ClinicalEvidence

Testicular cancer: germ cell tumours

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ABSTRACT

INTRODUCTION: More than half of painless solid swellings of the body of the testis are malignant, with a peak incidence in men aged 30 to 34 years. Most testicular cancers are germ cell tumours and half of these are seminomas, which tend to affect older men and have a good prognosis. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of treatments following orchidectomy in men diagnosed with stage 1 germ cell tumours (confined to testis)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, 76 records were screened for inclusion. Appraisal of titles and abstracts led to the exclusion of 47 studies and the further review of 29 full publications. Of the 29 full articles evaluated, two systematic reviews and one RCT, were added at this update. Data from long-term follow-up of an already reported study were also added. We performed a GRADE evaluation for seven PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for seven interventions based on information about the effectiveness and safety of adjuvant chemotherapy (including different drugs and the number of cycles), adjuvant radiotherapy (including different regimens), adjuvant surgery, and surveillance/observation.

QUESTIONS

What are the effects of treatments following orchidectomy in men diagnosed with stage 1 germ cell tumours (confined to testis)? 4

INTERVENTIONS

GOOD-PROGNOSIS STAGE 1 GERM CELL TUMOURS (CONFINED TO TESTIS)

Beneficial

Adjuvant irradiation of 20 Gy in 10 fractions to para-aortic area compared with 30 Gy in 15 fractions to para-aortic area and iliac nodes in patients with seminoma (lower dose irradiation is similarly effective and associated with less toxicity) 15

Trade off between benefits and harms

Adjuvant chemotherapy 4

Adjuvant radiotherapy 6

Adjuvant surgery in patients with non-seminona (retroperitoneal lymph node dissection) New 10

Surveillance 13

Unknown effectiveness

Comparative effects of different drug combinations for adjuvant chemotherapy 18

Comparative effects of different number of cycles of adjuvant chemotherapy 18

Key points

- More than half of painless solid swellings of the body of the testis are malignant, with a peak incidence in men aged 30 to 34 years.

  Most testicular cancers are germ cell tumours and about half of these are seminomas, which tend to affect older men and have a good prognosis.

- In men with germ cell tumours confined to the testis (stage 1), standard treatment is orchidectomy followed by radiotherapy (seminoma only), chemotherapy, surgery/retroperitoneal lymph node dissection (non-seminoma only), or surveillance. All management options are associated with cure rates approaching 100% because of successful salvage therapy.

  There may be no difference between adjuvant chemotherapy and adjuvant radiotherapy in relapse rates at 2 to 5 years for stage 1 seminoma, with adjuvant chemotherapy causing acute side effects that were short lived compared to adjuvant radiotherapy.

  We don't know which is the most effective chemotherapy regimen or what is the optimum number of cycles to use. The high cure rate with standard therapy makes it difficult to show which alternative therapy is superior.

  Toxicity is lower, but efficacy the same, with adjuvant irradiation of 20 Gy in 10 fractions compared with 30 Gy in 15 fractions, or with irradiation to para-aortic nodes compared with para-aortic and ipsilateral pelvic nodes in men who have undergone orchidectomy for stage 1 seminoma.

  Adjuvant surgery (retroperitoneal lymph node dissection) is less effective at reducing risk of relapse at 2 years after orchidectomy compared with chemotherapy in men with non-seminomatous testicular cancer.

  No adjuvant therapy has been demonstrated to improve survival compared with surveillance after orchidectomy. The choice of treatment following orchidectomy is influenced by factors such as the pattern of toxicity, the inconvenience and complexity of treatment, and patient preference, particularly the person's attitude to relapse.

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Clinical context

GENERAL BACKGROUND

Testicular cancer represents only 1% of all cancers, with germ cell tumours being by far the most common pathology. This disease is the most common form of cancer in men aged under 40 years, and is curable in a large majority of cases. However, it may be a significant burden to some men in the prime of their lives either due to the disease or to its treatment, or both. The primary treatment for testicular germ cell tumours is radical orchidectomy; this allows diagnosis and definitive histological subtyping. Further management depends on the histological subtype, extent of disease at diagnosis, and also the presence of elevated tumour markers, which is more likely in non-seminoma with loco-regional and/or distant metastases.

FOCUS OF THE REVIEW

The majority of men present with disease clinically confined to the testis (stage 1) and may be offered surveillance (observation with treatment at relapse), adjuvant chemotherapy, adjuvant radiotherapy (seminoma), or retroperitoneal lymph node dissection (non-seminoma). Despite the multiple available options for the management of stage 1 tumours, the optimal management is controversial. This overview focuses on the evidence for the various options and may help individual decision-making for patients and clinicians.

COMMENTS ON EVIDENCE

For a rare disease, several RCTs have been successfully completed to guide evidence-based decision making. However, one of the main options, surveillance, has been developed empirically over time.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, June 2010, to October 2014. A back search from 1966 was performed at this update to capture studies on non-seminomatous testicular germ-cell cancers, which were added at this update. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. After deduplication and removal of conference abstracts, 76 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 47 studies and the further review of 29 full publications. Of the 29 full articles evaluated, two systematic reviews and one RCT were added at this update. Data from long-term follow-up of an already reported study were also added.

ADDITIONAL INFORMATION

The management philosophy for determining individual treatment strategy of germ cell tumours has changed from a general approach where cure was the main concern, to one where the potential toxicity of active treatment is now very much taken into account. The best example of this is in stage 1 disease, where cure is almost universal regardless of the initial management route. The toxicity of adjuvant treatment is increasingly becoming recognised to be of much importance in the clinical decision-making about individual treatment choice.

