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REVIEW ARTICLE

Exploring the spectrum of late effects following radical orchidectomy for stage I testicular seminoma: a systematic review of the literature

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Abstract

Purpose Testicular seminomas occur in young men and are highly curable. Toxicities following treatment for men with extensive stage II-III seminomas may cause long-term morbidities. However, it is not clear whether the risk of late effects also increases following surgery for testis-confined seminoma. In this systematic review, we examined the available literature regarding the incidence of late effects in our target population of patients with stage I seminoma treated with orchidectomy alone.

Method Publications were identified through an electronic literature search using the MEDLINE, EMBASE and PsychInfo databases, identifying cohorts treated for stage I seminoma. Data on late effects were collected and classified as physical or psychological.

Results Six hundred and four articles were screened to identify 100 studies. In the target population, available evidence suggests no increased risk of cardiovascular disease, metabolic syndrome, or renal dysfunction compared to the general population. Sperm counts were initially lower than an age-matched cohort; however, counts normalised when re-assessed 5 years later. Data were not specifically reported for the target population regarding bone health, second malignancy, hypogonadism, fertility and all psychological domains. Heterogeneity of study design and reporting methods contributed to uncertainty regarding the true incidence and clinical significance of late effects.

Conclusions The curability of stage I seminoma and the wide range of potential late effects of treatment suggest the need for long-term monitoring alongside standard cancer surveillance. Important data are needed on the prevalence of late effects, specifically related to testicular cancer survivors undergoing surveillance following orchidectomy.

Implications for cancer survivors Awareness and screening for relevant late effects may prevent further morbidity in men treated for stage I seminoma.

Keywords Systematic review · Seminoma · Testicular cancer · Late effects · Survivorship · Germ cell tumour

Introduction

Although testicular cancer only accounts for 1.1% of all male cancers, it is the most common non-haematological malignancy affecting men in their second to fourth decades of life [1]. The incidence of testicular cancer is rising: from 1982 to 2007, the number of new cases in Australia rose from 4.2 to 6.8 per 100,000 [1]. Survival rates have also improved, with 5-year survival rates rising from 91 to 98%. This change has been attributed to earlier diagnosis, standardisation of platinum-based chemotherapy and improved supportive care [2–4].

The majority of testicular cancers can be classified by histology into either seminomas or a second category of mixed and non-seminoma germ cell histologies. Seminoma

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accounts for approximately 70% of diagnoses [5] and has a 5-year survival of 99%, which is higher than any other germ cell subtypes [6]. In the treatment of advanced testicular cancer, the current standard of care includes the use of platinum-based chemotherapy. The possible long-term complications of these agents are well documented and include peripheral neuropathy, nephrotoxicity, ototoxicity, and second malignancy [7–9]. The addition of bleomycin as described by Peckham et al. in 1983 [10] further improved the outcomes for advanced testicular cancer, albeit with an increased risk of bleomycin-induced pneumonitis, pulmonary fibrosis, and skin toxicity.

A diagnosis of stage I seminoma is made in patients with histological evidence of pure seminoma, normal alpha-fetoprotein, and no radiological evidence of lymph node involvement or distant metastases. It usually affects young men at their peak of their reproductive and working lives, who have an additional life expectancy of 40 to 50 years [11].

There is increasing evidence to suggest that active surveillance post-orchidectomy is a suitable alternative to adjuvant regimens involving chemotherapy or radiotherapy in stage I seminoma [12, 13]. Given the high cure rates and long life expectancy, there has been an increasing push to identify potential late effects or complications of the disease and its treatment in order to improve current survivorship programs [14]. The current body of evidence looking at late effects in this population consists mainly of retrospective data. Furthermore, these studies mostly include patients who have had some form of adjuvant treatment. There is, therefore, a paucity of evidence examining the late effects and survivorship challenges in men who are treated with orchidectomy alone. The aim of this paper was to perform a systematic review of the literature, adhering to the PRISMA guidelines [15], that explored the breadth and prevalence of late effects in men with stage I seminoma, treated with orchidectomy followed by surveillance.

