Men's Health Journal. 2023; 7(1): e13

ORIGINAL RESEARCH

Objective and Subjective Cognitive Decline in Patients with Testicular Cancer after Treatment: A systematic review

Bianka Karlíková[1]*, Branislav Uhrecký[1], Jitka Gurňáková[1]

1. Institute of Experimental Psychology, Centre of Social and Psychological Sciences, Slovak Academy of Sciences, Dúbravská cesta 9, 841 04 Bratislava, Slovakia.

Received: September 2023; Accepted: October 2023; Published online: December 2023

Abstract: **Background:** Patients with testicular cancer can live for several decades with completed treatment. Because of the availability of treatment, increasing attention is paid to its toxicity, which has adverse effects on physical, emotional, and cognitive functions. The results so far suggest that chemotherapy is responsible for multiple cognitive failures. On the other hand, the ambivalence of the results is shown by subjectively reported cognitive disorders, which are more frequent than in objective testing. This paper aims to review the literature and to identify and investigate the prevalence of affected domains, and the correlates of subjective and objective cognitive impairment in men treated for testicular cancer.

Methods: Scopus, Web of Science, EBSCO (MEDLINE, PsycINFO, Psychology and Behavioral Sciences Com-plete), and PubMed were searched for articles written in the English language that focused on objective and subjective cognitive difficulties in patients with testicular cancer with different types of oncological treatment. The PRISMA system was used to review the articles and ensure methodological accuracy. Of the 432 scientific articles, 24 articles were included in the systematic analysis.

Results: Most articles used a quantitative (n = 20) or mixed-methods design (n = 4). Using 10 articles with objective tests and 9 articles with subjectively perceived decline, cognitive difficulties were present in patients after surgical treatment and chemotherapy and at different time horizons compared with the healthy population. Most results were related to difficulties after chemotherapy, type of chemotherapy, and number of completed cycles. Subjectively perceived difficulties did not correlate with the results of objective tests, and the results were more related to experienced fatigue, emotional stress, etc.

Conclusion: Further research is needed to provide a more comprehensive view of the cognitive difficulties of testicular cancer patients and to develop a consistent battery of tests and scales.

Keywords: Cognition, Determinants, Objective cognition, Self-reported cognitive function, Testicular cancer, Treatment

Cite this article as: Karlíková B, Uhrecký B, Gurňáková J. Objective and Subjective Cognitive Decline in Patients with Testicular Cancer after Treatment: A systematic review. Mens Health J. 2023; 7(1): e13.

1. Introduction

Testicular cancer is an oncological disease that mainly affects men aged 15-49. The good news is that there is available treatment that is applied based on the clinical stage of the disease. Treatment in the form of orchiectomy, radiation therapy, or chemotherapy saves lives. However, at the same time, treatment toxicity contributes to changes in patients' quality of life [1-3]. After surgical treatment, patients are exposed to physical changes (body image) or increased levels of fatigue and pain related to chemotherapy [4,5]. The (long-term) physical consequences of the disease and treatment may lead to decreased well-being in patients, manifested by increased levels of anxiety and depressive symptoms, nervousness, or stress [6-8]. The response to acute or chronic stress leads to excessive activation of the hypothalamus, pituitary, and adrenal glands, resulting in increased production of glucocorticoids or cortisol, which can impair cognitive functions [9]. Changes in cognitive functions can be affected by stress, as well as intellect, education, age, and toxicity caused by completed treatment [10, 11].

*Corresponding Author: Bianka Karlíková; Address: Institute of Experimental Psychology, Centre of Social and Psychological Sciences, Slovak Academy of Sciences, Dúbravská cesta 9, 841 04 Bratislava, Slovakia. E-mail: bianka.karlikova@savba.sk, Phone: 00421919164317

Changes in cognitive functions, such as attention, learning, memory, information processing speed, and executive functions [12], may be temporary in some cases and can be subject to the current condition and type of treatment [13]. The results of patients with other oncological diseases showed that cognitive disorders were related to the type and amount of treatment received. In the case of radiation therapy and chemotherapy, they are shown to be toxic and associated with late adverse effects [14, 15]. Cisplatin-based chemotherapy has been shown to affect domains such as memory, speed of cognitive processes, executive function, attention, psychomotor performance, and executive function [16]. The available results suggest that long-term risks of toxicity, leading to ototoxicity, nephrotoxicity, neurotoxicity, and cognitive impairment, appear in treatment with cisplatin-based chemotherapy [15, 17-19]. A decrease in cognitive functions can also be related to biological factors, such as increased anemia, and decreased hemoglobin level [20, 21,]. Cognitive functions can be measured through neuropsychological tests focusing on different domains. However, despite the power of the tests, failures in cognitive functions may not be shown. In such a case, current experience may have an impact on perceived cognitive impairment to a greater extent than performance in objective testing alone [22]. Therefore, it is also necessary to measure cognitive functioning through subjective scales focusing on everyday functioning at home or work. So far, there is no systematic review that focused on subjective and objective reports of cognitive impairment in patients with testicular cancer with different types of treatment. At the same time, the question of what contributes to cognitive impairment has not yet been sufficiently answered. Are they biological parameters, sociodemographic variables, psychological status, or treatment? With what types of treatment are cognitive changes seen? This systematic review aimed to identify and examine the prevalence, affected domains, and correlates of subjective and objective cognitive difficulties in men treated for testicular cancer.

2. Methods

2.1. Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (PRISMA) system was used to review the literature and ensure methodological accuracy. Research articles were searched based on a set of keywords in internet databases of scientific p ublications. T here w as no lower limit for the period of the search. This was because no systematic studies had been conducted on the topic and the selected patient population. The search consisted of finding as many articles as possible, from the oldest to the newest. The oldest article found was from 1989 and the newest was from 2022. The search terms included categories of words related to subjective and objective cognitive difficulties in men with testicular cancer, regardless of age or ethnicity. The search for relevant articles was conducted in November and December 2022. Research articles were selected without year restriction in the following databases: Scopus, Web of Science, EBSCO (MEDLINE, PsycINFO, Psychology and Behavioral Sciences Complete), and PubMed. Table 1 provides additional information on the search strategy and information sources.

2.2. Selection process

Studies had to meet our criteria, which included aspects related to cognitive difficulties in men with testicular cancer (Tab. 1). The first criterion was a search for original research studies written in the English language. In addition, the studies had to include data on patients with different types of cancer treatment, data relevant to cognitive changes, and indicators that contribute to these changes. The final criterion was to include information on objective and subjective measures and determinants of cognitive deficits in patients with testicular cancer. The initial search focused on the titles and abstracts of the articles. The retrieved studies were transferred to the Mendeley Reference Manager. Sorting was done by filtering by titles and abstracts. Duplicates were removed manually. Abstracts that met the criteria were included in the next selection. All studies up to the final selection were independently assessed by two authors. Disagreements in selection were discussed until a consensus was reached. From 432 articles, 24 studies were selected that met the criteria. In the process of selecting articles for full-text reads, we have also calculated the level of inter-rater agreement. The raters agreed in 94.46% of cases whether the article should be included and the kappa agreement also reached a high level (= .800). The article selection process is illustrated in diagram 1 of PRISMA. The diagram (Figure 1) shows the search and the final number of 24 articles that met the selection criteria.

