# Recommendations for followup of stage I and II seminoma: The Princess Margaret Cancer Centre approach

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## Abstract

Testicular seminoma most commonly affects young men and is associated with favourable prognosis. Various followup schedules and imaging protocols for testicular seminoma have been described without overall consensus. We reviewed the literature together with our experience at the Princess Margaret Cancer Centre and present an evidence-based followup approach for patients with stage I and II seminoma.

## Introduction

Testicular seminoma accounts for less than 1% of malignancies, with median age at diagnosis of 30–40 years.[1] Early stage (stage I and IIA/B) testicular seminoma has five-year overall and disease-specific survival rates that exceed 90% and 95%, respectively.[2-9] Published guidelines for testicular seminoma provide consistent treatment recommendations, but followup schedules vary.[10-14] The aim of followup after cancer treatment is to detect and manage relapse, but monitoring and treating toxicity from therapy is also necessary. We reviewed the literature and the Princess Margaret Cancer Centre experience regarding followup of stage I and II testicular seminoma and make recommendations for an evidence-based followup approach.

## Stage I seminoma

After radical orchiectomy for stage I seminoma, management options include active surveillance, adjuvant radiotherapy, or adjuvant carboplatin. As relapse rates and patterns of failure differ with each treatment, a tailored followup program is needed.

### Surveillance

The risk of relapse after radical inguinal orchiectomy alone is estimated to be 13–20% at five years,[15-18] but long-term cure rates approach 100%.[19-21] At the Princess Margaret Cancer Centre, all men with stage I seminoma are advised of treatment options and recommended surveillance.

Each followup visit includes a history and physical examination. In the first three years, six-monthly low-dose computed tomography (CT) scans of the abdomen and pelvis are performed. Thereafter, CT scans are limited to the abdomen only and performed every 1–2 years, as outlined in Table 1. Serum hormone levels (total testosterone, luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) are measured annually, but serum tumour markers have been eliminated.

### History and physical examination

Physical examination to detect disease recurrence is of limited value, but should include examination of the scrotum, contralateral testis, and lymph node regions, particularly the inguinal and supraclavicular sites. A Danish study reported 5% of the 353 relapses were found by physical alone,[9] and in a pooled series of more than 1300 men, physical examination did not identify any relapses.[16] Isolated inguinal lymphadenopathy found by physical examination are usually associated with previous surgery and altered lymphatic drainage.[22] In our series of 766 surveillance patients, there were two cases of biopsy-confirmed inguinal lymphadenopathy.[23] Metachronous contralateral testicular tumours occur in 1–2 % of men with testicular seminoma.[24,25]

**Table 1. Surveillance protocol for stage I seminoma**

| Time post-orchiectomy | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Year 1 | | | | | | H&P<br>CT abdomen & pelvis | | | | | | H&P<br>CT abdomen & pelvis<br>Hormone levels* |
| Year 2 | | | | | | H&P<br>CT abdomen & pelvis | | | | | | H&P<br>CT abdomen & pelvis<br>Hormone levels* |
| Year 3 | | | | | | H&P<br>CT abdomen & pelvis | | | | | | H&P<br>CT abdomen & pelvis<br>Hormone levels* |
| Year 4 | | | | | | | | | | | | H&P<br>CT abdomen<br>Hormone levels* |
| Year 5 | | | | | | | | | | | | H&P<br>CT abdomen<br>Hormone levels* |
| Year 7 | | | | | | | | | | | | H&P<br>CT abdomen<br>Hormone levels* |
| Year 9 | | | | | | | | | | | | H&P<br>CT abdomen<br>Hormone levels* |

*Total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH). CT: low-dose computed tomography; H&P: history and physical examination.

At the Princess Margaret Cancer Centre, total testosterone, LH, and FSH levels are measured annually. A population-based study of testicular cancer survivors found these men were at greater risk of low testosterone and high FSH and LH levels over time compared to healthy controls.[26] Hypogonadal symptoms associated with consistently low testosterone levels may be managed with testosterone replacement and referral to endocrinology.[27]

A brief psychosocial review is performed to screen for underlying anxiety and depression.[28,29] Men with testicular cancer may have increased rates of anxiety and suicide compared to the general population.[30,31] We recommend the validated Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder seven-item scale (GAD-7) as screening tools, and at our institution, these are combined with other standardized validated measures of distress, and completed by patients prior to clinical review. Depending on their screened level of distress, interventions range from providing information on supportive services to referral to a specialist psychologist or psychiatrist for further assessment and management.