Method

Search strategy

The MEDLINE, EMBASE and PyschInfo electronic databases were examined for relevant papers. Studies published between 1971 and 2015 were included. The search terms were "testicular cancer", "seminoma", "non-seminoma", "late effects", "long-term effects", "second malignancies", "cardiotoxicity", "pulmonary toxicity", "nephrotoxicity", "fatigue", "infertility", "erectile dysfunction", "testosterone deficiency" and "anxiety". Our search was confined to papers published in English.

Study selection

One author (RL) screened titles and abstracts of all records for relevance. Two authors (JT, CP) then independently assessed the full texts for inclusion in the systematic review. Abstracts were included if sufficient information on study design, patient demographics and outcomes were available. Any study that included patients with stage I seminoma undergoing surveillance following orchidectomy and reported potential late effects, defined as a psychological and/or physical condition occurring after the acute treatment period, was included in the review.

Data collection and analysis

Each individual study was subsequently examined by at least two (JT, JS, AA) independent authors, and information on study type, histology and treatment received was collected. Clinical outcome data were also collected including, where possible, the relationship between treatment strategies and potential late effects. Any discrepancy was resolved by discussion among the authors.

Risk of bias was assessed for each included article using a modified "risk of bias" assessment tool developed from the Cochrane Handbook [16]. We rated the domains of selection, attrition and reporting bias separately for low, moderate and high risk of bias before assigning an overall risk assessment to each study. Criteria for this assessment are found in Table 1, and the results for each study are highlighted in Supplementary Tables 1 and 2.

Results

Study characteristics

The authors conducted the systematic review from September to October 2015. A total of 604 articles were screened. Of these, 110 articles were deemed to be relevant (Fig. 1). Some articles identified in our initial search addressed childhood (< 16 years) or non-testicular cancers and were also omitted. The relevant studies were further categorised according to their reporting of physical and/or psychological late effects.

Study quality and risk of bias

The summary-level findings are shown in Table 2 and Fig. 2, with individual study information in Supplementary Tables 1 and 2. The included studies had clearly defined outcomes. The majority of the studies were from Scandinavian countries, with limited representation of Asian or African cohorts. The majority of comparator populations were either general population

Table 1 Risk of bias assessment tool

Domain	Criteria for risk of bias
Selection bias • How were the patients selected? • Comparability	Low—truly representative of testicular cancer survivors (+ no significant exclusions) Moderate—somewhat representative of testicular cancer survivors (exclusion of relevant subjects/cohort derived from selected population, e.g. single centre) High—non-representative or no description of selection criteria
Attrition bias • How many patients were lost to follow up (%)?	Low 0–20% Moderate 21–50% High > 50%
Reporting bias, i.e. assessment of outcome • Questionnaires/tools • Interviews • Self-reported	Low—independent/blind assessment or objective measurement Moderate—medical records or self-reported via assessment tool + control group present for comparison High—self reported + no control group. Confounding factors not addressed.
Selective reporting bias of the authors?	

statistics or age-matched controls. Some studies used patients treated with orchidectomy alone as the control group.

There was heterogeneity of result reporting, with very few studies reporting outcomes according to cancer stage or treatment received. Furthermore, a significant number of articles did not differentiate testicular cancer by histology type. This left the review vulnerable to important confounding factors, particularly related to the effect of additional treatment modalities and resulted in low reportable figures for our target population of patients with stage I seminoma undergoing surveillance.

The majority of studies were retrospective in nature or cross-sectional with the use of questionnaires and interviews.