2.3. Data extraction and synthesis

Articles were removed and grouped based on our established criteria (Table 1). Information on objective and subjective cognitive difficulties in patients with testicular cancer and determinants that may contribute to changes in cognition were selected from each eligible article. Data for each article were recorded in the rows of an Excel spreadsheet. The table contained columns for writing data - first author and article year, study location, aim, design, sample, main findings, and quality assessment (Table 2).

2.4. Quality Assessment of Studies

The quality of the selected studies was assessed by all authors on a three-point scale (1-low; 2-medium; 3-high) based on the following criteria: inclusion of a control sample and the

method of its selection, the method of measuring cognitive functions (whether the measurement was made before the start of treatment, at what time intervals the measurements were made).

It does not matter whether cognitive functions were measured only objectively, subjectively, or a combination of both. Whether other methods were added to the selected methods, e.g., biological parameters (magnetic resonance imaging - MRI, blood, etc.). The assessment considered whether the sample size included a sufficient number of respondents (at least 30 per group) in the case of comparison of groups based on the type of treatment, whether variables (independent and intervening) were considered, e.g., in terms of the number of cycles of chemotherapy or time since treatment. Studies were assessed separately by each author. In case of disagreement, the assessment was repeated and discussed until agreement was reached.

3. Results

In this study, 432 research articles were identified using the search criteria. After removing duplicates and articles that did not meet the selected criteria, we obtained 24 articles. Most articles used a quantitative (n = 20) or mixed-methods design (n = 4). Research articles were from 1989 to 2022, and publication locations were Denmark (n = 7), the Netherlands (n = 4), Norway (n = 4), USA (n = 3), Germany (n = 2), Australia (n = 1), Brazil (n = 1), Slovakia (n = 1), and Sweden (n = 1). The overview of the reviewed articles is given in Table 2.

3.1. Study population

The total number of study participants with testicular cancer was 3292 and that of the control group (healthy population) was 163. The criteria for creating a control group varied among the articles. In some cases, it was a healthy population (e.g. Amidi et al. [23]) and in other cases, patients with surgical treatment were considered as a control group (e.g. Whitford et al. [24]). In terms of treatment – the orchiectomy group consisted of 1082 patients, the chemotherapy group consisted of 1632 patients, and the radiation therapy group consisted of 136 patients. They underwent different types of treatment (mix) – surgery and radiation therapy (n = 70); surgery and chemotherapy (n = 232); chemotherapy and radiation therapy (n = 7). The age of the study participants ranged from 18-75 years.

3.2. Objective cognitive difficulties

3.2.1. Orchiectomy

Most studies [13, 24-29] that assessed overall cognitive impairment studied it as a side effect of chemotherapy. However, three studies [23,30-31] also examined testicular cancer (TC) patients shortly after orchiectomy and before any further treatment. Wefel et al. [30] did not have a healthy control group, but they found cognitive impairment in 46% of patients, which is significantly above the assumed population standard (12%). The prevalence of cognitive impairment reached 58% in the study by Amidi et al. [23], compared with 24% in the healthy control group. Buskbjerg et al. [31] came to a similar conclusion – the prevalence of significant impairment in patients with testicular cancer was 65%, significantly higher than the prevalence in the healthy control group (36%). Therefore, all three studies imply that cognitive impairment may be associated with surgery, at least in the short term. Both Amidi et al. [23] and Buskbjerg et al. [31] also conducted 6-month follow-up studies showing that impairment persists. While Buskbjerg et al. [32] found no overall decline or improvement in the ochiectomized TC patients compared to the healthy control group, Amidi et al. [13] found a further significant decline. On the other hand, the studies by Schagen et al. [33] and Wefel et al. [26] suggest that the effect of orchiectomy may be short-lived, as they found no overall difference in the test scores of surgery-only patients with testicular cancer compared with population norms at 6 months [33] and 12 months after treatment [26].

Among specific cognitive domains, the most consistent finding is the effect of orchiectomy on verbal learning and memory [23, 26, 30-31], but there is also evidence of an effect on verbal fluency [23, 31], processing speed [23, 31], attention [23], visual learning [31], executive functions [30], and motor functions [26]. However, in some cases, this effect was demonstrated in one of two tests that targeted this specific function, specifically processing speed.

3.2.2. Chemotherapy

Overall cognitive impairment after chemotherapy was measured at different time intervals and mostly compared with the surgery-only group. Amidi et al. [13] found overall cognitive decline from baseline to 6-month follow-up compared with the healthy control group, with the difference from the surgery-only group on the margin of statistical significance and the chemotherapy group showing greater decline. However, the value of statistical significance was probably influenced by the small number of patients treated with chemotherapy (22 patients), as the proportion of patients who experienced cognitive decline was much higher in the chemotherapy group (63.6%) than in the surgery-only group (39.5%).

Wefel et al. [26] and Amidi et al. [34] showed a tendency to suggest that the combination of chemotherapy and surgery leads to greater cognitive decline at 12-month follow-up compared with surgery alone, but could not conclusively prove this, as the result in both studies was close to the margin of statistical significance. However, Skaali et al. [35] and Whitford et al. [24] showed no support for the afore-

mentioned hypothesis at the same follow-up period. While the evidence for overall cognitive decline from chemotherapy at 12 months post-surgery is not very convincing, the cognitive domains in which an effect has been demonstrated are processing speed/psychomotor function [24, 26], verbal learning [34], and motor functions [26]. Regarding the long-term effects of chemotherapy on cognition, TC survivors treated with a combination of surgery and chemotherapy performed poorer on neuropsychological batteries when compared to surgery-only survivors in studies by Schagen et al. [33] (mean time of 3 years since last treatment) and Stouten-Kemperman et al. [28] (14 years since last treatment), although this did not manifest in any specific cognitive domain in the first study while no results for specific domains were reported in the second study. However, Pedersen et al. [25] came to the opposite conclusion - TC survivors (2 to 7 years after last treatment) who received chemotherapy did not differ from surgery-only TC survivors in overall or any of the cognitive domains. Stelwagen et al. [29] found no differences between treatment forms in a sample of TC survivors 20 to 42 years after treatment but found that TC survivors as a whole had poorer cognitive performance in comparison to the healthy control group - particularly in verbal fluency, language, and partly (1 of 2 tests) in verbal learning. However, this effect cannot be attributed to chemotherapy alone, because they did not compare scores to the surgery-only group. The possibility of long-lasting effects of TC treatment on cognition is also supported by Amidi et al. [27], who found that 62.5% of TC survivors (2 to 7 years after treatment) were classified as having CI, significantly above the expected normative frequency of 25%. As with the previous study, this finding cannot be attributed to chemotherapy or any other treatment form, as they did not distinguish between treatment forms due to the limited sample size, which included survivors with surgery-only, surgery + chemotherapy, and surgery + radiation therapy.