## Imaging

### *1. Computed tomography (CT)*

Men on surveillance are most likely to relapse in the retroperitoneum.[9,15,23,32] At the Princess Margaret Cancer Centre,[23] similar to the Danish cohort study,[9] retroperitoneal metastases either in isolation or with synchronous pelvic or inguinal metastases accounted for 93% of relapses. Abdominopelvic CT is the main method of detecting infra-diaphragmatic relapses in 85–99% of surveillance cases.[9,16,23]

Given the duration of followup and frequency of imaging, radiation-induced malignancy is a concern in these young men. A single abdominopelvic CT scan is estimated to expose patients to 10–20 mSV of radiation,[33,34] with the Biological Effects of Ionizing Radiation (BEIR) VII phase 2 report estimating a 1 in 1000 risk of a radiation-induced cancer from 10 mSV based on epidemiological studies.[35] To minimize this risk, less frequent CT imaging, as well as the use of low-dose CT or magnetic resonance imaging (MRI) have been described.[19,36,37] A study of low-dose CT with model-based iterative reconstruction during followup of early-stage testicular germ cell tumours demonstrated comparable or superior image quality and a reduction in radiation dose by 67%, compared to conventional-dose imaging.[36] Our prospective phase 2 study of low-dose abdomen/pelvis CT during surveillance for stage I germ cell tumours found that although the diagnostic quality of low-dose CT was slightly inferior to standard-dose CT, image quality was acceptable in 99% of cases, with no false negative readings, and resulted in a median dose reduction of 55% compared to standard-dose CT.[37] At the Princess Margaret Cancer Centre, since 2012, all abdominopelvic CT imaging during followup of testicular germ cell tumours use this same low-dose scanning protocol.

Relapse during surveillance for stage I seminoma occurs most frequently within the first three years. [9,16,23,38] Pooled data

from five institutions found that in more than 1300 patients, 92% of recurrences were observed within three years.[16] The systematic review by Martin et al found the risk of relapse during surveillance is greatest in the first two years after orchiectomy, with hazard rates of more than 5% per year.[38] In years 2–3, annual hazard rates fall to 1–5%, then after four years to 0.3–1%, and after 10 years are even lower at <0.3% per annum. At the Princess Margaret Cancer Centre, all pelvic relapses during surveillance have occurred within three years of orchiectomy.[39] We perform CTs of the abdomen and pelvis every six month for the first three years, followed by CTs limited to the abdomen every 1–2 years thereafter.

The followup schedule intensity is adapted to the greatest risk of recurrence, balanced by the risk of cumulative radiation exposure. The timing of CT scans in our surveillance protocol is similar to the more frequent imaging arm in the MRC TE24 TRISST followup trial randomizing patients to one of four surveillance arms (6-monthly for two years, then annually until year 5).[40] The endpoint of TRISST was to measure the proportion relapsing with stage IIC or higher disease. The trial closed to accrual in 2014 and the results are awaited.

### *2. Chest X-ray (CXR)*

In patients on surveillance, thoracic recurrence is low, with no studies reporting the mediastinum or lung as an initial site of relapse in isolation. In a retrospective study of more than 1300 patients with stage I seminoma, no recurrences were identified by CXR.[16] In our cohort of patients on surveillance, only two relapses (2%) were to supradiaphragmatic sites, and both were associated with either para-aortic or inguinal nodal metastases.[23,41] Despite the low rates of isolated supradiaphragmatic relapses, chest imaging with CT or X-ray is described in many followup protocols,[10,11,13] although the National Comprehensive Cancer Network (NCCN) guidelines reserve chest imaging for patients with thoracic symptoms.[12] At the Princess Margaret Cancer Centre, we have eliminated chest imaging from our surveillance protocol.

## Serum tumour markers

There is no evidence to support the clinical utility of monitoring serum tumour markers (STMs) during followup of pure seminoma, even in the setting of elevated levels pre-orchiectomy; however, STMs are often included in followup protocols for testicular seminoma[11,13] despite <15% of pure seminoma producing beta-human chorionic gonadotropin (HCG), and alpha-fetoprotein (AFP) limited to non-seminomatous or mixed tumours. With modern histopathological techniques, seminoma diagnosis is more accurate, and it is rare to relapse with non-seminomatous disease.[14] Lactate dehydrogenase (LDH) is a less specific marker compared to AFP and HCG, and has limited sensitivity, specificity, and positive predictive value in detecting relapse of testicular germ cell tumours.[42]

Clinical practice guidelines from the American Society of Clinical Oncology (ASCO) advocate for monitoring marker levels to ensure normalization post-orchiectomy, but recommend against routine STM levels in post-treatment surveillance of stage I seminoma.[43] The pooled multi-institutional data reported an elevated HCG in 3% of relapses,[16] and a large Danish surveillance program described isolated elevated STMs in <1% of relapses.[9] In our series, abnormal STM levels were noted in 14% of relapsed cases during surveillance, but none in isolation with all patients having radiological evidence of relapsed disease.[23,44]

Although STMs are a minimally invasive investigation, given the low yield of detecting relapse when routine imaging is performed during followup, at our institution we no longer routinely measure STMs during followup of stage I seminoma.