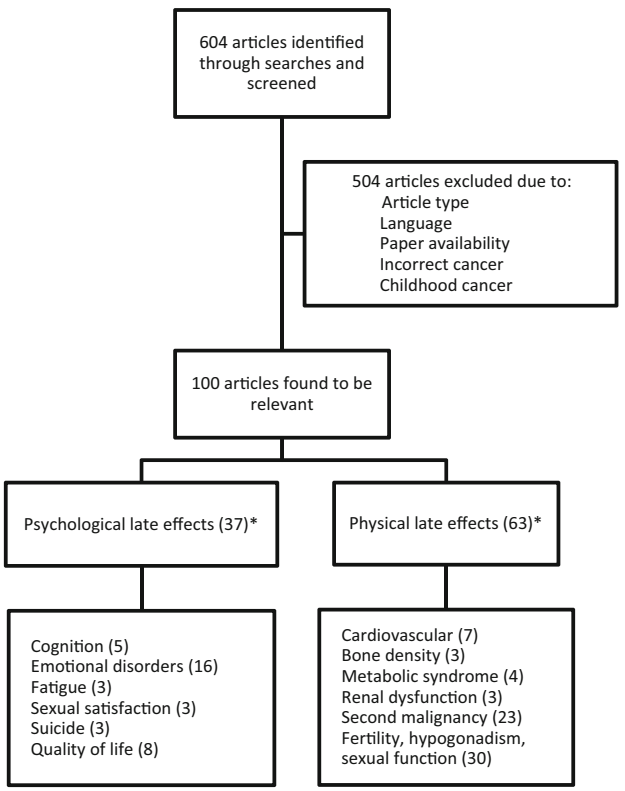

Fig. 1 Flowchart of study selection. Some studies have been included across multiple late effect groups and have therefore been counted twice (asterisk)

* Some studies have been included across multiple late effect groups and have therefore been counted twice

Table 2 Summary of findings

Late effect	No. of studies	Total study population	Patients treated with orchidectomy only		Conclusion
			Non-seminoma or not stated	Seminoma	
Cardiovascular	7	12,129	1240	140	Limited data available looking specifically at seminoma treated with orchidectomy alone. In the one study that reported outcomes for this patient, there was no increased risk of cardiovascular events compared to the general population. Cardiovascular risk was mostly associated in patients who had received radiotherapy or chemotherapy.
Bone density	3	981	26		Conflicting evidence regarding bone loss. The largest study included did not stratify by treatment received.
Metabolic syndrome	4	3013	607	6	One study found a lower rate of obesity in those treated with orchidectomy alone, although this study did not differentiate histology in this group. Most studies pointed to increased metabolic syndrome, obesity and hypertension in patients who were treated with chemotherapy.
Renal dysfunction	3	474	76		No evidence of increased incidence of renal impairment in patients who received orchidectomy alone.
Second malignancy	23	185,932	5285	807	Most of the studies did not report cancer incidence by treatment received. Of the ones that did orchidectomy only, patients appeared to have lower incidence of second malignancy compared to those treated with chemotherapy or radiotherapy. Among all testicular cancer survivors, there was an increased rate of second malignancy ranging from 1.4 to 7% and an increased risk of contralateral testicular cancer compared with the general population (2.1–5.2%).
Fertility, hypogonadism, sexual function	30	11,215	797	110	Few studies stratified data by histology as well as treatment modality received. Compared to healthy controls, there were conflicting reports regarding decreased sperm counts and sexual function in the orchidectomy alone patients with some studies showing no difference. Patients treated with chemotherapy or radiotherapy had a more pronounced negative impact on fertility, hypogonadism and sexual function than patients treated with surgery alone.
Cognition	5	499	195	35	Patients treated with orchiectomy alone reported higher rates of cognitive impairment than the general population; however, there was no significant difference in neuropsychiatric testing between the cohorts. Lower cognitive performance was identified in patients who received chemotherapy.
Emotional disorders	16	9743	933	1	No studies reported incidences specifically for patients treated with surgery only. Higher incidence of anxiety and fear of recurrence in all testicular cancer survivors compared with the general population. Conflicting evidence regarding depression.
Fatigue	3	3034	429		Higher rates of chronic fatigue across all testicular cancer survivors compared with the general population; however, these results were not stratified by histology or treatment received. Fatigue was associated with anxiety and depression.
Sexual satisfaction	3	661	272		Evidence of lower sexual satisfaction, reduced libido and erectile dysfunction across all testicular cancer survivors. Results were not reported for seminoma patients treated with orchidectomy alone.
Suicide	3	156,526			Trend towards increased incidence of suicide in survivors of testicular cancer compared to the general population. No subset of surgery only seminoma patients.
Quality of life	8	3331	457		Conflicting evidence regarding quality of life with limited data specifically examining patients who were treated with surgery only. Generally, quality of life was not dependent on type of treatment received. Two studies showed decreased quality of life and life satisfaction compared to the general population. Two studies reported no difference.