3.2.3. Radiation therapy

Evidence of objective cognitive decline in patients treated with radiation therapy is very sparse, with only two studies [33, 29], comparing their scores on objective cognitive tests with the healthy population or patients with other treatment forms. Both studies found no significant differences compared with other treatment forms. Several studies mentioned the inclusion of TC patients treated with radiation therapy but included them in the non-chemotherapy group along with surgery-only patients [25, 27, 34, 35].

3.3. Subjective cognitive difficulties

Thirteen articles used different methods to examine the perceived decline in cognitive functions in TC patients [36-42], some of them in combination with objective neuropsychological measures [23-24, 28-29, 33, 43]. To avoid misunderstanding, the results of selected studies are presented in terms of the methods they used.

Four studies assessed subjective cognitive decline by interview [33, 36, 38, 43], one of them in combination with The Fatigue Questionnaire [43], and another in combination with the EORTC-QLQ – C30 [33]. This questionnaire was also used in the study by Skaali et al. [37] to assess subjectively perceived cognitive decline. Stouten-Kemperman et al. [28] reported the EORTC-QLQ-C30 total score without separately reporting items related to attention and memory and used the Medical Outcomes Study's Cognitive Functioning Scale - Revised as a measure of cognitive decline. Three studies used The Cognitive Failures Questionnaire [23, 24, 29], two studies used FACT-Cog v.3 [40, 41], and one study used either EORTC QLQ-FA12 to measure cancer-related fatigue – including cognitive fatigue [42] or a selected item on concentration difficulties from the Memoria Symptom Assessment Scale [39].

3.4. Interview

In the first study to address the cognitive decline in TC patients (poor concentration, inability to think clearly, and inability to complete tasks), Gritz et al. [36] reported the results of interviews in which TC survivors retrospectively reported subjective cognitive complaints before treatment that significantly increased at the 6-month posttreatment time point (without distinguishing its type) and improved in the last month before the interview, but without fully returning to baseline. Later, four additional research articles incorporated the Likert scale as a method to explore subjective cognitive complaints in the interview [28, 33, 38, 41]. In one study [33], TC survivors with a median of 3 years after completion of the treatment assessed the extent to which their cognitive problems with memory, attention, thinking, and language occurred in their daily lives. Cognitive complaints occurred more frequently in patients who had orchiectomy combined with chemotherapy (four cycles of bleomycin, etoposide, platinum; BEP) (32%), and in patients who had a combination of orchiectomy and radiation therapy (32%) than in patients who had surgery alone (27%). However, the subjectively perceived cognitive decline of the first two groups was related to the period of treatment completion, emotional distress, and fatigue, but not to their actual cognitive test performance [33]. The second study [44], based on two interview questions focusing on memory and concentration problems immediately after orchiectomy and one year later, reported a higher prevalence of subjective cognitive decline of memory and concentration in the group of patients with one (29%) and more than 2 cycles of chemotherapy (25%), compared with the group without chemotherapy (3%). The difference between the group of patients with different numbers of chemotherapy cycles was not significant [43]. TC patients with subjective cognitive decline also reported higher

levels of fatigue and distress. No association was found between subjective cognitive decline and performance on neuropsychological tests.

On the other hand, Skoogh et al. [38], in their own set of 59 interview questions reflecting specific cognitive domains (difficulties with attention, memory, visual-spatial ability, language, speed, or executive function), demonstrated the impact of multiple cycles of chemotherapy. The set of survivors consisted of patients with only surgery, 1-2, 2-3, or more than 5 cycles of chemotherapy who were on average 11 years post-treatment. Cognitive decline was perceived more frequently in the group with more than 5 cycles of cisplatin-based chemotherapy. This group of patients reported long-term problems in memory, concentration, and language compared with those who had not received chemotherapy.

According to the authors, perceived language problems were related to the level of education [38]. Stouten-Kemperman et al. [28] reported a higher percentage of memory complaints mentioned in the interview 10 years after treatment in the chemotherapy and surgery group compared with the surgery-only group.

3.5. FACT-Cog Questionnaire

The study by Manhães et al. [41], which did not focus primarily on cognitive decline, found only a deterioration in the perceived cognitive abilities of chemotherapy patients using the FACT-Cog Questionnaire. In another study [40] using the same questionnaire with TC survivors 5 or more years after treatment, greater perceived cognitive decline and decline perceived by others was reported in the survivor group with radiation therapy, chemo + radiation therapy - compared with the surgery-only group. In this study, chemotherapy alone, without distinguishing its specific content, had no significant effect on cognitive function. However, according to a separate analysis of survivors who received a higher dosage of cisplatin ($\geq$ 400 mg/m^2), their cognitive decline was significantly higher compared with the surgery-only group [40].

3.6. Cognitive Failure Questionnaire

According to Amidi et al. [23], compared to a healthy sample, newly diagnosed TC patients did not show significantly different scores on The Cognitive Failure Questionnaire less than 30 days after surgery compared to a healthy sample, although they had significantly lower scores than the control group on 6 of 11 neuropsychological outcomes - processing speed, attention and working memory, verbal learning and memory, and verbal fluency. In the study by Whitford et al. [24], no difference in the level of subjective cognitive decline longitudinally, as measured by the Cognitive Failure Questionnaire (CFQ), was found between survivors with orchiectomy and chemotherapy immediately after surgery and 12-18 months after the treatment. An overall effect of chemotherapy on objective and subjective cognition was not found. When the groups were combined, baseline scores on the six objective cognitive function tasks were correlated with subjective (self-reported) cognitive decline. No significant relationships were found. Stelwagen et al. [29] also found no significant differences in CFQ between different treatment groups of TC survivors more than 20 years after treatment. Furthermore, TC survivors reported similar median scores on the CFQ as the healthy control group. However, TC survivors in this study had a lower combined score on the cognitive tests performance compared with the control group, and the chemotherapy group experienced more anxiety symptoms than the groups receiving radiation therapy or orchiectomy alone.

