Radiotherapy for Stage I seminoma testis: Results of treatment and complications

C. Hamilton, A. Horwich, D. Easton and M. J. Peckham*

Institute of Cancer Research and The Royal Marsden Hospital, London and Surrey, U.K.

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Summary

The results of treatment by infradiaphragmatic lymph node irradiation and orchiectomy in 232 patients with Stage I testicular seminoma seen between 1963 and 1983 are reported. Of this group, only five (2%) patients relapsed and none died from seminoma. Contralateral testicular tumours occurred in 12 patients and five developed second non-testicular malignancies. The acute and late morbidity of radiotherapy was low although 15 patients developed peptic ulceration. There was a significant association between prior abdominal surgery and a history of dyspepsia with ensuing peptic ulceration. Future management policy is discussed on the basis of these observations.

Introduction

The results of treatment by orchiectomy and radiotherapy for Stage I testicular seminoma are excellent with cure rates exceeding 90% [1,2,6,13,14,16]. These results may reflect the radiosensitivity of seminoma and the consequent high probability of eradicating occult tumour, on the other hand, they may also be attributable to a low incidence of retroperitoneal lymph node metastases. Limited data from lymphadenectomy series suggest that less than 10% of patients with clinical Stage I seminoma have histologically positive nodes [7]. A policy of surveillance after orchiectomy has been pursued successfully in non-seminomatous testicular germ-cell tumour patients [10,11] and it is appropriate to consider whether a similar approach would be justifiable in seminoma, particularly in view of the high cure rates now achievable in advanced disease with chemotherapy [12]. In this report we analyse the results of treatment and the complications of lymph node irradiation in patients with Stage I seminoma as a basis for considering the appropriateness of surveillance as a management policy.

Patients and methods

A total of 232 patients with clinical Stage I seminoma receiving para-aortic and ipsilateral pelvic
lymph node irradiation following orchiectomy between 1963 and 1983 are included in the study. Details were obtained from patients records. It is our policy to maintain regular follow-up on all patients referred to the Unit. Patients have been followed for 12 months to 20 years (median 7 years). The age range was 19 to 70 years, mean 39 years (Fig. 1). All patients had a histologically verified diagnosis of pure seminoma. The tumour was right-sided in 140 (61%) of patients, left-sided in 90 (38%) and occurred as bilateral synchronous presentations in two patients. Eighteen patients (8%) had a history of maldescent and in six this was bilateral. Of the 12 patients with unilateral maldescent, tumour occurred in the contralateral normally descended testis in four.

Staging and staging classification

Between 1963 and 1977 staging included chest radiographs, lymphography, intravenous urography and liver function tests. CT scanning became available in 1977 and was employed on a selective basis. Serum human chorionic gonadotrophin and alpha-fetoprotein titres were routinely assayed after 1973.

The Royal Marsden Hospital staging classification was employed [8]. Stage I disease is defined as tumour confined to the testis with no evidence of metastases after clinical staging.

Radiotherapy

Details of radiotherapy have been published elsewhere [9]. Treatment was by equally weighted opposed anterior and posterior fields extending from D10/11 to the mid-obturator foramen. The para-aortic field was wide enough to cover nodes opacified at lymphography and extended laterally to the renal hila. Inferiorly the field was shaped to include the ipsilateral pelvic lymph nodes, the point of inflexion between the para-aortic and pelvic area being at the lower border of L5 medially and the transverse process of L4 laterally. The remaining testis was protected by 1 cm thick lead cups. If there had been a scrotal incision (39 patients; 17%) scrotal involvement by tumour or a history of orchidopexy, the ipsilateral scrotal sac was irradiated using 250 kV X-rays with a lead cut-out to protect the contralateral testis. In these cases the pelvic field was extended down to include the inguinal nodes. The para-aortic and pelvic nodes were irradiated with 6–8 MeV photons delivering mid-plane doses of the order of 30 Gy in 3–3.5 weeks. In earlier years there was some variation of dose employed and the anterior and posterior fields were not routinely treated each day. In latter years the tumour dose has been 30 Gy in 15 fractions over 21 days with anterior and posterior fields treated each day.