## Duration of followup

The optimal duration of followup for men with testicular seminoma is unknown and often based on consensus opinion. The systematic review by Martin et al found the risk of recurrence was highest in the first two years, then decreased thereafter independent of treatment, with annual hazard rates of <1% after four years.[38] We acknowledge that followup can be discontinued at five years, as described by other guidelines;[11-13] however, at the Princess Margaret Cancer Centre, we continue to follow patients to nine years, as 8% of our relapsed cases have occurred after five years[23] and we are able to minimize radiation exposure by using low-dose CT imaging limited to the abdomen only. All late relapses in our series were cured with salvage therapy.[23]

Late relapse beyond 10 years has been described,[9,23,45] but is uncommon; there would be little benefit in extending followup to identify this small percentage of patients.[16] At the last clinic visit prior to discharge, patients and their primary care provider should be advised of the risk of late relapse and the need to represent if they develop concerning symptoms or signs, but no further surveillance imaging is required after discharge.

## Adjuvant therapy

The reported risk of relapse after adjuvant therapy for stage 1 seminoma is <5%[20,46] and thus followup intensity may be less than surveillance. In the MRC combined analysis of the TE10, TE18, and TE19 trials for stage I seminoma, the risk of recurrence more than three years after adjuvant therapy with either radiotherapy or carboplatin chemotherapy was very low, with only four cases of recurrence (0.2%) beyond three years.[47] A recent retrospective study by Fischer et al found 15% of the 185 relapses following adjuvant carboplatin

occurred after three years.[48] Sites of relapse vary depending on treatment modality and technique, as described below.

### *Adjuvant radiotherapy*

At the Princess Margaret Cancer Centre, we rarely use adjuvant radiotherapy for stage I seminoma,[49] but followup is similar to that described after definitive radiation treatment for stage II seminoma because of the similar patterns of relapse (Table 2). Our protocol includes regular CXR, but abdominal imaging is omitted due to high rates of retroperitoneal disease control.

In-field recurrences following para-aortic field radiation are rare, and the commonest sites of relapse are to the pelvis and supradiaphragmatic sites.[47,50-55] In the MRC TE10 trial, the two in-field recurrences occurred in conjunction with pelvic or mediastinal recurrence.[55] The combined analysis found that in those men receiving adjuvant para-aortic field, 37% of the 54 relapses were to the pelvis, 26% to the mediastinum or neck, and 7% to the abdomen alone.[47]

Patients who received adjuvant dog-leg field radiotherapy in the MRC TE10 trial had supradiaphragmatic, but no abdominopelvic relapses.[55] The combined MRC analysis reported 17 relapses after adjuvant dog-leg radiotherapy. Supradiaphragmatic sites accounted for 65% of cases, with isolated pelvic or isolated abdominal relapses each accounting for 6%.[47] In our series of men with stage I seminoma treated with adjuvant radiotherapy using a dog-leg technique, relapse to supradiaphragmatic sites was also most common, followed by the inguinal region; no abdominopelvic relapses were noted.[23]

We therefore recommend that pelvic CT imaging should be performed routinely after adjuvant para-aortic radiotherapy, but not after dog-leg field radiotherapy. We suggest pelvic CT be performed during the period of highest risk of relapse, that is, every six months for the first three years. Although the risk of relapse to the chest after adjuvant radiotherapy would not be expected to be higher than surveillance, as the mediastinum is one of the first sites of disease recurrence and can be detected on chest imaging before growing to a size large enough to cause symptoms, we recommend regular CXR, as outlined in Table 2.