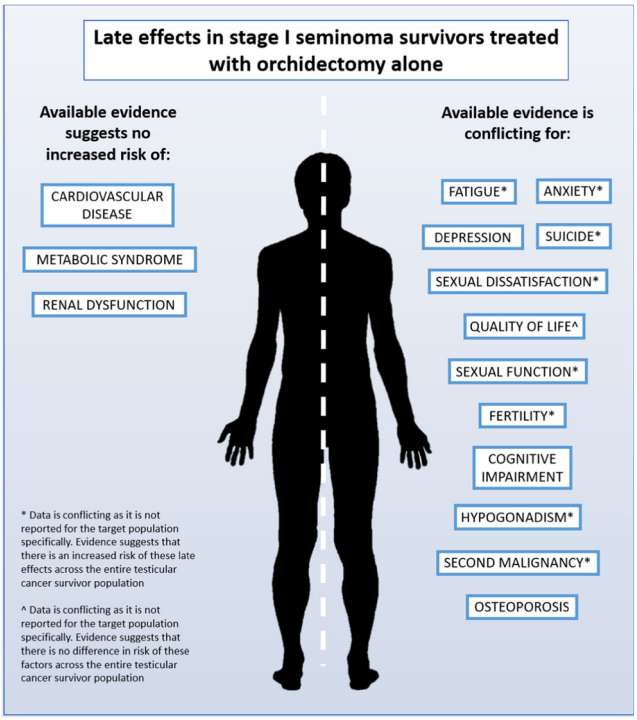

Fig. 2 Diagrammatic summary of late effects supported by evidence

These study designs may have introduced interviewer and reporter bias. Furthermore, many of the studies included data spanning several decades, with some extending as far back as the 1940s. Over that time, the care of men with testicular cancer has evolved, with the introduction of cisplatin-based chemotherapy regimens in the late 1970s and more judicious use of radiotherapy. This change in treatment over the years may have introduced confounding factors that impact the applicability of these results to our current standard of care.

In summary, the risk of bias was found to be low to moderate among the studies looking at physical late effects and moderate in the studies looking at psychological late effects. There was marked heterogeneity of study design, data collection and reporting. As a result, it is difficult to draw definitive conclusions regarding the potential late effects in men with stage I seminoma specifically, especially those treated with orchidectomy alone. Therefore, any data relating to our target population was included in our summary below. Where available, data that were stratified based on histology or treatment modality were specifically highlighted in the review.

Physical effects (see Supplementary Table 1)

Cardiovascular health

There were seven relevant studies, including over 12,000 patients with median follow-up ranging from 10.2 to 19 years. Of these patients, 1240 were treated with orchidectomy alone, with only 140 identifiable specifically as seminoma [17]. Most of the studies compared patients treated with orchidectomy alone to patients who received chemotherapy and radiotherapy. The latter subset of patients had significantly higher cardiovascular risk and events, postulated due to chemotherapy and radiotherapy-induced endothelial injury, which led to increased rates of atherosclerosis. One study reported rates specifically for stage I seminoma patients treated with orchidectomy alone and found that the cardiovascular event rate was similar to that of the general population [18].

Bone density

There were few data available with regard to bone health. Three studies included 981 patients but did not specifically report the number of seminoma patients treated with orchidectomy. Two of the studies showed no evidence of osteoporosis in testicular cancer survivors treated with orchidectomy alone [19]. The study by Murugaesu et al. went further and found that the rate of osteoporosis did not change over 5–28 years of follow-up, regardless of the type of treatment received [20]. In contrast, a study of 879 testicular cancer survivors reported testosterone deficiency in 84% that was associated with decreased bone density in 73% [21]. This study did not report outcomes by treatment received or histology.