DEFINITION

Although testicular symptoms are common, testicular cancer is relatively rare. Solid swellings affecting the body of the testis have a high probability (>50%) of being due to cancer. The most common presenting symptom of cancer is a painless lump or swelling (>85%). About 10% of men present with acute pain, and 20% to 30% experience a heavy dragging feeling or general ache. These symptoms may lead the cancer to be initially wrongly diagnosed as epididymitis or acute testicular torsion. A small percentage present with symptoms of metastatic disease or infertility. Testicular germ cell tumours are divided into **seminomas**, which make up about half of all testicular tumours and which occur in older patients; and **non-seminomatous tumours**, of which there are multiple subtypes, such as choriocarcinoma, embryonal carcinoma, yolk sac tumour, teratoma, and mixed tumours among others, and which tend to occur in younger men. Several staging systems for testicular cancer have been developed. The most commonly used system is the UICC/AJCC TNM classification, which divides patients into categories of localised, regional metastatic, and distant metastatic disease. For metastatic disease, the International Germ Cell Consensus Classification divides patients with metastatic testicular tumours into good prognosis, intermediate prognosis, or poor prognosis groups and is most frequently used to prognosticate and direct treatment after orchidectomy. [1] This system is less useful in seminoma, as 90% are classified as good prognosis. The majority of men with testicular germ cell tumours (TGCT) present with disease confined to the testis and thus are stage 1.

INCIDENCE/ PREVALENCE

There are about 2200 new cases of testicular cancer (seminomas, non-seminomas) in the UK annually, with the peak incidence in men aged 30 to 34 years. [2] [3] This cancer comprises 1% of all cancers in men and is the most common tumour in young men. Incidence varies markedly with

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geography; a study among 10 cancer registries in northern Europe identified a 10-fold variation, with the highest incidence rate in Denmark (7.8 per 100,000) and lowest in Lithuania (0.9 per 100,000). [4] Reviews of the incidence of testicular cancer have reported a clear trend towards increased incidence in the majority of industrialised countries in North America, Europe, and Oceania. [5] [6]

AETIOLOGY/ RISK FACTORS

There seem to be both individual and environmental risk factors for testicular cancer. [2] Having a close relative who has had testicular cancer increases the risk of developing the disease. Inherited genetic factors may play a role in up to 1 in 5 cancers. Men are more at risk of developing testicular cancer if they have a history of developmental abnormality (e.g., maldescent or gonadal dysgenesis); previous cancer in the opposite testis; HIV infection, AIDS, or both; torsion; trauma (although this may be coincidental); and Klinefelter's syndrome. [2] The wide geographical variation and changes over time in incidence rates imply that there are likely to be important environmental factors because the individual risk factors described above do not explain global disease patterns. [4]

PROGNOSIS

Testicular tumour patients generally have an excellent prognosis, particularly those with localised disease at diagnosis, where survival exceeds 99%. Of men with testicular tumours, 75% present with stage 1 disease. Seminoma is a radio-sensitive tumour, and the standard treatment after orchidectomy for stage 1 seminoma may include adjuvant radiotherapy, adjuvant chemotherapy, or surveillance. [7] For non-seminoma, standard treatment after orchidectomy may consist of adjuvant chemotherapy, retroperitoneal lymph node dissection, or surveillance. For those with metastatic disease, the first site of spread is often via the lymphatic system, particularly the para-aortic and, less frequently, the pelvic lymph nodes for seminoma. Haematological spread leading to lung, liver, and brain metastases is less common in seminomas than in non-seminomas. For those with metastatic disease, the International Germ Cell Consensus Classification indicates that overall survival figures in the 'good prognosis' category, 'intermediate prognosis' category, and 'poor prognosis' category are expected to be in the order of 86%–92%, 72%–80%, and 48%, respectively, at 5 years.

AIMS OF INTERVENTION

To reduce morbidity, mortality, and relapse rates, while minimising adverse effects.

OUTCOMES

Mortality; **cure rates**; **relapse rates**, including relapse-free survival; **quality of life**; **adverse effects**.

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date October 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to October 2014, Embase 1980 to October 2014, The Cochrane Database of Systematic Reviews 2014, issue 10 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, with any level of blinding, no minimum size, and with any maximum loss to follow-up. There was no minimum length of follow-up. Wherever possible we have adhered to the TNM staging system and International Germ Cell Consensus Classification (IGCCC) when assessing the evidence. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributors. In consultation with the expert contributors, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section. **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported, even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributors may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previ-

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ously reported questions: What are the effects of treatments in men with good-prognosis non-stage 1 seminoma who have undergone orchidectomy? What are the effects of maintenance chemotherapy in men who are in remission after orchidectomy and chemotherapy for good-prognosis non-stage 1 seminoma? What are the effects of treatments in men with intermediate-prognosis non-stage 1 seminomas who have undergone orchidectomy? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 21). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments following orchidectomy in men diagnosed with stage 1 germ cell tumours (confined to testis)?**

OPTION ADJUVANT CHEMOTHERAPY

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- We found no RCTs comparing adjuvant chemotherapy with surveillance following orchidectomy in men diagnosed with stage 1 germ cell tumours.
- There may be no difference between adjuvant chemotherapy and adjuvant radiotherapy in relapse rates at 2 to 5 years for stage 1 seminoma, with adjuvant chemotherapy causing acute side effects that were short lived compared to adjuvant radiotherapy. We don't know if adjuvant chemotherapy increases the rate of overall survival at 5 years compared with adjuvant radiotherapy, as the trial was not powered to detect a difference in this outcome.
- Adjuvant chemotherapy seems to be more effective than adjuvant surgery at increasing the rate of relapse-free survival at 2 years after orchidectomy in men with stage 1 non-seminoma. However, we don't know about other germ cell tumours or other outcomes, including mortality and quality of life.

Benefits and harms

Adjuvant chemotherapy versus surveillance:

See option on Surveillance, p 13 .

Adjuvant chemotherapy versus adjuvant radiotherapy:

See option on Adjuvant radiotherapy, p 6 .

Adjuvant chemotherapy versus adjuvant surgery:

See option on Adjuvant surgery, p 10 .

Different drug combinations for adjuvant chemotherapy:

See option on Adjuvant chemotherapy using different drug combinations, p 18 .

Different number of cycles of adjuvant chemotherapy:

See option on Different number of cycles of adjuvant chemotherapy, p 18 .