Statistical methods

Survival rates were calculated using the Kaplan-Meier method [5].

Results

As shown in Table I, only 5 of 232 patients (2%) relapsed and there were no deaths from seminoma. Actuarial survival rates at 5 and 10 years were 99 and 94%, respectively. The time from orchiectomy to relapse was 10, 12, 21, 44 and 60 months (Fig. 2). The sites of relapse and outcome of salvage treatment which was successful in all five patients is summarized in Table II.
TABLE I
Clinical Stage I testicular seminoma: outcome of treatment by orchiectomy and infradiaphragmatic lymph node irradiation (The Royal Marsden Hospital 1963–1983).

<table>
<thead>
<tr>
<th>Total patients</th>
<th>Number relapsing*</th>
<th>Deaths from seminoma</th>
<th>Deaths from teratoma*</th>
<th>Deaths from other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>232</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>10</td>
</tr>
</tbody>
</table>

a Actuarial 5 and 10 year survival rates are 99 and 94%, respectively.
b Non-seminomatous germ-cell tumour.

Causes of death and second malignancy

In the total group there were 12 deaths as shown in Table III. Bilateral testicular tumours occurred in 12 cases; seminoma in 7; mixed seminoma/teratoma in one and teratoma in 4. The interval between first and second tumours ranged from zero (synchronous tumours) to 6 years (Fig. 2). In one of the seven patients with bilateral seminomas the tumours appeared synchronously. This patient received inverted Y-irradiation and is disease-free at 4 years. Of the six patients with metachronous bilateral seminomas all had Stage I disease when restaged after the second orchiectomy. Two patients have been observed and have not relapsed and four received further radiotherapy to the ipsilateral pelvic nodes. One irradiated patient developed disseminated tumour which at autopsy proved to be teratoma. The others are disease-free at 8, 14 and 15 years. The patient who developed a contralateral mixed seminoma/teratoma is being observed and is well. Of the four patients who developed teratomatous second tumours one relapsed with mediastinal and pulmonary metastases and has been salvaged with platinum-containing chemotherapy. A second patient rapidly disseminated and died prior to the era of effective chemotherapy.

TABLE II
Clinical Stage I testicular seminoma treated by orchiectomy and lymph node irradiation: sites of relapse and outcome of salvage treatment (The Royal Marsden Hospital 1963–1983).

<table>
<thead>
<tr>
<th>Site of relapse</th>
<th>Time to relapse after start of radiotherapy (mths)</th>
<th>Treatment of relapse</th>
<th>Outcome from time of relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>44</td>
<td>Lobectomy</td>
<td>Disease-free at 11 years</td>
</tr>
<tr>
<td>Left supraclavicular nodes</td>
<td>60</td>
<td>Radiotherapy</td>
<td>Disease-free at 1 year*</td>
</tr>
<tr>
<td>Mediastinal nodes</td>
<td>12</td>
<td>Radiotherapy</td>
<td>Disease-free at 11 years</td>
</tr>
<tr>
<td>Lung/pleura</td>
<td>10</td>
<td>Chemotherapy</td>
<td>Disease-free at 2 years</td>
</tr>
<tr>
<td>Mediastinal, supraclavicular and axilla nodes</td>
<td>21</td>
<td>Chemotherapy</td>
<td>Disease-free at 2 years</td>
</tr>
</tbody>
</table>

* Lost to follow-up 7 years ago.
TABLE III
Clinical Stage I testicular seminoma: causes of death in patients treated by orchiectomy and lymph node irradiation (The Royal Marsden Hospital 1963–1983).