Metabolic syndrome

Hypertension, dyslipidaemia, obesity and insulin resistance are all markers of metabolic syndrome that confer an increased risk of cardiovascular disease, stroke and type 2 diabetes. Of 3013 patients assessed, 607 were treated with orchidectomy alone, although histology was not specified. One study found that patients treated with surgery alone had a lower prevalence of obesity compared to patients treated with chemotherapy or radiotherapy (OR 0.8, 95% CI 0.6–1.0) [22]. Those undergoing orchidectomy alone appeared to have similar rates of metabolic syndrome as the general population. Chemotherapy was consistently associated with an increased risk of hypertension, dyslipidaemia and metabolic syndrome.

Renal dysfunction

Three studies of small populations examined the rate of renal dysfunction in testicular cancer survivors. Of 474 patients examined, 76 with unspecified histology were treated with orchidectomy alone. No increased risk of renal dysfunction was identified in these patients.

Second malignancy

In total, there were 23 studies. Several of these studies used overlapping study cohorts, and it was difficult to separate the data. Orchidectomy was the sole treatment in 5285 patients,

with at least 807 of these cancers identified histologically as seminomas.

The reported rate of second malignancy specifically in seminoma treated with orchidectomy alone was reported in only one study as 1.4% [23] compared with 7% in patients who were treated with either chemotherapy or radiotherapy [24]. Twelve studies reported increased rates of second malignancy among testicular cancer survivors in general. This was most marked for patients who were also treated with chemotherapy and radiotherapy. The type of second malignancy diagnosed depended on the extent and site of initial radiotherapy, for instance patients who received para-aortic lymph node irradiation were at an increased risk of gastric malignancy [25]. Other second malignancies included pancreatic, renal, bowel, bladder and soft tissue cancers, as well as haematological malignancies such as acute myeloid leukaemia. The increased second malignancy rate in patients receiving multimodality treatment extended beyond 20 years from initial diagnosis [26] and for as long as 35 years [27].

Many of the studies identified an increased risk of contralateral testicular cancer in survivors compared to the general population. Relative risk of second germ cell cancers, compared to an aged-matched general population, ranged from 24.8 to 44.8, with a lifetime cumulative risk of 2.6–3.9%. These studies did not report rates specifically for our target population of stage I seminoma treated with orchidectomy alone.

Fertility and hypogonadism

Only 154 patients were clearly identified as having stage I seminoma treated with orchidectomy alone from a combined study population of 11,215 across 30 studies. It was therefore difficult to draw any conclusions regarding our target population specifically.

Low sperm counts were identified in 55% of patients with stage I seminoma (treatment not specified) [28] and 60–70% of all testicular cancer survivors [29–31]. However, there were conflicting data regarding fertility, with rates of successful conception among all testicular cancer survivors ranging from 39 to 92% [32]. Rates of conception among patients who underwent surveillance post-orchidectomy appeared higher, with a paternity rate of 85 to 92% compared to 48% in patients who received high-dose chemotherapy [33]. This is on par with the reported infertility rate for the general population of 15% by a French study in the 1980s [34]. Another study of 246 testicular cancer survivors found higher rates of fertility distress in patients treated with surgery alone compared with the non-cancer population, but no difference in paternity rates [35].

Generally, studies were consistent in reporting higher rates of sexual dysfunction in testicular cancer survivors compared with the general population. Only one study reported no significant difference [36]. These results were not stratified by histology or treatment received. A key point of conflict was whether the modality of treatment received had an impact on the survivors' sexual function. One small study of 76 testicular cancer survivors found no difference among the treatment groups based on self-reported outcomes [37]. However, chemotherapy was considered to be the main influential factor on sexual function in another study [38].

Nine of eleven studies, each examining small patient cohorts, demonstrated an increased rate of hypogonadism in testicular cancer survivors—only two did not [39, 40]. The rate of hypogonadism ranged from 26.5 to 84%. Testosterone deficiency or hypogonadism were two to three times more common in patients treated with chemotherapy versus those treated with orchidectomy alone [41–44]. Interestingly, despite a higher incidence of hypogonadism compared to healthy controls, this did not translate into a statistically significant increase in metabolic syndrome or poorer bone health. These results may have been limited by the follow-up time, given that clinically significant osteoporosis may take decades to manifest.

