168 patients with stage I NSGCT referred to the Wessex Medical Oncology Unit over a period of 13 years (1986–1998). These patients entered onto a surveillance programme that included serial chest X-ray follow up rather than thoracic CT.

Results: Forty-two out of 168 patients (25%) evaluated suffered relapse during the follow up period. Eight of 42 patients (19%) relapsed with intrathoracic disease. Seven out of eight of these patients (87.5%) had at least one other indicator of disease recurrence (elevated serum marker, abnormal abdominal CT). One of 42 patients (2.4%) relapsed with isolated intrathoracic disease with no other indicator of relapse. All patients with intrathoracic relapse had evidence of disease on chest X-ray. Of the 42 relapsing patients, 93% could be categorised as having good prognosis metastatic disease. Seven per cent relapsed with intermediate or poor prognostic disease; relapse in these patients would not have been detected earlier with the inclusion of routine thoracic CT. Only one patient has died giving a cure rate of 98% for relapsing patients.

Conclusions: The elimination of chest CT did not compromise outcome but significantly reduced radiation exposure thereby minimising the risk of radiation-induced secondary malignancy. Continued review of surveillance programmes is essential if we are to optimise management of this disease.

Key words: stage I non-seminomatous germ-cell cancer, surveillance programme, thoracic computed tomography scans

Introduction

Testicular non-seminomatous germ-cell tumours (NSGCT) are a comparatively rare but highly curable cancer of young adult males. Following staging, ~50% of cases will be found to be stage I with a normal physical examination, normal α-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) levels and normal computerised tomography (CT) of the chest, abdomen and pelvis. For many years the standard management approach in the UK for this group of patients has been a surveillance policy, with an anticipated risk of relapse of approximately 25–30% [1]; virtually all patients can be cured at relapse with standard BEP (bleomycin, etoposide, cisplatin) chemotherapy [2].

In recent years, a subgroup of patients with stage I disease has been recognised as having an increased risk of relapse (40–50%). This subgroup can be predicted histopathologically following the identification of tumour vascular invasion (lymphatic or venous) [1, 3]. Adjuvant chemotherapy is an accepted management approach for these patients; two cycles of adjuvant BEP chemotherapy (etoposide 360 mg/m²/course) will reduce the risk of developing metastatic disease to 1% [4]. Patients without vascular invasion (low risk) are managed in the UK within a surveillance programme with an anticipated risk of relapse of around 15%.

Surveillance policies vary nationally and internationally but historically have included history and physical examination, serum marker assay (AFP, HCG), serial chest X-ray and CT scans of the chest and abdomen [1, 5]. The intent is to diagnose relapsed disease at the earliest stage possible, thereby optimis-
ing the cure rate with salvage chemotherapy (BEP). This approach avoids the unnecessary administration of toxic chemotherapy to the majority of patients who will be cured by surgery alone. However, the optimal frequency and extent of CT scanning in surveillance programmes remains unclear.

Over a 13 year period (from 1986 to 1998), patients referred to Southampton with stage I NSGCT were entered onto a formal surveillance programme. Initial staging investigations included history, physical examination, serum marker levels, chest X-ray and CT scanning of the chest, abdomen and pelvis. No further routine CT scans of the chest were performed. We present our experience using this surveillance approach and provide recommendations about the future management of such patients.

**Patients and methods**

The clinical records of 168 patients with stage I NSGCT followed with surveillance were reviewed. All patients were referred for further management to the Wessex Medical Oncology Unit between 1986 and 1998 from nine regional centres. All patients had been treated surgically (inguinal orchidectomy) by the referring centre. All histopathology specimens were subject to expert review in Southampton.

Following initial staging (history, physical examination, serum AFP and HCG levels, chest X-ray and CT scanning of the chest, abdomen and pelvis) all patients with stage I testicular NSGCT were entered onto a formal surveillance programme. This consisted of monthly visits for 6 months, two six-weekly visits, five two-monthly visits, then in turn, three-, four- and six-monthly visits followed by annual review for 3 years after which patients were discharged. At each follow-up visit, a recent history was taken, a physical examination performed, serum markers checked (HCG and AFP) and chest X-ray obtained. Computed tomography scans of the abdomen were performed routinely at 3, 9 and 19 months following entry onto the surveillance programme. Computed tomography scans of the chest were not performed as part of routine surveillance following the initial staging scan. All radiology was performed centrally and subject to expert oncological radiology review (Table 1).