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Time from presentation (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contralateral non-seminomatous germ-cell testicular tumour</td>
<td>1, 6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5, 8, 9</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>8, 10</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>10</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>12</td>
</tr>
<tr>
<td>Non-testicular malignancy</td>
<td>5, 8, 19</td>
</tr>
</tbody>
</table>

Five patients developed second non-testicular malignancies as follows: acute myeloid leukaemia at 7 years, pancreatic cancer at 2 years, gastric cancer at 16 years, prostatic cancer at 12 years and a carcinoma of the buccal mucosa at 8 years (Fig. 2). The expected number of tumours based on age-standardized national incidence rates is 5.2.

Peptic ulceration following radiotherapy

Symptoms compatible with peptic ulceration occurred in 15 patients. In 13 the diagnosis was established by barium studies which showed a duodenal ulcer in 11 patients, gastric in one and gastric and duodenal ulceration in a further patient. In all 15 patients the pain was described as severe and in five patients symptomatology persisted for more than one year. Twelve patients were treated medically and three came to surgery, one of whom developed pyloric stenosis and died of peritonitis post-operatively. There was no apparent association between the appearance of this complication and total dose, dose per fraction, overall time or number of fields treated each day. Of the 25 patients who had moderate or severe acute gastrointestinal toxicity, seven developed peptic ulceration. As shown in Table IV, prior abdominal surgery or a history of dyspepsia strongly predisposed the patient to subsequent peptic ulceration.

TABLE IV
Clinical Stage I testicular seminoma treated by orchiectomy and lymph node irradiation: influence of prior surgery and dyspepsia on the development of peptic ulceration (The Royal Marsden Hospital 1963–1983).

<table>
<thead>
<tr>
<th>Factor</th>
<th>Peptic ulceration</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior abdominal surgery</td>
<td>5/27 (19%)</td>
<td>0.02</td>
</tr>
<tr>
<td>No prior abdominal surgery</td>
<td>10/205 (5%)</td>
<td></td>
</tr>
<tr>
<td>Prior history of dyspepsia</td>
<td>4/10 (40%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No prior history of dyspepsia</td>
<td>11/222 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

Post-orchiectomy lymph node irradiation in seminoma is based on the assumption that a proportion of patients with clinical Stage I disease will have occult metastases in the draining lymph nodes. The stage distribution at presentation of patients with testicular seminoma shows that more than 70% have Stage I disease indicating that this tumour type has a low propensity for spread. Limited data from lymph node dissection adds support to this contention. In the series of Stage I patients undergoing surgery reported by Maier et al. [7], only 8% proved to have histologically demonstrable metastases. Since in this era patients were not investigated by lymphography and CT scanning it is possible that this figure could be even lower. It is likely therefore that the large majority of Stage I patients receiving post-orchiectomy radiotherapy do so unnecessarily. Furthermore, if the small proportion of patients relapsing after radiotherapy (2% in the present series) represent part of the population with occult metastases (approximately 8%), then the cure rate with radiotherapy or clinical Stage I patients with metastatic disease may be of the order of 60–70%.

The tumour dose for small-size metastases of seminoma is unknown, but may be lower than the dose of 30 Gy employed in the present series. With doses of this order late morbidity is rarely a problem although our results suggest that there may be
an increased risk of peptic ulceration particularly in patients with a history of dyspepsia. However, it is difficult to be sure of the aetiological role of irradiation in this context and there are not comparable control series with which the incidence of peptic ulceration can be compared. Five second non-testicular malignancies were observed in the present series but there was no evidence that this represented an increased risk over the expected number of cancers in an unirradiated population. Hay et al. [3] in a study of 547 testicular tumour patients treated with radiotherapy between 1950 and 1969 found 51 second malignancies of which 7 were testicular. The incidence of second non-testicular cancers was significantly increased compared with the expected rate. The difference in incidence of second non-testicular tumours in the series of Hay et al. [3] and in the present series (8 and 2%, respectively) is likely to be explained by the longer observation period in the Edinburgh study. During the first 5 years after radiotherapy most second tumours are testicular, as shown in Fig. 2. As reported by Hay et al. [3], the second period during which there is a significant increase in observed compared with expected rates of malignancy is attributable to non-testicular tumours and occurs between 15 and 19 years.