### *Adjuvant chemotherapy*

Adjuvant single-agent carboplatin chemotherapy is an alternative treatment to radiotherapy if surveillance is not pursued. Single-agent carboplatin results in 5.3% relapse at five years compared to 4.0%, as seen in the MRC TE19 randomized trial.[56]

The literature guiding followup after carboplatin is sparse. Based on the similar pattern of relapse to the retroperitoneum as surveillance,[32,48,56-61] following adjuvant carboplatin we recommend abdominal imaging every six months for the first three years. Of the 27 relapses reported in the MRC TE19 trial, 67% were to the retroperitoneum, 3% to the supradiaphragmatic site, and there were no cases of isolated pelvic relapse.[58] A retrospective study of 517 patients treated

**Table 2. Followup protocol for stage II seminoma treated with modified dog-leg field radiotherapy after complete radiological response**

| Time post-orchiectomy | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Year 1 | | | | | | H&P<br>CXR | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 2 | | | | | | H&P<br>CXR | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 3 | | | | | | H&P<br>CXR | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 4 | | | | | | | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 5 | | | | | | | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 7 | | | | | | | | | | | | H&P<br>CXR<br>Hormone levels* |
| Year 9 | | | | | | | | | | | | H&P<br>CXR<br>Hormone levels* |

*Total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH). CXR: chest x-ray; H&P: history and physical examination.

with single-dose adjuvant carboplatin for stage I disease reported 80% of relapses occurred within three years, with 90% of cases relapsing in the retroperitoneum.[57] Of the 21 relapses in that series, two mediastinal recurrences were reported, but both occurred with synchronous retroperitoneal disease. We do not recommend regular CXR following adjuvant carboplatin based on the very low rates of isolated chest relapse. The overall risk of relapse after carboplatin appears to be higher when using one course compared to two, and with carboplatin doses of less than 7x area under the curve (AUC 7).[20,56,59,61] In general, as relapse rates after adjuvant therapy are lower than that for surveillance, consideration should be given to less frequent imaging, as well as imaging the abdomen only based on the low risk of isolated pelvic relapse, to minimize radiation exposure.

## Stage II seminoma

At the Princess Margaret Cancer Centre, all patients who present with stage II seminoma are discussed by a multidisciplinary team of urologists, radiation and medical oncologists. We define "bulky" retroperitoneal disease as a single retroperitoneal node measuring more than 4 cm or multiple enlarged retroperitoneal lymph nodes, with the largest node at least 3 cm in size.[62] Our practice is for those patients with stage IIA and low-bulk stage IIB disease to be treated with definitive radiotherapy to the para-aortic and ipsilateral pelvic lymph nodes using a modified dog-leg technique,[4] if the disease can safely be encompassed in the radiation treatment volume, with no contraindications to radiotherapy and no concerns about aberrant lymphatic drainage due to prior scrotal surgery. For all other patients with stage II disease, platinum-based chemotherapy with three cycles of bleomycin-etoposide-cisplatin (BEP), or four cycles of etoposide-cisplatin (EP) if there is a contraindication to bleomycin, is recommended.[63] Platinum-based chemotherapy is also recommended for patients with stage IIC or bulky stage IIB disease because of the high risk of distant disease associated with tumour volume. The rates of relapse after radiation treatment for bulky retroperitoneal disease are significantly higher compared to treatment with cisplatin-based chemotherapy.[3] We use the same treatment approach for patients who develop retroperitoneal relapse while on surveillance, and the same followup regimen depending on treatment modality.

### Definitive radiotherapy

Radiotherapy for stage IIA and IIB disease is an effective treatment resulting in relapse-free survival rates of more than 80%.[3,4,64] Upon completion of radiotherapy, we perform a CT abdomen and pelvis at three months, then every 3–6 months until a complete radiological response with normalization of imaging is observed. Because of the reported high rates of in-field disease control and pattern of relapse to supradiaphragmatic sites,[3,4,8,65,66] we do not routinely perform further abdominal imaging after radiological response is documented. Based on patterns of failure, our followup protocol includes chest imaging, and given the high doses of radiation associated with chest CTs, we recommend CXRs at six-month intervals for the first three years, then annually until year five, with biennial imaging until year nine (Table 2). Similar to our surveillance program, at each clinic visit a history and physical examination is performed, and serum hormone levels are measured.

One of the larger studies of definitive radiotherapy for stage IIA and IIB seminoma treated 94 patients with a modified dog-leg field and reported four cases of relapse within 40 months, including three mediastinal relapses and one recurrence at the field edge.[4] The Mayo Clinic's series of 52 patients found in-field relapses to be uncommon, with only one para-aortic relapse in a man with stage IIC disease who relapsed within six months, suggesting that bulky disease may not respond to radiation alone.[8] The majority of relapses were to supradiaphragmatic sites, such as the mediastinum, supraclavicular fossa, and lung, and occurred within two years of treatment. Other small series of patients receiving definitive radiotherapy for stage II seminoma have reported similar patterns of relapse to supradiaphragmatic sites, with in-field relapses rare.[64-66]

Our report of 49 men with stage IIA seminoma treated with radiotherapy to the para-aortic nodes and pelvis found none of the four relapses were in the radiation volume; of the 30 men with stage IIB seminoma who received abdominopelvic radiotherapy, three experienced disease relapse, including two cases of relapse to the left supraclavicular nodes +/left axilla, and one case of para-aortic relapse. [3] The commonest time to relapse was in the first two years after treatment, with all relapses occurring by four years. Other studies of radiotherapy for stage II seminoma describe relapses up to six years from treatment.[4,32,64,65] Similar to our stage I surveillance program, we continue to follow patients to nine years.