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Comment:

Observational harms data

Sexual dysfunction

We found two systematic reviews (search dates 1999) assessing sexual dysfunction after treatment for testicular cancer. [8] [9] The first review did not report results for different treatments separately (see option on Surveillance, p 13). [8] The second review identified seven prospective and 29 retrospective observational studies (2775 men with seminoma, teratoma, or mixed tumours). [9] The prospective studies provided insufficient data to compare directly the effects on sexual function of orchidectomy plus surveillance, radiotherapy, or chemotherapy. The review found that, in men with teratoma or mixed tumours, orchidectomy plus chemotherapy was associated with loss of desire in 25% of men, reduced or absent orgasm in 28%, erectile dysfunction in 11%, and sexual dissatisfaction in 15%. Sexual dissatisfaction might not have been caused by treatment. The review found limited evidence from indirect comparisons of data from retrospective studies that orchidectomy plus chemotherapy was associated with less erectile dysfunction than orchidectomy plus radiotherapy, but was associated with more loss of desire. Rates of erectile dysfunction and loss of desire were similar between adjuvant chemotherapy and surveillance.

Development of second malignancies and other late effects associated with chemotherapy

Secondary malignancies develop more commonly in survivors of germ cell tumours than in the general population, partly as a result of radiotherapy and chemotherapy. One review identified 13 studies, including in people who were treated for (any) testicular cancer with a variety of chemotherapy regimens, including regimens containing alkylating agents. [10] The largest of these studies examined 40,576 survivors of testicular cancer with at least 1 year follow-up, some of whom had data from more than 35 years of follow-up. The review reported that, overall, the use of chemotherapy treatment alone was associated with an increased risk of second cancer (RR 1.8, 95% CI 1.3 to 2.5). However, the review found that, among the relatively small number of seminoma patients treated with chemotherapy alone (808 people), there was no significant statistical increase in risk of second cancer (RR 1.6, 95% CI <1 to 4.3). Other studies included in the review examining risk of secondary leukaemia found low incidence but excess risk (RR 3 to 7), compared to the general population, during the first 10 years after treatment. The risk, however, seemed to return to near normal after 10 to 20 years. [10] More recently, chemotherapy use has been estimated to be similar, in terms of cancer induction risk, to smoking. One study examining 12,691 survivors of non-seminoma testicular cancer estimated an increased risk of second cancer associated with the use of chemotherapy alone (SIR 1.43, 95% CI 1.18 to 1.73). [11] Other potentially harmful effects include hearing loss and reduced renal function associated with cisplatin, Raynaud's phenomenon associated with combined chemotherapy with etoposide plus cisplatin plus bleomycin, and pulmonary fibrosis associated with bleomycin. However, adjuvant chemotherapy for stage 1 seminoma is almost exclusively single-agent carboplatin, and long-term data with regard to second malignancy in this setting are not yet available. Thus it is unknown whether the same risks apply.

Relapse

A prospective single-arm phase 2 trial aimed to deliver two cycles of BEP chemotherapy in the adjuvant setting after orchidectomy to patients who were deemed to be at high risk of relapse. Out of a total of 104 patients with germ cell tumours confirmed by reference pathology review, only one patient developed relapse. These high-risk patients were considered to have a 50% risk of relapse, and, although treatment-related toxicity was low, half of these men would have received unnecessary treatment. [12]

Clinical guide

Orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant radiotherapy all produce equally high cure rates in men with stage 1 seminoma. Similarly, orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant surgery produce equally high cure rates in stage 1 non-seminoma. This is because salvage therapy at time of relapse is highly effective and curative. The choice of treatment is determined by factors such as the pattern of toxicity, the inconvenience and complexity of treatment, and patient preference, particularly the person's attitude to relapse. With surveillance, most people can avoid the toxicity of adjuvant treatment, but they must face the uncertainty of relapse as well as regular hospital follow-up. Adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant surgery can substantially reduce the risk of relapse, but are associated with some short-term and long-term toxicity. Radiotherapy and chemotherapy may also be associated with a low but definite long-term risk of second malignancy and reduced fertility. The long-term risks associated with adjuvant chemotherapy are as yet not fully quantified. For seminoma,

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the pattern of relapse also differs after adjuvant radiotherapy or chemotherapy. After radiotherapy, relapse in the pelvic nodes (in those treated with para-aortic radiotherapy), mediastinum, or supra-clavicular area is most common. After chemotherapy, relapse is most common in the para-aortic nodes. For non-seminoma, the pattern of relapse may differ between adjuvant chemotherapy and adjuvant surgery, but there have been relatively few reports of patients overall treated in this manner. Relapse patterns do appear to mirror those in seminoma in that retroperitoneal nodal relapse and distant metastatic relapse may occur with higher rates of haematogenous metastases. However, relapse detected by serum tumour markers is much more common, and occasionally tumour markers may be detected without gross disease relapse; this is treated the same way, often with salvage chemotherapy.

For stage 1 non-seminoma, the use of adjuvant (BEP) chemotherapy even in high-risk disease (i.e., with pathological features in the primary tumour that may increase risk of relapse after orchidectomy alone) remains controversial. Use of BEP chemotherapy in low-risk disease is generally felt to be of minimal benefit, and surveillance is the most often used strategy in this setting.

OPTION ADJUVANT RADIOTHERAPY

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- There may be no difference between adjuvant radiotherapy and adjuvant chemotherapy in relapse rates at 2 to 5 years for stage 1 seminoma. We don't know if adjuvant radiotherapy increases the rate of overall survival at 5 years compared with adjuvant chemotherapy, as the trial was not powered to detect a difference in this outcome.
- We don't know how adjuvant radiotherapy compares with surveillance or adjuvant surgery. However, clinical consensus is that there is less toxicity associated with surveillance compared with adjuvant radiotherapy, but a higher relapse rate.

Benefits and harms

Adjuvant radiotherapy versus surveillance:

See option on Surveillance, p 13 .

Adjuvant radiotherapy versus adjuvant surgery:

See option on Adjuvant surgery, p 10 .