3.7. EORTC-QLQ-C30

A longitudinal study of attention and memory measured by two individual items from EORTC-QLQ-C30 [37] in a chemotherapy group showed an increase in these cognitive complaints at the 3-month follow-up. After 9 months they returned to baseline. The radiation therapy group showed no changes in cognitive complaints during this period. According to the authors, cognitive complaints were associated with current fatigue at each time point, but not with treatment form (chemotherapy vs. radiation therapy) [37]. In the study by Schagen et al. [33], no differences in the cognitive difficulty subscale of the EORTC-QLQ-C30 were found between three groups of survivors at a median of 3 years after treatment with chemotherapy and surgery, radiation therapy and surgery, and surgery only.

Other methods of assessing perceived cognitive decline [28] reported only the total score of EORTC-QLQ-C30, not the individual items on memory and concentration. However, they assessed cognitive decline using the Cognitive Function Scale Revised of the Medical Outcomes Study. In any case, 10 years after treatment, they found no significant difference in subjectively perceived cognitive decline between the chemotherapy and surgery groups compared with the surgery-only group, although the survivors with chemotherapy had lower cognitive performance than the surgery-only group.

Difficulties concentrating during the last week according to the Memorial Symptom Assessment Scale – Short Form (MSAS-SF) ranked fourth in frequency (32%) among 32 physical and psychological symptoms, after lack of energy (49%), fatigue/sleepiness (42%), and sleep disturbances (36%) in the group of 164 TC survivors with 1 or more years after treatment [39].

3.8. Cancer-related fatigue

Since almost half of the selected studies [24, 33, 37, 39, 42, 43] in any way link possible cognitive decline to cancer-related

fatigue (CRF) - physical, emotional, stress-related, and cognitive fatigue that is more severe and persistent than normal fatigue [44, 45], we included two additional studies in this review: Nowe et al. [42] studied the prevalence of cancer-related fatigue (CRF) with EORTC-QLQ-FA12 in 577 patients with various cancer diagnoses. Compared with other oncologic conditions, TC patients had the lowest levels of cognitive fatigue in each dimension (physical, emotional, and cognitive fatigue), but they also had the most uneven distribution - being either on one side or the other of the spectrum. In the follow-up study by Skaali et al. [43], a higher proportion of chemotherapy-treated patients with an increase in self-reported memory and concentration problems one year after treatment showed an increase in total fatigue score measured by The Fatigue Questionnaire in comparison to the group of patients without an increase in cognitive decline (50% vs. 22%).

3.9. Determinants of cognitive functions

Chemotherapy contributes to physiological, biological, and emotional changes that are also associated with a decline in cognitive functions. 9 studies used biological measurements of hormone levels and MRI brain scans [13, 23, 24, 28, 29, 31, 32, 34, 46]. Results showed that chemotherapy contributed to changes in the gray cortex of the prefrontal lobe and long-term hyperconnectivity in the areas of motor functions, attention, and working memory, which may be related to the results in objective tests [13, 46]. Lower testosterone levels lead to poorer test scores, which are measured more than 20 years after treatment [29]. For cortisol, no relationship was found between treatment types and cognitive scores [46]. Chemotherapy with one or more cycles was associated with higher levels of fatigue but did not correlate with performance on objective tests [43]. Subjective cognitive decline related to chemotherapy was associated with fatigue at each time point, namely before treatment, 3 months later, and 12 months later [33].

BEP-based chemotherapy combined with increased stress correlated with lower scores on tests of working (WAIS-III DS Fw) and visual memory (RCFT) [33]. However, recent results showed that the combination of orchiectomy and chemotherapy (BEP) resulted in increased stress levels that affected not only cognition but also general quality of life [42]. In the case of depression, there are conflicting opinions from several studies [26, 33, 38]. Performance on objective tests was not related to depression [26]. Another study reported that depression was related to subjectively reported cognitive decline, while another study found no association between these variables [33, 38]. Regardless of treatment form, depression is associated with impaired performance on tests of working (WAIS-III LN) and visual memory (RCFT immediate and delayed recall) [25].

An association between anxiety and psychomotor test performance was observed in patients with orchiectomy alone or combination with EP (etoposide, cisplatin) or BEP-based chemotherapy [24, 30], with the chemotherapy group having higher anxiety scores. Longer follow-ups showed that anxiety scores decreased over time in both groups [24]. Subjective scales did not capture the impact of anxiety on the results [38]. Most research articles reported that intellect, education, and social support were found to be predictors of cognitive decline [25, 27, 38].

Two articles [33, 35] showed no relationship between educational level and type of treatment and decline in neuropsychological tests. Chemotherapy with more than 5 cycles was associated with language impairment. The extent of the outcome was related to educational level, with a college degree moderating this effect [30]. Low social support, which was correlated with performance on tests of working memory (WAIS-III DS Fw), processing speed (WAIS-III CD), and verbal fluency (F-words) [25], was a predictor that did not discriminate the completed treatment.

Higher rates of depression were observed after surgery, which subsequently affected scores on tests of verbal learning and memory (RAVLT) and psychomotor speed [30, 27]. In orchiectomies, stress is correlated with cognitive problems in attention, working memory, and executive functions [47].

3.10. Rating of study quality

The review also included an assessment of the quality of selected studies, evaluating criteria such as the inclusion of a control group and the method of its selection, and the method of measuring cognitive functions on a scale of 1-3 (1-low; 2-medium; 3-high).

Six studies were rated on Scale 1 [26, 36, 37, 39, 41, 42]. The critical factor in the evaluation was the methodology used, as in most cases only subjective measurement was used with an insufficient number of items on cognitive functions or with-out a primary focus on cognitive functions. Studies had in-sufficient numbers of respondents or respondents were un-evenly distributed by treatment. A medium rating (2) was given to 15 studies [13, 23 - 25, 27-29, 30, 31, 33, 34, 38, 40, 43], which included healthy control (HC) groups in addition to TC survivors. The studies were limited by unequal group sizes, which may have reduced statistical power for treatment comparisons. In the case of chemotherapy, chemotherapy patients with different regimens were grouped. The high-est rating (3) was given to 3 studies [32, 35, 47] based on the methodology used and the research set, which was divided according to all types of cancer treatment.

4. Discussion

The aim of our systematic review was to identify and examine the prevalence, affected domains, and correlates of subjective and objective cognitive decline in men treated for testicular cancer. The systematic review included 24 studies that provided answers to our research questions.

4.1. Treatment modality

4.1.1. Objective results

One of the most frequently studied factors for objective or subjective cognitive decline in TC patients has been the form of treatment. There is some evidence of objective cognitive decline in TC patients after surgery [23, 30, 31] and most after chemotherapy [13, 24-29]. Some studies [e.g. 33] show that chemotherapy leads to greater cognitive decline overall, but this was not shown on individual tests (cumulative effect - non-significant differences in tests became significant when summed). Another question is the duration of cognitive changes in TC patients. Previous findings suggest that cognitive difficulties are most pronounced during treatment, while at least one year later the effects of treatment are minimal or absent and cognition should return to normal [48, 49]. A systematic review has shown that surgery leads to short-term changes in cognition [26, 33], whereas the results for chemotherapy are contradictory. On the one hand, no difference was found between surgery and chemotherapy, even 2-7 years [25] and 20-42 years after treatment [29]. Other studies focusing on breast cancer patients showed that cognitive difficulties persisted during chemotherapy for 1-2 years [50, 51] or even 10 years after treatment [52, 53]. For reproductive organ cancers, difficulties in women have been attributed to the treatment protocol and a higher rate of cognitive fatigue, which is higher in female cancer patients [57].