With a median follow-up of 7.3 years (range 2.2–14.9), 42 of 168 patients (25%) have relapsed with metastatic disease whilst on surveillance following the initial staging scan. At relapse, all patients underwent complete restaging by history, physical examination, serum marker levels (AFP, HCG and LDH), chest X-ray and CT scanning of the chest, abdomen and pelvis.

**Results**

The baseline characteristics of the 42 relapsing patients were as follows. Age ranged from 18 to 74 years with a median of age of 30 years. The interval between orchidectomy and subsequent relapse ranged from 3 to 172 weeks with a mean of 42 weeks and median of 34 weeks. Of the 42 relapsing patients, 15 patients (35.8%) showed definite evidence of vascular invasion in the primary orchidectomy specimen and could be categorised as high risk. Twenty-one (50%) did not exhibit vascular invasion and could be classified as low risk. Six cases (14.2%) were equivocal.

The International Germ Cell Consensus Classification has classified non-seminomatous metastatic testicular germ-cell cancer into three prognostic groups: good, intermediate and poor prognosis [6]. Of the 42 relapsing patients, 39 (92.8%) relapsed with good prognosis disease. Two (4.7%) relapsed with intermediate prognosis disease (LDH >1.5 but <10 x upper limit of normal) and one (2.4%) with poor prognosis disease (spleenic metastasis). Five patients (11.9%) relapsed with raised serum markers alone. Twenty-nine patients (69.1%) relapsed with non-visceral extrathoracic disease; 14 of these patients (48.3%) also had elevated serum markers at relapse. Eight patients (19%) relapsed with intrathoracic disease (Table 2).

All eight patients relapsing with intrathoracic disease had an abnormal chest X-ray at relapse. Seven out of the eight patients (87.5%) also had elevated serum markers (all within good prognosis levels; AFP <1000 ng/ml, HCG <5000 IU/l). In addition, three of the eight (37.5%) had evidence of relapse at extrathoracic sites. The only patient relapsing within the chest alone with normal serum markers had clear evidence of disease on chest X-ray (2 mm pulmonary nodule).

Forty-one of the 42 relapsing patients (97.6%) were treated with chemotherapy at relapse. One patient (2.4%) relapsed locally and required curative surgery alone (this constituted scrotal relapse secondary to an initial scrotal breach prior to referral). Of patients receiving chemotherapy, 36 out of 41 patients (87.8%) received three or four courses of standard

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Follow up including history, examination, tumour markers and chest X-ray.

Follow up at 7.5 months.

CT, abdominal computerised tomography.
BEP chemotherapy: five (12.1%) received four cycles of CEB chemotherapy (carboplatin, etoposide and bleomycin) as part of the MRC TE09 trial [7]. One patient (age 74 years) received etoposide/carboplatin chemotherapy off trial.

Following chemotherapy 28 out of 41 patients (68.2%) achieved a complete response (CR), 12 (29.3%) achieved a partial response (PR) and one (2.4%) achieved stable disease (SD). Twelve of 13 patients achieving PR or SD underwent post chemotherapy surgery. The remaining patient who relapsed initially with retroperitoneal disease and normal serum markers progressed rapidly following completion of first-line chemotherapy. This patient died of sepsis during high-dose chemotherapy treatment having failed two previous lines of conventional salvage chemotherapy treatment. There have been no other deaths in this patient group to date.

The treatment and outcome for those patients relapsing with intrathoracic disease is illustrated in Table 3. Following initial treatment, two out of 42 patients (4.7%) went on to suffer further disease relapse. Neither patient was one of the eight patients relapsing on surveillance with intrathoracic disease. Both patients achieved complete response with second-line salvage chemotherapy, and remain alive and disease free.