Adjuvant radiotherapy versus adjuvant chemotherapy:

We found one RCT [13] and one follow-up study. [14]

Mortality

Adjuvant radiotherapy compared with adjuvant chemotherapy We don't know if adjuvant radiotherapy compared with adjuvant chemotherapy increases the rate of overall survival at 5 years in men who have undergone orchidectomy for stage 1 seminoma, as we found insufficient evidence from one RCT with a small number of events; mortality rates were similar but the trial was not powered to detect a difference in this outcome (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[14] RCT	1477 men with stage 1 seminoma, 5:3 randomisation Further report of reference [13]	**Mortality , 5 years** 10/904 (1%) with adjuvant radiotherapy 6/573 (1%) with adjuvant chemotherapy using carboplatin Irradiation involved 20 Gy in 10 fractions or 30 Gy in 15 fractions; 13% of men had irradiation of the ipsilateral iliac and inguinal lymph nodes (dogleg field) and 87% had irradiation to the para-aortic strip	Significance not assessed		

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No data from the following reference on this outcome. [13]

Cure rates

No data from the following reference on this outcome. [13] [14]

Relapse rates

Adjuvant radiotherapy compared with adjuvant chemotherapy Adjuvant radiotherapy does not seem to increase the rate of relapse-free survival at 2 to 5 years in men with stage 1 seminoma, compared with adjuvant chemotherapy (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Relapse-free survival , 2 years** 97% with adjuvant radiotherapy 98% with adjuvant chemotherapy using carboplatin Absolute results reported graphically Irradiation involved 20 Gy in 10 fractions or 30 Gy in 15 fractions; 13% of men had irradiation of the ipsilateral iliac and inguinal lymph nodes (dogleg field) and 87% had irradiation to the para-aortic strip	P = 0.32 HR 1.28 90% CI 0.85 to 1.93 The 90% CI excludes an increase in relapse rates in men taking carboplatin of >3% at 2 years	⟷	Not significant
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Relapse-free survival , 3 years** 96% with adjuvant radiotherapy 95% with adjuvant chemotherapy using carboplatin Absolute results reported graphically Irradiation involved 20 Gy in 10 fractions or 30 Gy in 15 fractions; 13% of men had irradiation of the ipsilateral iliac and inguinal lymph nodes (dogleg field) and 87% had irradiation to the para-aortic strip	P = 0.32 HR 1.28 90% CI 0.85 to 1.93 The 90% CI excludes an increase in relapse rates in men taking carboplatin of >4% at 3 years	⟷	Not significant
[14] RCT	1477 men with stage 1 seminoma, 5:3 randomisation Further report of reference [13]	**Relapse-free survival , 5 years** 867/904 (96%) with adjuvant radiotherapy 544/573 (95%) with adjuvant chemotherapy using carboplatin Irradiation involved 20 Gy in 10 fractions or 30 Gy in 15 fractions; 13% of men had irradiation of the ipsilateral iliac and inguinal lymph nodes (dogleg field) and 87% had irradiation to the para-aortic strip	P = 0.37 HR 1.25 90% CI 0.83 to 1.89 The 90% CI excludes rates above 3% at 2 years and above 3.5% at 5 years	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [13] [14]

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Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Proportion of men unable to do normal work , 25 days** 38% with adjuvant radiotherapy 19% with adjuvant chemotherapy using carboplatin Absolute results reported graphically	P <0.0001	○○○	adjuvant chemotherapy
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Proportion of men with moderate or severe lethargy , 25 days** 24% with adjuvant radiotherapy 7% with adjuvant chemotherapy using carboplatin Absolute results reported graphically	P <0.0001	○○○	adjuvant chemotherapy
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**New second primary germ cell tumours , 5 years** 10/904 (1.1%) with adjuvant radiotherapy 2/573 (0.4%) with adjuvant chemotherapy using carboplatin 5-year event rate: 1.96% with adjuvant radiotherapy *v* 0.54% with adjuvant chemotherapy	P = 0.04	○○○	adjuvant chemotherapy
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Proportion of men with thrombocytopenia grades 1 or 2** 12/904 (2%) with adjuvant radiotherapy 58/573 (12%) with adjuvant chemotherapy using carboplatin No bleeding was reported	P <0.0001	○○○	adjuvant radiotherapy
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Thrombocytopenia grades 3 or 4** 0/904 (0%) with adjuvant radiotherapy 17/573 (4%) with adjuvant chemotherapy using carboplatin No bleeding was reported	P <0.0001	○○○	adjuvant radiotherapy
[13] RCT	1477 men with stage 1 seminoma, 5:3 randomisation	**Dyspepsia** 127/904 (17%) with adjuvant radiotherapy 40/573 (8%) with adjuvant chemotherapy using carboplatin	P <0.0001	○○○	adjuvant chemotherapy

Different adjuvant radiotherapy regimens versus each other:

See option on Different adjuvant radiotherapy regimens, p 15 .

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Comment:

Observational harms data

Sexual dysfunction

We found two systematic reviews (search dates 1999) assessing sexual dysfunction after treatment for testicular cancer. [8] [9] The first review did not report results for different treatments separately (see option on Surveillance, p 13). [8] The second review identified 7 prospective and 29 retrospective observational studies (2775 men with seminoma, teratoma, or mixed tumours) assessing sexual dysfunction after surveillance, radiotherapy, or chemotherapy. [9] The prospective studies provided insufficient data to compare directly the effects of orchidectomy plus surveillance, adjuvant radiotherapy, or adjuvant chemotherapy on sexual function. The review pooled data on sexual dysfunction after radiotherapy from nine studies (417 men), chemotherapy from six studies (160 men), and chemotherapy plus surgery from nine studies (404 men). It found a loss of desire in 14% of men with radiotherapy, 25% with chemotherapy, and 13% with chemotherapy plus surgery; reduced or absent orgasm in 23% of men with radiotherapy, 28% with chemotherapy, and 22% with chemotherapy plus surgery; ejaculatory problems in 40% of men with radiotherapy, 28% with chemotherapy, and 62% with chemotherapy plus surgery; and sexual dissatisfaction in 16% of men with radiotherapy, 15% with chemotherapy, and 20% with chemotherapy plus surgery. The review found limited evidence from indirect comparisons of data from retrospective studies that orchidectomy plus radiotherapy was associated with more erectile dysfunction but less loss of desire than orchidectomy plus surveillance.