In addition, there is weak evidence that the combination of surgery and chemotherapy leads to a greater decline than surgery alone, and even if this is the case, this effect lasts only for a few months after treatment [25, 29]. Radiation therapy treatment was not studied in detail in the selected studies, and our analysis showed rare results in only two studies [29, 33]. No decline in cognitive abilities was found compared with other forms of treatment or even with a healthy population.

4.1.2. Subjective results

In 7 [28, 33, 37, 38, 40, 41, 43] of 9 studies that analyzed the form of treatment, chemotherapy was found to be an important factor in subjectively perceived cognitive decline. In 2 studies, no difference was found between groups with different forms of treatment 1 year after treatment [24] or more than 20 years after treatment [29]. Most studies that have confirmed the effect of chemotherapy on cognition have included surgery and radiotherapy patients in the cohort [e.g. 28, 33], but none have included a healthy group. The studies also had an uneven representation of the different types of treatment, with a predominance of patients who received chemotherapy [e.g. 40]. At the same time, one of the studies [41] had not only cognitive function as its main objective but also measured biopsychological variables, which may have had an impact on data analysis and bias. Significant results may also have been caused by the use of an untested questionnaire that was only qualitatively addressed [38 Skoogh]. At the same time, another study used a low number of attention and memory items for subjective measurement, which may not have adequately mapped patients' cognitive failures in the selected domains [37].

A higher level of cognitive decline was reported by survivors 5 or more years after surgery in combination with radiation therapy, chemotherapy with higher doses of cisplatin, and both compared with surgery-only treatment [40].

The results suggest that undergoing chemotherapy, its composition, and a higher number of completed cycles may be responsible for cognitive impairment [33, 38, 43, 55] which has also been shown in other studies [15, 19]. Studies conducted on cancer patients also report that cognitive decline is related to chemotherapy and several completed cycles, as well as factors such as genetics, ethnicity, and age [56]. In patients with testicular cancer, the aforementioned variables, as well as the type of measurement tool and its validity, must also be considered.

Subjectively reported decline may be affected by treatment and awareness of treatment side effects, stress, depression, and poor quality of life [57-59]. Emotional distress or higher levels of fatigue did not show a clear relationship with objective results and were more related to subjective cognitive decline [43, 55]. Some of the studies [e.g.60] state that self-reported cognitive decline is not always reported on objective tests and only 15-50% report mild to moderate cognitive decline by neuropsychological testing. The aforementioned emotional experience, as well as the environment of controlled testing in which patients are more aware of their difficulties and have room to share them, maybe the cause of the inconsistency in results [30, 61].

4.2. Cognitive functions and treatment

In objective tests, the most consistent results were obtained with surgical treatment that affected verbal learning and memory [23, 26, 30, 31], but there is also evidence of impact on verbal fluency [23, 31], processing speed [23, 31], attention [23], visual learning [31], executive functions [30], and motor function [26]. During chemotherapy, a decline in processing speed, verbal learning, and motor function has been shown [24, 26, 34]. Chemotherapy causes the so-called chemobrain, which leads to changes in the prefrontal cortex and hippocampus responsible for learning and memory

[62, 63]. The chemobrain phenomenon is best demonstrated in patients with breast cancer, while results in other cancers are more controversial or complicated [64]. In selected studies, chemotherapy has been associated with impairments in attention, verbal and visual memory, processing speed, and executive functions [60, 65]. It would be necessary to use more detailed neuropsychological batteries to study processing speed and executive functions [55]. Vitali et al. [64] also noted that to detect small changes in cognitions, it would be necessary to identify and standardize methods that are used systematically.

The subjective results yielded different outcomes. The most frequently measured and reported perceived difficulties in TC patients were found in concentration [33, 36-39, 43], memory [28, 33, 37, 38, 43], followed by thinking [33, 36] and language [33, 38]. These functions were more frequently associated with the use of chemotherapy in combination with surgery than with surgery-only treatment in the above studies (with exception of the studies Gritz et al. [36] and Oechsle et al. [39], in which the form of treatment was not distinguished). Combining of different types of possible perceived cognitive difficulties, as measured by the FACT-Cog Questionnaire, yielded more complex results. Patients shortly after surgery did not differ from the healthy control group on this scale [23] despite significant differences in their actual cognitive performance. However, TC survivors, where treatment was longer ago, showed significant deterioration on the same scale without distinguishing the treatment form [41]. Survivors who had received radiation therapy more than 5 years ago, a higher dose of cisplatin in chemotherapy, or a combination of both reported stronger cognitive decline compared with surgery-only treatment [40]. From the results, TC patients who have undergone any type of treatment have cognitive difficulties. After orchiectomy, hormonal changes (decrease in testosterone after bilateral orchiectomy), low hemoglobin levels, insomnia, or increased fatigue, which is different from fatigue in the general population, may be behind cognitive decline [20, 68]. Psychological changes include the prevalence of negative mood, and higher rates of depression, which are associated with verbal learning, memory, and psychomotor speed [30, 27]. Patients experience increased stress after the intervention. This has been correlated with dysfunction in attention, working memory, and executive function [47]. In the case of chemotherapy, the biological factor behind the decline in mental function is the treatment, which is involved in the functioning and changes in the structure of the brain. For example, in patients, there are changes in brain activation associated with a reduction in the volume or density of white matter, which reduces the integrity of the white matter in the prefrontal cortex. The prefrontal cortex and hippocampus are the main centers for learning and memory. Any damage to these areas can lead to cognitive dysfunction [63]. In terms of physical functioning, chemotherapy acts in the form of increased fatigue, which can affect patients' attention. At the same time, the response to acute or chronic stress leads to excessive activation of the hypothalamus, pituitary, and adrenal glands. This leads to increased production of glucocorticoids, including cortisol, which affects mental function [9]. Increased rates of depression and anxiety have been reported in men, reducing intellectual activity and leading to sleep problems [69]. In line with these findings, patients' overall well-being scores were worse after chemotherapy than in the surgery group [70].

In the case of radiotherapy, the effect of neurotoxicity depended on the radiation dose and the patient's comorbidities [71]. The neurotoxicity of radiotherapy affects the central nervous system and leads to neurocognitive deficits. The aforementioned fatigue and headache may be behind the possible decline in cognitive function, affecting patients' attention and memory [72].