### Definitive chemotherapy

For stage II seminoma, cisplatin-based chemotherapy is typically reserved for bulky disease, but may be considered for low-volume disease if there are contraindications to radiation treatment.

The evidence for followup after chemotherapy for stage II seminoma is limited, with many studies including both seminoma and non-seminoma, as well as patients with more advanced disease.[67-71] It is thus difficult to make recommendations for followup in this rare group of patients and we advise that these cases should be managed at expert centres with an individualized treatment and followup approach.

In general, as with stage II seminoma treated with radiotherapy, followup abdominal imaging is required to ensure disease regression after chemotherapy. Disease resolution can take many months to years, and tumours that demonstrate ongoing shrinkage can often be observed with close followup. In some cases residual fibrotic lesions may remain, particularly in men with large-volume disease prior to treatment. Fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful to determine the presence of active residual disease.[72] Residual masses that do not demonstrate regression post-chemotherapy or that remain PET-avid on serial imaging more than six weeks apart should be referred to an expert centre. Treatment of suspected residual disease includes surgical resection or second-line chemotherapy.[12,70,73,74]

Once there is no evidence of active disease, our followup protocol for advanced seminoma is the same as that for non-seminomatous germ cell tumours treated with chemotherapy (Table 3). Patients may be at risk of both nodal and distant relapse most commonly within two years of treatment,[3,32] and imaging includes CT scans of the chest, abdomen and pelvis every six months for the first two years, then at five and nine years.

As elevated STMs may be one of the first signs of relapse in initial advanced disease, the ASCO guidelines recommend regular monitoring of STMs during followup, and we also measure STMs after chemotherapy for advanced seminoma.[43]

## Conclusion

Our followup recommendations have been modelled on the timing and patterns of relapse for early-stage testicular seminoma based on the existing literature, our institution's experience, and opinion of our centre's expert oncologists.

**Table 3. Followup protocol for stage II seminoma treated with chemotherapy**

| Time post-orchiectomy | Month | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Year 1 | | | H&P<br>STMs | | | H&P<br>STMs<br>CT chest/abdomen/pelvis | | | H&P<br>STMs | | | H&P<br>STMs<br>CT chest/abdomen/pelvis<br>Hormone levels*<br>Creatinine |
| Year 2 | | | H&P<br>STMs | | | H&P<br>STMs<br>CT chest/abdomen/pelvis | | | H&P<br>STMs | | | H&P<br>STMs<br>CT chest/abdomen/pelvis<br>Hormone levels*<br>Creatinine |
| Year 3 | | | | H&P<br>STMs | | | | H&P<br>STMs | | | | H&P<br>STMs<br>Hormone levels*<br>Creatinine |
| Year 4 | | | | | | H&P<br>STMs | | | | | | H&P<br>STMs<br>Hormone levels*<br>Creatinine |
| Year 5 | | | | | | | | | | | | H&P<br>STMs<br>CT chest/abdomen/pelvis<br>Hormone levels*<br>Creatinine |
| Year 6 | | | | | | | | | | | | H&P<br>STMs<br>Hormone levels* |
| Year 7 | | | | | | | | | | | | H&P<br>STMs<br>Hormone levels* |
| Year 8 | | | | | | | | | | | | H&P<br>STMs<br>Hormone levels* |
| Year 9 | | | | | | | | | | | | H&P<br>STMs<br>CT chest/abdomen/pelvis<br>Hormone levels* |

*Total testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH). CT: low-dose computed tomography; H&P: history and physical examination; STMs: serum tumour markers.

Limitations include basing our recommendations, particularly for stage II seminoma, on single-institution reports due to the lack of randomized evidence. Other limitations are the variations in treatment technique, including chemotherapy and radiotherapy doses and radiotherapy fields in reported studies, variability in imaging and followup regimens that may affect relapse detection, and in the case of adjuvant carboplatin for stage I disease, the lack of long-term data to guide followup protocols.

The followup program described has been implemented at the Princess Margaret Cancer Centre, and may serve as a framework for other institutions that manage testicular seminoma.

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