The relapse rate observed in the present study is closely similar to that recently reported by Schultz et al. [13] who described 13 treatment failures (3%) in 424 Stage I seminoma patients treated by orchiectomy and radiotherapy between 1976 and 1980 in Denmark. In the Danish series 5/8 relapses were non-seminomatous and 2 of the 8 cases with seminoma metastases died of their disease. In the present series all Stage I patients relapsing after radiotherapy were successfully salvaged and there has been no death attributable to metastatic seminoma. Given the high degree of effectiveness of platinum-containing chemotherapy in advanced seminoma, the salvage of relapsing patients after irradiation or in a surveillance study should rarely be associated with treatment failure [12]. The appearance of second testicular tumours is a well-documented phenomenon and unlikely to be related to radiotherapy since similar patterns are observed in patients treated surgically for non-seminomatous tumours and in patients undergoing surveillance.

The question arises as to whether radiotherapy after orchiectomy can be abandoned in favour of a policy of close surveillance, as has been conducted successfully for non-seminomatous germ-cell tumours [10,11]. Surveillance in non-seminomatous tumours is facilitated by the generally short interval between orchiectomy and the appearance of metastatic tumour in relapsing patients and by employing alpha-fetoprotein and human chorionic gonadotrophin as tumour markers. As shown in the present study, the time interval between orchiectomy and diagnosis of metastases in the five patients who relapsed ranged from 0 to 60 months. Three relapses occurred within the first 2 years and it is possible that the intervals in the remaining two patients might have been shorter if current imaging techniques including CT scans had been available. Until recently, there has been an absence of reliable tumour markers for seminoma, although a proportion produce human chorionic gonadotrophin and more recent studies have demonstrated that placental alkaline phosphatase levels are elevated in patients with demonstrable metastatic tumour [4,17]. However, the value of placental alkaline phosphatase in longitudinal studies particular in the surveillance of Stage I disease, remains to be established.

In our view the routine treatment of choice for patients with Stage I seminoma is radiotherapy and surveillance should be regarded as a clinical research exercise to be conducted in centres where close monitoring can be assured, where modern imaging facilities are readily available and where placental alkaline phosphatase assays can be carried out. Certainly, if the reliability of the patients’ attendance is in doubt radiotherapy should be given. On the other hand, if there is a prior history of peptic ulceration a policy of surveillance will avoid the risks of producing an exacerbation by radiotherapy. Furthermore, when issues of fertility are at stake then the omission of radiotherapy should also be considered. This includes those situations where according to traditional practice the treatment field is extended inferiorly to include the inguinal nodes and where the ipsilateral scrotal sac is irradiated, for example, after scrotal orchiectomy.
transcrotal biopsy or prior orchidopexy. Although fertility may be recovered after scrotal irradiation this is an uncommon event and the large majority of patients are sterilised. We have previously reported that in patients treated with a linear accelerator in whom the fields do not extend below the ipsilateral obturator foramen the radiation dose to the contralateral testis (0.33–0.52 Gy) is compatible with recovery of spermatogenesis [15]. However, when scrotal and inguinal irradiation are employed the dose to the contralateral testis is substantially higher (0.75–1.38 Gy) and permanent azoospermia is likely to occur.

Since the proportion of clinical Stage I seminoma patients harbouring occult metastases is unknown and data bearing on this point are extremely scanty, we felt it justifiable in 1983 to initiate a surveillance study, to better define the natural history of Stage I seminoma and provide a firm basis for future practice. So far, 46 patients have been entered into the study, two relapses have occurred both in the retroperitoneum and both patients are in complete remission following infradiaphragmatic irradiation. Although both relapses have occurred within one year of orchiectomy, longer observation times in larger numbers of patients will be necessary before the proportion of patients with occult metastases can be identified with confidence. Details of the seminoma surveillance study will be published in due course.

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References