Psychological effects (see Supplementary Table 2)

Sexual satisfaction

Sexual satisfaction, based on qualitative outcomes such as performance distress and anxiety, was examined as a distinct late effect compared to sexual health, which addressed impotence and erectile dysfunction. No study specifically reported data related to stage I seminoma patients undergoing surveillance. Three studies evaluated the impact of the diagnosis on testicular cancer survivors' sexual satisfaction and interest. Two of these reported lower levels compared to healthy controls [45, 46], whereas one reported no significant difference in sexual satisfaction, anxiety or depression [47]. Fertility distress was four times higher than in the general population (22 vs 5%), which mirrored an increased rate of sexual performance distress (30 vs 3%) [48]. Marital satisfaction was similar to matched controls and a qualitative study of 34 survivors reported that the majority of couples' relationships were strengthened by the experience [46, 49].

Emotional disorders

Sixteen studies included an assessment of emotional disorders, none of which specifically reported outcomes for stage I seminoma survivors undergoing surveillance (Table 2). Outcomes were measured using self-reported questionnaires, generally consisting of several pre-existing assessment scales such as the Hospital Anxiety and Depression scale (HADS) and Profile of Mood States (POMS). Many studies reported a higher incidence of anxiety or depression in survivors of testicular cancer overall compared with the general population. In survivors, the reported incidence of depression ranged

between 7.9 and 20%. Reported rates of anxiety ranged from 6.1 to 19.2% between studies and correlated with mental morbidity in one study of 1013 stage I testicular cancer survivors [50]. A recent systematic review published by Smith et al. in 2018 reported that anxiety and fear of cancer recurrence were more prevalent among testicular cancer survivors overall, whereas depression rates were similar to the general population [51]. Only one study in our review identified a decreased rate of depression and anxiety compared to the reported general population rates [52].

Some studies addressed potential confounding factors that may influence the reported rates of emotional disorders. For example, Eberhard et al. examined the link between hypogonadism and anxiety or depression and found no statistically significant relationship [53]. Physical activity was associated with lower rates of depression and anxiety in survivors [54, 55]. A Norwegian study looking at a small cohort of testicular cancer survivors compared with the general population found that coping mechanisms were similar between the two groups; however, "avoidant coping" was associated with significantly more anxiety and depression, compared to "approach coping" [56]. Histology or type of treatment received was not associated with differing rates in the fear of recurrence in testicular cancer survivors.

Quality of life

We identified eight studies relating to quality of life in testicular cancer survivors. Outcomes were measured using self-reported questionnaires, which included assessment scales involving health-related quality of life, perceptions of general health, health behaviours and life satisfaction. Five studies showed no significant difference in quality of life compared to the general population [57–61]. Negative effects on sexual health resulted in lower life satisfaction scores. No results were reported specifically for our population of interest. Only one study reported results stratified by treatment modality received and found that patients who received chemotherapy reported a higher prevalence of physical side effects, whereas patients who received radiotherapy alone had a higher incidence of anxiety and depression [62]. In another study, testicular cancer survivors overall reported better indices for physical functioning and pain, but poorer indices for mental health and vitality [63].

Suicide

There were three American studies comparing rates of suicide between testicular cancer survivors and age-matched general population controls. These data were derived from pre-existing databases, and it was not possible to specifically identify seminoma survivors undergoing surveillance alone. Overall, there was a trend towards an increased incidence of suicide among cancer survivors, with a standardised mortality ratio ranging from 1.2 [64] to 1.72 [38].

Fatigue

Three studies evaluated self-reported rates of fatigue through questionnaires such as the Fatigue Questionnaire (FQ). Where there was no other underlying pathology identified, rates of fatigue were consistently higher in testicular cancer survivors compared to the general population in all three Norwegian studies. The overall incidence of chronic cancer-related fatigue ranged from 16 to 17.1% compared to 9.7–10% in the general population. The studies differentiated outcomes by treatment modalities received and the incidence of fatigue in one study among patients who were treated with orchidectomy alone was slightly higher at 18% and was associated with anxiety and depression [65].