Discussion

Approximately 15–30% of patients with stage I NSGCT will relapse with intrathoracic disease [8–11]. Our series is entirely in keeping with this, with a relapse rate of 19%. For this group of patients, it is unusual for relapse to occur solely within the chest with no other indicator of disease recurrence. In our series of 168 patients followed on surveillance, it accounted for only one patient (0.6%). This patient’s pulmonary disease relapse was easily visible on chest X-ray, as indeed were all intrathoracic relapses in our series. All the other patients relapsing with intrathoracic disease had at least one other indicator of relapse (elevated serum marker/other disease site).

As previously indicated, the vast majority of patients relapsing within a good prognosis group and there is no evidence to suggest that the three patients relapsing with intermediate or poor prognosis disease would have been detected at an earlier stage (i.e. good prognosis group) with the addition of chest CT to the surveillance protocol.

Computed tomography scanning is the standard radiological surveillance tool in stage I NSGCT and the current Royal College of Radiology and UK Clinical Oncology Information Network (COIN) guidelines recommend that CT scans of the thorax and abdomen should be routinely performed as part of the follow up of patients with germ-cell tumours [12, 13]. A current Medical Research Council (MRC) study seeks to address the safest and most economical frequency of CT scanning in a prospective randomised trial (TE08); however, in this study all patients undergo a minimum of three thoracic CT scans. The results from this trial are awaited with interest. The extent of CT scanning (abdominal versus thoraco-

### Table 2. Characteristics of patients relapsing with intrathoracic disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Histology</th>
<th>Vascular invasion</th>
<th>Relapse interval (days)</th>
<th>Relapse sites</th>
<th>Serum marker level (if elevated)</th>
<th>Prognostic group</th>
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<td>1</td>
<td>27</td>
<td>MTI</td>
<td>Positive</td>
<td>66</td>
<td>Pulmonary nodules (8 mm)</td>
<td>Elevated</td>
<td>Good</td>
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<td>Mediastinal lymph nodes</td>
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<td>30</td>
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<td>Pulmonary nodules (12mm)</td>
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<td>116</td>
<td>Pulmonary nodules (13mm)</td>
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<td>Good</td>
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<td>33</td>
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<td>Pulmonary nodules (10 mm)</td>
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<td></td>
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<td>Pulmonary nodules (35 mm)</td>
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<td>Poor</td>
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<td>6</td>
<td>33</td>
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<td>7</td>
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<td>Hilar lymph nodes</td>
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<tr>
<td>8</td>
<td>18</td>
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<td>108</td>
<td>Pulmonary nodules (15 mm)</td>
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abdominal) has not been investigated within a randomised trial.

Pelvic CT scanning is no longer considered mandatory in all patients on surveillance with stage I testicular NSGCT. This decision is supported by White et al. [14] in a retrospective series examining the CT imaging of 167 patients with testicular germ-cell cancer. The paper concludes that following an initial staging CT scan of the chest, abdomen and pelvis, subsequent pelvic CT scanning is only required in the follow up of patients with an identifiable risk factor for pelvic recurrence. Those patients with pelvic disease but without an identifiable risk factor by conventional criteria all had unequivocal metastatic disease within the abdomen with the assumption that pelvic disease had occurred as a result of retrograde spread. The removal of routine pelvic CT scanning from surveillance programmes significantly reduces patient radiation exposure and has led to a substantial resource saving.

A CT scan of the chest delivers an appreciable radiation dose equivalent to 200–300 chest X-rays depending upon the scanning protocol used. It can only be justified if it significantly influences management or prognosis. Chest X-rays are widely available, easily interpretable and associated with substantially less radiation exposure than CT. The objective of thoracic surveillance in stage I testicular NSGCT is to detect low volume recurrence within a good prognosis group, thereby optimising cure rates [15]. Conversely, the risk of not monitoring the chest is that large asymptomatic pulmonary metastases may occur, thereby potentially worsening prognosis and complicating subsequent treatment [16]. In comparison to CT, chest X-ray is generally not considered to be a sensitive method of detecting small pulmonary nodules [11, 17]. However, plain chest X-ray can detect pulmonary nodules as small as 5 mm in size depending on location. CT cannot detect pulmonary parenchymal disease much smaller than this, the smallest detectable lesion measuring 3 mm [18]. Mediastinal visualisation is obviously better with CT but in the absence of other indicators of relapse, disease would still be detected at good prognosis stage using serial chest X-ray assessment. Solitary, marker negative mediastinal relapse is rare and was not encountered in our study population.