Development of secondary malignancies associated with radiotherapy

Second malignancies develop more commonly in survivors of germ cell tumours than in the general population, partly as a result of radiotherapy and chemotherapy. One systematic review identified 12 studies, each including 400 people or more, who were treated for (any) testicular cancer with radiotherapy, chemotherapy, or both. [15] There was overlap between some of these studies; however, the largest of these examined 40,576 1-year survivors of testicular cancer treated between 1943 and 2001, some of whom had data from more than 35 years of follow-up. The use of radiotherapy treatment alone was associated with increased risk of second solid cancer (RR 2.0, 95% CI 1.9 to 2.2), and these risks remained elevated even up to 35 years after treatment. The risks seemed to be slightly higher for men treated from 1975 onwards (RR 2.5) than for those treated before 1975 (RR 1.7), but it is unclear as to the cause of this finding. Cancers of the pleura, oesophagus, lung, colon, bladder, pancreas, and stomach accounted for about 60% of sites involved. A similar study included in the review (28,843 men treated between 1935 and 1993) examining risk of secondary leukaemia found low incidence but excess risk (RR 3.28, 95% CI 1.69 to 5.72 before 1975 and RR 2.53, 95% CI 0.93 to 5.52 from 1975 onwards) compared to the general population. [15]

Clinical guide

Orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant radiotherapy all produce equally high cure rates in men with stage 1 seminoma. Similarly, orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant surgery produce equally high cure rates in stage 1 non-seminoma. This is because salvage therapy at time of relapse is highly effective and curative. The choice of treatment is determined by factors such as the pattern of toxicity, the inconvenience and complexity of treatment, and patient preference, particularly the individual's attitude to relapse. With surveillance, most people can avoid the toxicity of adjuvant treatment, but they must face the uncertainty of relapse as well as regular hospital follow-up. Adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant surgery can substantially reduce the risk of relapse, but are associated with some short-term and long-term toxicity. Radiotherapy and chemotherapy may also be associated with a low but definite long-term risk of second malignancy and reduced fertility. For seminoma, the pattern of relapse also differs after adjuvant radiotherapy or chemotherapy. After radiotherapy, relapse in the pelvic nodes (in those treated with para-aortic radiotherapy), mediastinum, or supraclavicular area is most common. After chemotherapy, relapse is most common in the para-aortic nodes. For non-seminoma, the pattern of relapse may differ between adjuvant chemotherapy and adjuvant surgery, but there have been relatively few patients overall treated in this manner. Relapse patterns do appear to mirror those in seminoma in that retroperitoneal nodal relapse and distant metastatic relapse may occur. However, relapse detected by serum tumour markers is much more common, and occasionally tumour markers may be detected without gross disease relapse; this is treated in the same way, often with salvage chemotherapy. Adjuvant radiotherapy in non-seminoma has been abandoned as a management strategy in favour of surveillance or adjuvant chemotherapy and is not recommended.

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OPTION ADJUVANT SURGERY New

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- Adjuvant surgery seems to be less effective than adjuvant chemotherapy at increasing the rate of relapse-free survival at 2 years after orchidectomy in men with stage 1 non-seminoma. However, we don't know about other germ cell tumours or other outcomes including mortality and quality of life.
- We don't know how adjuvant surgery compares to surveillance as we found no RCTs.

Benefits and harms

Adjuvant surgery versus adjuvant chemotherapy:

We found one systematic review (search date 2007) evaluating the effects of treatments for stage 1 non-seminomatous testicular cancer. [16] The review identified one RCT comparing adjuvant retroperitoneal lymph node dissection with adjuvant chemotherapy. The review identified two publications presenting results from the RCT, both of which were conference abstracts. Results from the RCT have subsequently been published in full, and we report them directly here. [17]

Mortality

Adjuvant surgery compared with adjuvant chemotherapy We don't know how adjuvant surgery and adjuvant chemotherapy compare at reducing mortality in men who have undergone orchidectomy for stage 1 non-seminoma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality: cancer-related					
[17] RCT	382 men with histologically confirmed stage 1 non-seminomatous germ cell tumours of the testis who had undergone orchidectomy In review [16]	**Cancer-related deaths , follow-up unclear** 0/191 (0%) with adjuvant retroperitoneal lymph node dissection 0/191 (0%) with adjuvant chemotherapy See Further information on studies for description of chemotherapy regimen Treatment in both groups had to start <4 weeks after orchidectomy and directly after random assignment	Significance not assessed		

Cure rates

No data from the following reference on this outcome. [17]

Relapse rates

Adjuvant surgery compared with adjuvant chemotherapy Adjuvant surgery seems to be less effective than adjuvant chemotherapy at increasing the rate of relapse-free survival at 2 years in men who have undergone orchidectomy for stage 1 non-seminoma; however, the evidence is limited to one RCT (moderate-quality evidence).

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rate					
[17] RCT	382 men with histologically confirmed stage 1 non-seminomatous germ cell tumours of the testis who had undergone orchidectomy In review [16]	**Proportion of men who were relapse free , 2 years** 176/191 (92%) with adjuvant retroperitoneal lymph node dissection 189/191 (99%) with adjuvant chemotherapy See Further information on studies for description of chemotherapy regimen Treatment in both groups had to start <4 weeks after orchidectomy and directly after random assignment	HR 7.94 95% CI 1.81 to 34.48	○○○	adjuvant chemotherapy

Quality of life

No data from the following reference on this outcome. [17]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	382 men with histologically confirmed stage 1 non-seminomatous germ cell tumours of the testis who had undergone orchidectomy In review [16]	**Life-threatening or disabling adverse effects , 2 years** 4/173 (2%) with adjuvant retroperitoneal lymph node dissection 4/174 (2%) with adjuvant chemotherapy 2% of men who received 1 course of chemotherapy or surgery followed by additional adjuvant chemotherapy had life-threatening toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events grade 4) See Further information on studies for description of chemotherapy regimen			
[17] RCT	382 men with histologically confirmed stage 1 non-seminomatous germ cell tumours of the testis who had undergone orchidectomy In review [16]	**Severe adverse effects , 2 years** 15/173 (8.7%) with adjuvant retroperitoneal lymph node dissection 65/174 (37.4%) with adjuvant chemotherapy Most of these events in the surgical arm were haematological and non-haematological toxicities due to the additional 2 courses of adjuvant chemotherapy in cases of pathological stage 2			

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Most events in the chemotherapy arm were a short-lasting episode of leukopenia (37 of 65 events) without clinical complications Neutropenic fever occurred in only 4 patients See Further information on studies for description of chemotherapy regimen			

Adjuvant surgery versus radiotherapy:

We found no systematic review or RCTs.