It is clear from the results that there is some mental decline in men with testicular cancer with different types of treatment. We could discuss what are the specific characteristics of the patients that have an impact on their cognitive function. Testicular cancer is less severe than prostate or breast cancer. In this case, the advantage is that patients are excluded from the burden of the disease compared to other patients being studied, and therefore a greater effect of treatment on cognitive function can be captured. Another common feature is that testicular cancer affects young men (15-49 years) who are sexually active and mainly of reproductive age. During this period, they undergo psychosocial development and face challenges such as identity, self-image, career, and starting a family [73]. Patients perceive physical scarring, weight loss, or gain, as well as the removal of the testicle(s) following cancer treatment [74]. Perceived missing testicles, and changes in weight and appearance (e.g. loss of hair) cause discomfort and shame. Men may perceive their bodies differently, feel uncomfortable dressing in the presence of men, or have difficulty initiating sexual contact [75,76]. Sexuality after treatment may be absent or manifest as decreased sexual interest, decreased sexual pleasure, erectile dysfunction, problems with ejaculation, and increased sexual discomfort [77]. The loss of fertility and reduced sexual satisfaction can lead to an increase in emotional vulnerability and low self-esteem. Men not only face the loss of a reproductive organ, but also increased levels of anxiety, depression, and post-traumatic stress disorder (PTSD) following the illness and treatment, which affect not only family planning, relationships, and careers, but also patients' cognitive functioning [27, 78].

Because testicular cancer predominantly affects young men, their return to a normal life may include obstacles in the form of physical but also cognitive changes that can cause feelings

of incapacity, resulting in altered emotional experience and quality of life after treatment [66].

Persistent cognitive decline can impact the completion of studies or overall career [67]. Decreased attention and working memory function can affect their ability to focus effectively. Disruption of processing speed reduces the efficiency with which a person works on a task, while learning may involve failure to recall information from short and long-term memory. When executive functions are impaired, there are problems with planning and organization, and in motor functions, there is decreased coordination of movement of both muscles and behavior.

4.3. Limitations

The systematic review contains several limitations, primarily related to the diversity of articles and the methodological approach used. Of the selected articles, not all focused primarily on cognitive failures, but also included the study of emotional experiences or neurophysiological changes (e.g., Amidi et al. [34]; Manhães et al. [41]). Second, many studies reported differences in specific subtests but not in cognitive function as a whole. In addition, not all studies using neuropsychological studies focused on each domain. A discrepancy emerged in the case of the categorization of cognitive domains. At the same time, the same test could be categorized into different domains. There is also an inconsistency across studies on objective cognitive decline in terms of statistical analysis and reporting of results, thus making meta-analysis including all of the available studies impossible and synthesis of findings difficult. Consequently, we recommend reporting means, standard deviations, p-values, and effect sizes for overall cognitive performance and specific domains or tests in future research on this topic.

For the subjective scales, measurement was performed using different methods, ranging from a self-constructed questionnaire through verified multi-item scales with sufficient validity and reliability to the assessment of cognitive deficit using two items selected from a complex scale with a broader focus. Inconsistency was also shown in the specifications of the research sample, which was highly heterogeneous within groups. Patients had different chemotherapy regimens/cycles or chemotherapy patients were mixed with surgical patients. Especially in chemotherapy treatment, testicular cancer stages were not reported, which could lead to bias and ambiguity in the results. In addition, the groups were unbalanced in size, and there was also a drop-out rate for not very large sets of respondents. Regarding the ethnic focus, only one ethnic group (Caucasian) was used in the articles. Regarding outcomes, confusing results were reported even in the sample of survivors. Many of the studies reported the proportion of patients with cognitive impairment instead of a p-value or statistical test, and most lacked power analyses. We consider non-significant results to be the limit. At the same time, many results would perhaps be significant with a slightly larger sample (e.g., Amidi et al. [34]).

4.4. Implications

Further research could focus on developing a consistent battery of tests and scales that examine individual cognitive domains. The results could help intervene early in cognitive changes and ensure sufficient intervention to reduce the adverse effects of treatment. At the same time, subjective perception of cognitive changes in patients may help clinicians identify internal experiences early. Based on future research, more consistent neuropsychological batteries could be developed that would set the standard for measuring cognitive decline and provide more accurate results. More accurate results could aid in the development of rehabilitation programs or cognitive interventions.

5. Conclusion

In conclusion, this review aimed to identify and investigate the prevalence of the affected domains and correlate subjective and objective cognitive decline in men treated for testicular cancer. According to the results of the studies, we can say that there is a visible difference in cognitive decline in TC patients compared with the healthy population, for all types of completed treatment (e.g., Wefel et al. [30]; Stelwagen et al. [29]). Cognitive decline in different periods has been demonstrated in objective assessment in several studies [13, 23- 31]. The presence of subjectively perceived cognitive decline at different periods after treatment has been noted in many studies [28, 33, 36 - 41, 43]. Be that as it may, even though according to Nowe et al. [42] TC survivors among other cancer diagnoses had the lowest cognitive fatigue scores on each dimension (physical, emotional, and cognitive fatigue), they also had the most uneven distribution - they were either on one side of the spectrum or the other. The presence of subjectively perceived cognitive decline at different periods after treatment has been noted in many studies [28, 33, 36 - 41, 43].

According to the results, we can say that there is a decrease in the cognitive domain in patients, but the results are not completely clear, although we can see a certain trend related to the adverse effects of chemotherapy. At the same time, cancer and the type of treatment are also related to variables such as the patient's health status, sociodemographic variables, biological parameters, psychological state (emotional stress, fatigue), and time since treatment. In addition, the chosen option of the control group, the choice of measurement method (scales, tests), its variability, and reliability must also be taken into account.

Further studies could resolve the diversity of assessment

of individual cognitive functions. The research conducted could develop a consistent tool for assessing objective, as well as subjectively perceived, cognitive decline that could lead to a clearer idea of specific changes and restore the quality of life in patients after cancer treatment.

6. Appendix

6.1. Acknowledgment

I would like to thank my colleagues for their help in selecting and evaluating the articles.

6.2. Conflict of interest

The authors declare that they have no potential conflicts of interest.

6.3. Funding and support

This work was supported by the European Regional Development Fund project "Systematic public research infrastructure - Biobank for cancer and rare diseases" (313011AFG5) and Doctogrand No. APP0360. The agencies did not participate in the design of the literature review, collection, synthesis, interpretation of data, and writing the manuscript.

6.4. Author's contributions

All authors contributed to the study's conception and design. Bianka Karlíková and Branislav Uhrecký performed the literature searches and screening. Bianka Karlíková., Branislav Uhrecký., and Jitka Gurňáková reviewed articles for eligibility and synthesis process. All authors discussed the results and contributed to the final manuscript.