Cognition

Five studies relating to cognitive changes in testicular cancer survivors were included in the review. All reported results differentiated by treatment modality, but only one study included a control group and none reported results specific to stage I seminoma survivors. Overall, data regarding cognition was conflicting. Two studies reported higher rates of cognitive problems in those treated with chemotherapy compared to surveillance [66, 67]. However, the self-reported rates did not correlate with objective neuropsychiatric tests in one of these studies [67]. In testicular cancer survivors overall, 62.5% (45 of 72) were assessed as cognitively impaired compared with the expected general population rate of 25% [68]. A further two studies reported no differences in neuropsychiatric test results between treatment groups [69, 70].

Discussion

Late effects in the stage I seminoma population treated with orchidectomy alone are not well described in the literature. This systematic review highlights the paucity of good quality data available specifically for this demographic.

The review found that, in the target population, available evidence suggests no increased risk of cardiovascular disease, metabolic syndrome or renal dysfunction compared to the general population. Sperm counts were initially lower than an age-matched cohort, however counts normalised when reassessed 5 years later. Data were not specifically reported for the target population regarding bone health, second malignancy, hypogonadism, fertility and all psychological domains (Fig. 2).

Most studies included data on patients who received adjuvant treatments such as radiotherapy and/or chemotherapy.

These treatment modalities have well-documented late effects which have been summarised in a commentary by Travis et al. published in 2010 [7]. This systematic review supported higher rates of cardiovascular disease, metabolic syndrome, self-reported cognitive impairment and second malignancy in patients who were treated with chemotherapy or radiotherapy compared with the general population or patients who were treated with orchidectomy alone. However, it is important to note that these data do not establish causal relationships between treatment received and reported outcomes.

Heterogeneity of study design and potential under-reporting of effects contributed to uncertainty regarding the true incidence and clinical significance of late effects. Due to the heterogeneity of study design, our choice of search terms may not have covered all possible outcome measures and it is possible that some relevant studies may not have been identified. There was significant variation in the methods of reporting results, with very few studies stratifying results according to stage, histology or treatment modality received. This made it difficult to elicit data specifically addressing late effects in our target population of stage I seminoma patients treated with orchidectomy alone. Variation in the definition and measurement of end points also made it difficult to accurately classify and interpret the results. This was particularly evident on review of data involving qualitative end points, which usually relied on self-reporting.

Cross-sectional studies were conducted using questionnaires of self-reported outcomes. This study method leaves the data vulnerable to information biases such as interviewer and recall bias. Selection bias may have been introduced, as survivors who experienced outlying outcomes may be more likely to participate in evaluation and follow-up studies. In all other instances, data was collected retrospectively from pre-existing databases. There was limited geographical diversity, with the majority of databases based in Scandinavia. Some studies used study populations from the same database, which had been updated over time. These studies were not excluded from our review in order to capture all data related to the target population. As a result, there may be duplication of data, which may have led to conflation of results. Overlapping study populations have been identified within Supplementary Tables 1 and 2.

Importantly, the long follow-up required to document late effects gives rise to the potential for population attrition and subsequent under-reporting of clinically significant outcomes. Many of these late effects become evident only after several years of follow-up, for instance osteoporosis, cardiovascular disease and cognitive impairment. Oncology patients are often discharged from clinic after 5 years, and there is no clear delineation of responsibility or guidelines regarding the long-term follow-up and monitoring for late effects in cancer survivors.

Conclusions and implications

This systematic review summarised the current body of evidence examining late effects in stage I seminoma survivors undergoing surveillance following orchidectomy. Due to variation in the reporting of data, it is difficult to draw firm conclusions about the spectrum of late effects in this specific population. The wide range of potential late effects reported among the general testicular cancer survivor population suggests the need for long-term monitoring alongside standard cancer surveillance to prevent further morbidity in these men. This is especially important given the curability of testicular cancer and the long-term survivorship rates. Further studies with standardisation of end points, methods of assessment and reporting are required in order to clarify the true incidence and prevalence of late effects following stage I seminoma treated with orchidectomy alone.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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