Adjuvant surgery versus surveillance/watchful waiting:

We found no systematic review or RCTs.

Further information on studies

[17] The study was open label in design. Method of randomisation was robust. Chemotherapy involved one cycle of a combination of cisplatin (20 mg/m^2, days 1 to 5, 60-minute infusion), etoposide (100 mg/m^2, days 1 to 5, 60-minute infusion), and bleomycin 30,000 IU (30 mg, days 1, 8, and 15, bolus infusion). Two cycles of chemotherapy were administered if the man had metastasis in the retroperitoneal regions. Recurrence was defined as one or more of: serum tumour marker elevation after exclusion of false-positive values; progressive lesion with serum tumour marker elevation; or progressive lesion without serum tumour marker elevation, but histological confirmation.

Comment:

Clinical guide

Orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant radiotherapy all produce equally high cure rates in men with stage 1 seminoma. Similarly, orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant surgery produce equally high cure rates in stage 1 non-seminoma. This is because salvage therapy at time of relapse is highly effective and curative. The choice of treatment is determined by factors such as the pattern of toxicity, the inconvenience and complexity of treatment, and patient preference, particularly the individual's attitude to relapse. With surveillance, most people can avoid the toxicity of adjuvant treatment, but they must face the uncertainty of relapse as well as regular hospital follow-up. Adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant surgery can substantially reduce the risk of relapse, but are associated with some short-term and long-term toxicity. Radiotherapy and chemotherapy may also be associated with a low but definite long-term risk of second malignancy and reduced fertility. For seminoma, the pattern of relapse also differs after adjuvant radiotherapy or chemotherapy. After radiotherapy, relapse in the pelvic nodes (in those treated with para-aortic radiotherapy), mediastinum, or supraclavicular area is most common. After chemotherapy, relapse is most common in the para-aortic nodes. For non-seminoma, the pattern of relapse may differ between adjuvant chemotherapy and adjuvant surgery, but there have been relatively few patients overall treated in this manner. Relapse patterns do appear to mirror those in seminoma in that retroperitoneal nodal relapse and distant metastatic relapse may occur. However, relapse detected by serum tumour markers is much more common, and occasionally tumour markers may be detected without gross disease relapse; this is treated in the same way, often with salvage chemotherapy.

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OPTION SURVEILLANCE

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- We don't know how surveillance compares with adjuvant chemotherapy, radiotherapy, or surgery following orchidectomy as we found limited RCT evidence.

Benefits and harms

Surveillance versus adjuvant radiotherapy:

We found two systematic reviews (search dates 2002; [7] and 2007 [16]) that reported on the effects of treatments for testicular germ-cell cancer. The review with the later search date identified the first review, [7] but did not discuss the data presented in the review as the studies identified did not meet the reporting criteria of the review. [16] The second review identified no RCTs meeting *BMJ Clinical Evidence* reporting criteria. [16] The review with the earlier search date identified one RCT comparing surveillance with adjuvant radiotherapy in men who have undergone orchidectomy for stage 1 non-seminomatous testicular germ-cell cancer. [18] An RCT assessing survival is unlikely to be conducted; it would be difficult to detect differences in mortality between groups because of the excellent prognosis and small differences in long-term outcomes.

Mortality

No data from the following reference on this outcome. [18]

Cure rates

No data from the following reference on this outcome. [18]

Relapse rates

Surveillance compared with adjuvant radiotherapy We don't know how surveillance and adjuvant radiotherapy compare at improving relapse rates at 5 years in men who have undergone orchidectomy for stage 1 non-seminoma (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[18] RCT	156 men with stage 1 non-seminomatous testicular cancer who underwent orchidectomy within the study	**Proportion of relapse-free men , median follow-up of 64 months** 62/73 (85%) with adjuvant radiotherapy (40 Gy in 25 fractions, 5 fractions per week) 54/77 (70%) with surveillance	Significance not assessed		

Quality of life

No data from the following reference on this outcome. [18]

Adverse effects

No data from the following reference on this outcome. [18]

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Surveillance versus adjuvant chemotherapy:

We found no RCTs comparing surveillance versus adjuvant chemotherapy in men who have undergone orchidectomy for stage 1 germ cell cancer. An RCT assessing survival is unlikely to be conducted; it would be difficult to detect differences in mortality between groups because of the excellent prognosis and small differences in long-term outcomes.

Surveillance versus adjuvant surgery:

We found no systematic review or RCTs.

Comment:

Observational harms data: sexual dysfunction

We found two systematic reviews (search dates 1999) that assessed sexual dysfunction after treatment for testicular cancer. [8] [9] The first review (79 observational studies: 66 retrospective studies, six controlled studies in 709 men, and seven uncontrolled studies in 337 men, all with seminoma, teratoma, or mixed tumours) found that men undergoing any treatment (orchidectomy plus surveillance, radiotherapy, or chemotherapy) for testicular cancer had significantly reduced or absent orgasm (13 controlled and uncontrolled studies: OR 4.62, 95% CI 2.47 to 8.63) and erectile dysfunction (OR 2.47, 95% CI 1.54 to 3.96) at up to 2 years after treatment. However, the review did not report results for individual treatments, so it does not help in determining which treatment is least likely to cause sexual dysfunction. The second review identified seven prospective and 29 retrospective observational studies (2775 men with seminoma, teratoma, or mixed tumours) assessing sexual dysfunction after surveillance, radiotherapy, or chemotherapy. [9] The prospective studies provided insufficient data to compare directly the effects of orchidectomy plus surveillance, radiotherapy, or chemotherapy on sexual function. The review found that orchidectomy plus surveillance was associated with loss of desire in 25% of people, reduced or absent orgasm in 24%, erectile dysfunction in 7%, and sexual dissatisfaction in 8%. Sexual dissatisfaction may not be caused by treatment. The review found limited evidence from indirect comparisons of data from retrospective studies that orchidectomy plus surveillance was associated with less erectile dysfunction but more loss of desire than orchidectomy plus radiotherapy. Rates of erectile dysfunction and loss of desire were similar with surveillance and adjuvant chemotherapy.