6.5. Abbreviations

BEP: Bleomycin, etoposide, cisplatin; CRF: Cancer-related fatigue EP: Etoposide, cisplatin; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; TC: Testicular Cancer

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Table 1: Information sources, search strategy, and inclusion and exclusion criteria

	Information sources	
Searching electronic databases	Scopus, Web of Science, EBSCO (MEDLINE, PsycINFO, Psychology and Behavioral Sciences Complete), PubMed	
Hand-Searching	Search strategy Testicular patients ("testicular cancer"OR "testis cancer" OR "testicular germ cell tumour" OR "testicular carcinoma" OR "testis carcinoma" OR "testis neoplasm" OR "testicular neoplasm" OR "seminoma") AND	
Cognitive function	("cognitive impairment"OR MCI OR cognitive decline" OR "cognitive deficit" OR "cognitive problems" OR "cognitive changes" OR "cognitive *function* OR "cognitive difficulties" OR "cognitive fatigue" OR "cognitive complaints" OR cognitive ability* OR "cognitive performance")	
	Inclusion criteria	Exclusion criteria
Language	Articles written in English	Articles not written in English
Publication type	Original research studies	Peer-rewiewed research, Review articles, Book chapters, editorials, commentaries, letters, gray literature
Population	Articles containing data relevant to patients with only testicular cancer with different types of cancer treatment	Articles containing data relevant only to universal cancer patients (e.g., breast, prostate...) with different type of treatment
Topic	Articles containing data relevant to cognitive changes and indicators that contribute to these changes	Articles containing data relevant to cognitive changes with one specific treatment
Outcome	Articles containing objective and subjective data about aspects and determinants involved in cognitive deficit	Review articles containing data about cognitive problems, or articles with some interventions

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Gritz 1989	United States	To assess the psychosocial sequelae among long-term survivors of the disease and their wives or partners.	Longitudinal study Mixed: interview and subjective scale	Testicular Survivors (n =88)	Subjective difficulties with concentration, thinking clearly and inability to complete task. These findings were reported 6 months after treatment.	1
Schagen 2008	Netherlands	To examine cognitive complaints (subjective & objective) and neuropsychological performance of patients following BEP chemotherapy in comparison with patients treated with radiation therapy or surgery only.	Comparative study Mixed: interview (cognitive problems), subjective scales (anxiety, depression, fatigue) and objective tests	Testicular patients (n= 182) Chemotherapy (n = 70); Radiation therapy (n = 57); Surgery (n = 55)	Interview showed cognitive problems in patients with chemotherapy. Cognitive problems were not related to cognitive performance, but to emotional distress and fatigue.	2
Pedersen 2009	Denmark	To compare cognitive function of testicular patients with surgery and chemotherapy (BEP), with men with surgery and radiation therapy or surgery only.	Comparative study Quantitative: subjective scales (stress, depression, social support, mood)	Testicular patients/ survivors (n=72) Surgery and chemotherapy (n= 36); Surgery and radiation therapy (n= 13); Surgery only (n = 23)	Between groups were not found significant differences. The difference was close to significance in RAVLT test. Cognitive decline was not specifically linked to chemotherapy. Stress and depression was associated with poorer performance on working and visual memory tests. Also, social support was associated with poorer performance on working memory, processing speed and verbal fluency tests.	2
Skoogh 2011	Sweden	To study self-reported behaviors (specific activities and behavior in everyday life) that may depend on cognitive function, among testicular-cancer survivors who received various cycles of cisplatin-based chemotherapy by comparing them with those who did not.	Correlation study Quantitative: constructed subjective scale (cognitive problems, well-being, sexual activity, neurological symptoms, anxiety)	TC patients/ survivors (n = 960) No chemotherapy = (n = 268); 1-2 cycles of chemotherapy (BEP) (n= 259); 3-4 cycles (n = 366); 5 or more cycles (n = 67)	Patients with five or more cycles chemotherapy (BEP) had long-term experience with language, memory, concentration compared with patients without chemotherapy. Outcomes were related with education – university education dumped this effect. On the other hand, outcomes were not related to either depression or anxiety.	2
Skaali 2011c	Norway	To explore self-reported cognitive problems of TC patients in relation to chemotherapy and other associated factors.	Correlation study Mixed: cognitive interview, objective tests and subjective scales (event scale, fatigue, neurotoxicity, neuroticism)	Testicular patients (n = 122); No chemotherapy (n = 31); 1 cycle of chemotherapy (n = 38); 2 or more cycles of chemotherapy (n = 53)	25 of chemotherapy patients (20%) had self-reported cognitive problems form baseline to follow up. Significant differences were across treatment – between once chemotherapy group and multiple chemotherapy group. Between one chemo group and multiple group was not significant differences. Patients with self-reported cognitive problems had also worsening fatigue, lower education level and psychological problems before TC. Patients with subjective cognitive decline had higher level of fatigue and distress. No association was found between subjective cognitive impairment and performance in neuropsychological tests.	2

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Skaali 2011b	International (data from EORTC) – publicly available data, not own	To explore cognitive complaints in patients with testicular cancer treated with chemotherapy or radiation therapy during the 1990s, before today's increased awareness of this possible side effect.	Longitudinal study Quantitative: subjective scale	Testicular patients (n = 347) Chemotherapy (n = 276); Radiation therapy (n = 71)	Chemotherapy patients had an increase in cognitive complaints at 3-month follow-up, then they returned to baseline. Radiation therapy group had no changes in cognitive complaints. Cognitive complaints were associated with current fatigue at each time point.	1
Skaali 2011a	Norway	To compare changes from baseline to follow-up of neuropsychological test performance in testicular patients exposed to three different treatment modalities: no chemotherapy, one cycle of chemotherapy and multiple cycles of chemotherapy and to study variables associated with a decline in neuropsychological test performance from baseline to follow-up.	Comparative longitudinal study Mixed: objective tests, subjective scales and interview	Testicular patients (n = 122) No chemotherapy (n = 31); 1 cycle of chemotherapy (n = 38); 2 or more cycles of chemotherapy (n = 53)	No differences in groups. Decline in neuropsychological test was not associated with chemotherapy or demographic variables or distress, fatigue.	3
Skaali 2011d	Norway	To explore the following research questions: (1) What proportion of the recently diagnosed testicular patients report clinically significant cancer-related distress (CRD)? (2) Which variables are significantly associated with increased level of CRD? (3) Does the current distress-level significantly affect the results on any of the neuropsychological tests at baseline evaluation?	Correlation study Mixed: objective tests, subjective scales and interview	Testicular patients after surgery (n = 135) No sample distribution	The three distress-measures (IES, HADS and PANAS-NA) used to explore the impact of distress on neuropsychological test performance capture somewhat different aspects of distress, since more than half of their variance was not shared. We found that 4 of the 18 tests scores were associated with at least one of the distress-measures. These four scores represent measures of attention, working memory and executive functions, whereas none of the plain memory or motor function tasks displayed significant associations.	3
Wefel 2011	United States	To characterize cognitive dysfunction before adjuvant chemotherapy in a sample of men diagnosed with non-seminomatous germ cell tumors.	Correlation study Mixed: objective tests and subjective scales (anxiety, depression)	Testicular patients with surgery (n = 69)	46% of patients exhibited cognitive impairment at the time of assessment. Patients exhibited impairments in motor function, verbal learning, and executive function. 10% of patients (7 of 69) = symptoms of depression; 7% (5 of 69) anxiety. Psychomotor speed were associated with depression and anxiety. Years of education associated with cognitive impairment – learning and memory as well as executive function.	2
Wefel 2014	United States	To determine if adjuvant chemotherapy was associated with cognitive dysfunction in men with non-seminomatous germ cell tumors.	Longitudinal study Mixed: objective tests and subjective scales (anxiety & depression)	Testicular patients (n = 69) Chemotherapy (n = 55); Radiation therapy (n = 14)	No differences between groups on age, education, stage of disease, anxiety, depression on objective tests. Decline in learning and memory was at 12 months follow up in group with patients who received more cycles of chemotherapy. Post treatment men with chemotherapy reported improvements with psychomotor speed.	1