A number of authors have previously addressed the issue of serial chest X-ray/thoracic CT as part of routine surveillance. Gels et al. [11] evaluated data from 154 patients with stage I non-seminomatous testicular germ-cell cancer on surveillance. Patients underwent regular surveillance thoracic CT scanning and as such they concluded that chest X-ray could be omitted from their surveillance policy. Sharir et al. [9] reached a similar conclusion having evaluated the contribution of the various follow up modalities in stage I non-seminomatous testicular germ-cell cancer. They concluded that removal of chest X-ray from the protocol would not have changed progression detection despite 4/48 (8.3%) of patients recurrence initially being diagnosed on chest X-ray. The accompanying editorial comment disputes their conclusion stating that the failure to include a simple, inexpensive yet effective test with minimal morbidity was not acceptable. In the same year,
White et al. [10] published a retrospective review of 623 staging and re-assessment CT scans from 207 patients with testicular seminomatous and NSGCT. Intrathoracic metastatic disease was found in 20% of non-seminomatous patients. They found chest CT to be more sensitive than chest X-ray when compared with a ‘standard of reference’ 0.95 (95% CI 0.91 to 0.99) versus 0.35 (95% CI 0.25 to 0.45) but less specific 0.97 (95% CI 0.96 to 0.98) versus 0.99 (95% CI 0.98 to 1). On the basis of this study, they concluded that routine chest X-rays were unnecessary for patients followed on surveillance which included the use of routine thoracic CT.

A standard chest X-ray taken with a high kV technique in a dedicated room involves a small effective radiation dose to the patient estimated at 0.02 mSv. This compares to a effective dose of up to 6 mSv for a typical thoracic spiral CT scan (10 mm slices, pitch 1) [19]. In other words, approximately 300 times the effective radiation dose per examination is delivered using spiral CT compared with chest X-ray as a surveillance tool. A typical surveillance programme utilising routine chest CT might lead to a total dose of around 28–42 mSv (one baseline plus six reassessment CT scans) compared with 0.36 mSv for serial chest X-ray examination over the same period (monthly chest X-rays for the first year then 2 monthly for the second year). Excluding the baseline staging scan, this represents a 66–100-fold increase in radiation exposure for thoracic CT over serial chest X-ray. The consequences of radiation exposure are well documented. Stochastic risk represents the statistical risk of genetic damage occurring with radiation exposure. It has no lower threshold but increases in likelihood as the absorbed dose increases. This in turn leads to an increasing risk of secondary malignancy. For patients included within the White paper [10], the calculated risk of fatal cancer induction for patients undergoing surveillance was substantial at 18.3% for the cohort as a whole. It follows that switching from routine surveillance thoracic CT to chest X-ray would decrease this risk considerably.

Conclusions

In our series, only one individual out of 168 patients undergoing surveillance for stage I NSGCT relapsed with isolated intrathoracic disease. Disease relapse in this case was detected on chest X-ray alone and treatment was initiated at an early stage whilst the disease remained within a good prognosis group. In this series, all patients with intrathoracic relapse had abnormal chest X-ray findings. The three patients who relapsed with disease in intermediate or poor prognostic groups on surveillance did so because of an elevated LDH (without thoracic relapse) or because of extrapulmonary visceral disease (spleen). In conclusion, the elimination of routine surveillance chest CT in our series did not appear to compromise outcome but did significantly reduce radiation exposure. Continued review of surveillance programmes and protocols is essential if we are to minimise radiation exposure and its associated risks and optimise management of this disease.

Acknowledgements

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