Clinical guide

Orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant radiotherapy all produce equally high cure rates in men with stage 1 seminoma. Similarly, orchidectomy plus surveillance, adjuvant chemotherapy, or adjuvant surgery produce equally high cure rates in stage 1 non-seminoma. This is because salvage therapy at time of relapse is highly effective and curative. The choice of treatment is determined by factors such as the pattern of toxicity, the inconvenience and complexity of treatment, and patient preference, particularly the person's attitude to relapse. With surveillance, most people can avoid the toxicity of adjuvant treatment, but they must face the uncertainty of relapse as well as regular hospital follow-up. Adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant surgery can substantially reduce the risk of relapse, but are associated with some short-term and long-term toxicity. Radiotherapy and chemotherapy may also be associated with a low but definite long-term risk of second malignancy and reduced fertility. For seminoma, the pattern of relapse also differs after adjuvant radiotherapy or chemotherapy. After radiotherapy, relapse in the pelvic nodes (in those treated with para-aortic radiotherapy), mediastinum, or supraclavicular area is most common. After chemotherapy, relapse is most common in the para-aortic nodes. For non-seminoma, the pattern of relapse may differ between adjuvant chemotherapy and adjuvant surgery, but there have been relatively few patients overall treated in this manner. Relapse patterns do appear to mirror those in seminoma in that retroperitoneal nodal relapse and distant metastatic relapse may occur. However, relapse detected by serum tumour markers is much more common, and occasionally tumour markers may be detected without gross disease relapse; this is treated in the same way, often with salvage chemotherapy. Adjuvant radiotherapy in non-seminoma has been abandoned as a management strategy in favour of surveillance or adjuvant chemotherapy and is not recommended.

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OPTION DIFFERENT ADJUVANT RADIOTHERAPY REGIMENS

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- Toxicity is lower, but efficacy the same, with adjuvant irradiation of 20 Gy in 10 fractions compared with 30 Gy in 15 fractions, or with restricted irradiation (to para-aortic nodes only) compared with irradiation to both para-aortic and ipsilateral iliac nodes, in men who have undergone orchidectomy for stage 1 seminoma.

Benefits and harms

Para-aortic strip adjuvant radiotherapy versus para-aortic plus ipsilateral adjuvant radiotherapy:

We found one systematic review (search date 2009), [15] which identified one RCT comparing para-aortic strip adjuvant radiotherapy with para-aortic plus ipsilateral adjuvant radiotherapy. [19]

Mortality

No data from the following reference on this outcome. [19]

Cure rates

No data from the following reference on this outcome. [19]

Relapse rates

Para-aortic strip compared with para-aortic plus ipsilateral iliac lymph node irradiation Para-aortic strip (restricted) irradiation is as effective as para-aortic plus ipsilateral iliac lymph node irradiation at 3 years in men who have undergone orchidectomy for stage 1 seminoma (high-quality evidence). Note: toxicity increases with increases in irradiation field.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[19] RCT	478 men In review [15]	**Rates of relapse-free survival , 3 years** 227/236 (96%) with para-aortic strip (restricted field) irradiation (30 Gy in 15 fractions for 3 weeks) 233/242 (97%) with para-aortic strip plus ipsilateral iliac lymph node (traditional field) irradiation (30 Gy in 15 fractions for 3 weeks)	Mean difference +0.6% 95% CI –3.4 to +4.6 P value not reported	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [19]

Adverse effects

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT	478 men In review [15]	**Adverse effects** with para-aortic strip (restricted field) irradiation (30 Gy in 15 fractions for 3 weeks) with para-aortic strip plus ipsilateral iliac lymph node (traditional field) irradiation (30 Gy in 15 fractions for 3 weeks) Men receiving para-aortic irradiation had less severe and less frequent acute toxicities such as nausea, vomiting, and leukopenia than did men receiving para-aortic plus ipsilateral iliac lymph node irradiation, and had higher sperm counts at 18 months (no further data reported)			
[19] RCT	478 men In review [15]	**Secondary malignancies (adenocarcinoma or non-seminomatous testicular tumours)** 2/478 (0.4%) with para-aortic strip (restricted field) irradiation (30 Gy in 15 fractions for 3 weeks) 1/478 (0.2%) with para-aortic strip plus ipsilateral iliac lymph node (traditional field) irradiation (30 Gy in 15 fractions for 3 weeks)			

20 Gy adjuvant radiotherapy versus 30 Gy adjuvant radiotherapy:

We found one systematic review (search date 2009), [15] which identified one RCT comparing 20 Gy adjuvant radiotherapy with 30 Gy adjuvant radiotherapy. [20]

Mortality

No data from the following reference on this outcome. [20]

Cure rates

No data from the following reference on this outcome. [20]

Relapse rates

20 Gy compared with 30 Gy irradiation 20 Gy irradiation in 10 fractions is as effective as 30 Gy irradiation at reducing relapse rates at 61 months in men who have undergone orchidectomy for stage 1 seminoma (high-quality evidence). Note: toxicity increases as dose increases.

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Relapse rates					
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Relapse rates , median of 61 months** 11/312 (4%) with irradiation to the para-aortic strip of 20 Gy in 10 fractions over 2 weeks 10/313 (3%) with irradiation to the para-aortic strip of 30 Gy in 15 fractions over 3 weeks One man in the 20 Gy group had died at 61 months	HR 1.11 90% CI 0.54 to 2.28	⟷	Not significant

Quality of life

No data from the following reference on this outcome. [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Moderate or severe lethargy , 4 weeks** 5% with 20 Gy in 10 fractions over 2 weeks 20% with 30 Gy in 15 fractions over 3 weeks Absolute numbers not reported	P <0.01 CI values not reported	○○○	20 Gy in 10 fractions over 2 weeks
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Moderate or severe lethargy , 12 weeks** with 20 Gy in 10 fractions over 2 weeks with 30 Gy in 15 fractions over 3 weeks Absolute results not reported	Reported as not significant CI values not reported	⟷	Not significant
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Inability to return to work , 4 weeks** 28% with 20 Gy in 10 fractions over 2 weeks 46% with 30 Gy in 15 fractions over 3 weeks Absolute numbers not reported	P <0.01 CI values not reported	○○○	20 Gy in 10 fractions over 2 weeks
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Inability to return to work , 12 weeks** with 20 Gy in 10 fractions over 2 weeks with 30 Gy in 15 fractions over 3 weeks Absolute results not reported	Reported as not significant CI values not reported	⟷	Not significant

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Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**WHO grade 3 to 4 nausea and vomiting** 57/313 (18%) with 20 Gy in 10 fractions over 2 weeks 61/312 (20%) with 30 Gy in 15 fractions over 3 weeks	P = 0.06	⟷	Not significant
[20] RCT	625 men with stage 1 seminoma who had received orchidectomy in the previous 8 weeks In review [15]	**Development of non-germ cell tumours , 61 months** with 20 Gy in 10 fractions over 2 weeks with 30 Gy in 15 fractions over 3 weeks Absolute results not reported	The RCT found that 6 men, all in the 30-Gy irradiation group (6/313 [2%]), developed non-germ cell tumours over 61 months; of these, 3 may have been associated near or within the radiotherapy fields		

Comment: **Clinical guide**
Adjuvant radiotherapy continues to be a treatment option used for stage 1 seminoma. Equally good results can be achieved using lower doses of radiation to smaller treatment volumes, thus leading to less toxicity and quicker recovery. It should be noted that while radiotherapy to a para-aortic strip results in similar overall relapse rates to that with para-aortic and ipsilateral iliac field, there may be a change in the relapse pattern such that there is an increased number of iliac node relapses in those treated with para-aortic strip.

OPTION DIFFERENT ADJUVANT CHEMOTHERAPY DRUG COMBINATIONS

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- We don't know which is the most effective chemotherapy regimen, nor the optimal number of cycles, in stage 1 seminoma. The high cure rate with standard therapy makes it difficult to show that any alternative therapy is superior.

Benefits and harms

Different adjuvant chemotherapy drug combinations versus each other:
We found one systematic review (search date 2009), which identified no RCTs of sufficient quality. [15]

Comment: **Clinical guide**
Given the modest toxicity and high efficacy of adjuvant radiotherapy, any adjuvant chemotherapy would also need to be simple and relatively non-toxic as well as being effective. Single-agent carboplatin fits these criteria. However, other more complex or toxic regimens would not, so there is no reason for RCTs assessing such regimens to be conducted.

OPTION DIFFERENT NUMBER OF CYCLES OF ADJUVANT CHEMOTHERAPY

- For GRADE evaluation of interventions for Testicular cancer: germ cell tumours, see table, p 21 .
- We don't know the optimum number of cycles of adjuvant chemotherapy to use. The high cure rate with standard therapy makes it difficult to show that any alternative therapy is superior.

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Benefits and harms

Different numbers of cycles of adjuvant chemotherapy versus each other:

We found one systematic review (search date 2009), which identified no RCTs comparing different chemotherapy regimens in men who had undergone orchidectomy for stage 1 seminoma. [15]

Comment: **Clinical guide**
In stage 1 seminoma, it is unclear whether the relapse rate is lower after two cycles of carboplatin, especially with the difference in calculation of the dose both between and within studies. Given that two cycles of chemotherapy are likely to produce more toxicity than one cycle, most oncologists would recommend a single cycle of adjuvant carboplatin.

GLOSSARY

Adjuvant treatment Anticancer treatment given after surgical removal of the primary tumour and in the absence of any detectable residual tumour in order to prevent or reduce the risk of subsequent relapse.

Gonadal dysgenesis A condition in which primordial germ cells reach the testes but are progressively destroyed so that few remain by the time of puberty. It is clinically characterised by small testicular size, poor testicular function, and infertility.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Orchidectomy Total surgical removal of the affected testicle; also known as orchiectomy. When it is done for suspected malignancy, orchidectomy is often done via the trans-inguinal route in order to minimise the risk of tumour spillage and consequent local recurrence.

Surveillance A policy of systematic clinical, biochemical, and radiological follow-up undertaken with the aim of detecting relapse at an early stage so that effective therapy can be given promptly. Current guidelines (European Society for Medical Oncology) [21] [22] recommend follow-up for 5 years after initial treatment. However, relapse can occur after this, and others recommend follow-up for 10 years. [23]

SUBSTANTIVE CHANGES

Adjuvant surgery New option. One systematic review added, [16] which identified one RCT, the results of which were published subsequent to the search date of the review and we have reported results from the full publication. [17] Categorised as 'trade-off between benefits and harms'.

Surveillance Two systematic reviews added. [7] [16] Evidence re-evaluated. Categorisation unchanged (trade-off between benefits and harms).

Adjuvant chemotherapy Evidence re-evaluated. Categorisation unchanged (trade-off between benefits and harms).

Adjuvant radiotherapy Follow-up to previously included RCT added. [14] Evidence re-evaluated. Categorisation unchanged (trade-off between benefits and harms).

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GRADE **Evaluation of interventions for Testicular cancer: germ cell tumours.**

Important outcomes			Cure rates, Mortality, Quality of life, Relapse rates						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments following orchidectomy in men diagnosed with stage 1 germ cell tumours (confined to testis)?									
1 (1477) [14]	Mortality	Adjuvant radiotherapy versus adjuvant chemotherapy	4	–2	0	0	0	Low	Quality points deducted for methodological flaws (lack of statistical assessment and lack of power)
1 (1477) [13] [14]	Relapse rates	Adjuvant radiotherapy versus adjuvant chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for methodological flaws (exclusion of some men from analysis)
1 (382) [17]	Mortality	Adjuvant surgery versus adjuvant chemotherapy	4	–1	0	–1	0	Low	Quality point deducted for open-label design of study; directness point deducted for low event rate, which leads to uncertainty as to whether there is a true difference in effect between treatments
1 (382) [17]	Relapse rates	Adjuvant surgery versus adjuvant chemotherapy	4	–1	0	0	0	Moderate	Quality point deducted for open-label design of study
1 (156) [18]	Relapse rates	Surveillance versus adjuvant radiotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and lack of statistical analysis of between-group difference
1 (478) [19]	Relapse rates	Para-aortic strip adjuvant radiotherapy versus para-aortic plus ipsilateral adjuvant radiotherapy	4	0	0	0	0	High	
1 (625) [20]	Relapse rates	20 Gy adjuvant radiotherapy versus 30 Gy adjuvant radiotherapy	4	0	0	0	0	High	

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.

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