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Amidi 2015b	Denmark	To determine the prevalence of cognitive impairment (CI) in a group of testicular survivors by comparing their neuropsychological test scores with normative data.	Comparative study Quantitative: objective tests and subjective scales (stress, depression)	Testicular cancer survivors (n = 72) Surgery and 3 cycles of chemotherapy (n = 36); Only surgery (n = 36) No distribution of sample	Cognitive impairment was found in 62.5%. Between treatment and cognitive impairment was not association. The highest cognitive decline was in verbal learning, visual memory, executive functions and attention and working memory. Processing speed showed a larger spread depending on the specific neuropsychological outcomes. Significant predictor of cognitive impairment/decline was intellectual functioning.	2
Amidi 2015a	Denmark	To determine the prevalence of cognitive impairment (CI) in newly diagnosed and orchiectomized testicular cancer (TC) patients prior to systemic treatment, and to explore biological and psychological correlates.	Correlation study Quantitative: objective tests, subjective scales (distress, stress, posttraumatic stress, cognitive complaints) biological test (blood)	Newly Testicular patients (n = 66) & Healthy group (n = 25)	TC patients had lower score/cognitive decline in domain like processing speed, attention and working memory, verbal learning and memory and verbal fluency. Patients also reported higher level of stress, but they did not differ from healthy group on anxiety or depressed mood. Depression was associated with verbal learning and memory. In biological test, level of cortisol predicted overall neuropsychological performance.	2
Oechsle 2015	Germany	To examine self-reported symptom frequency and distress as well as the impact of demographic and medical characteristics in GCT survivors.	Correlation study Quantitative: Subjective scale	Testicular survivors (n = 164) No sample distribution	32% survivors report difficulties with concentration, 42% report feeling drowsy. According to authors, these cognitive symptoms are a part of the overall fatigue.	1
Stouten-Kemperman 2015	Netherlands	To compare psychosocial functioning, cognitive performance and brain (micro)structure following surgery and chemotherapy for testicular patients, against surgery only.	Comparative study Quantitative: objective tests and subjective scales (Quality of life, stress, trauma, cognitive functioning, biological test (MRI)	Testicular survivors (n = 51) Chemotherapy (n = 28); Surgery (control) (n = 23)	Chemotherapy (CT) survivors had a lower cognitive performance with moderate effect size. In group with chemotherapy was reported memory complaints.	1
Amidi 2017b	Denmark	To prospectively compare cognitive functioning in TC patients receiving surgery ± BEP chemotherapy and a HC group; 2) to compare possible morphological changes in brain GM between patients treated with and without BEP chemotherapy; 3) to examine associations between potential GM reductions and cognitive performance; and finally 4) to explore the role of immune, endocrine, and inflammatory markers, and the APOE genotype, in relation to CRCI.	Comparative longitudinal study Quantitative: objective tests and biological tests (MRI, blood)	Testicular patients (n = 65) Chemotherapy (n = 22); Surgery only (n = 43); Healthy (control) group (n = 25)	At 6-month follow-up, group of TC patients showed decline in cognitive performance, especially in chemotherapy group, but the results did not reach significance. Reduction in gray matter compared to healthy control, especially in chemotherapy group in the prefrontal lobe, which correlated with cognitive decline. The study does not support domain-specific effect of TC treatment.	2

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Amidi 2017a	Denmark	To longitudinally investigate the impact of cisplatin-based chemotherapy on whole-brain networks in testicular cancer patients undergoing treatment; b) to explore whether possible changes are related to decline in cognitive functioning.	Longitudinal study Quantitative: objective tests and biological tests (MRI)	Newly testicular patients (n = 64) Surgery + chemotherapy (3/4 cycles of BEP) (n = 22); Surgery only (n = 42)	Treatment with cisplatin chemotherapy may result in large-scale brain network change. Authors found higher frequency of overall cognitive decline in chemotherapy group. Also, this group higher frequency of learning and memory decline in the CT group (28.6%) compared with the S group (7.5%). The chemotherapy evidenced changes in both global and local network measures compared with patients who did not receive such treatment. Changes in the brain network induced by chemotherapy reduced cognitive performance. reduced local efficiency was related to overall poorer cognitive performance over time as well as verbal fluency. Lower premorbid intellectual functioning was statistically significantly associated with decreased local and global efficiency and decreased clustering in the CT group, but not in the S group.	2
Chovanec 2018	Slovakia	To assess long-term cognitive effects of therapy for testicular survivors 5 or more years later.	Correlation study Quantitative subjective scale	Testicular survivors (n = 155); Chemotherapy (n = 119); Radiation therapy (n =12; Chemotherapy and radiation therapy (n = 7), Surgery only (n = 17)	Survivors treated with radiation therapy had greater perceived cognitive impairment and impairment perceived by others. Combination of radiation therapy with chemotherapy caused decline in all FACT-Cog subscales. Chemotherapy alone did not significantly alter cognitive functions. Age, time from treatment, education, and marital status had no statistical association with cognitive impairment.	2
Stouten-Kemperman 2018	Netherlands	To investigate differences between patients with and without chemotherapy in functional brain networks at rest and during an affective processing functional magnetic resonance imaging (fMRI) task on average >14 years post-treatment; 2) to report changes in cognitive functioning during survivorship by comparing present and previous performance on a neuropsychological test battery on average 11 years earlier (3 years post-treatment).	Comparative study Quantitative: objective and biological tests (fMRI, hair cortisol)	Testicular survivors (n = 51) Chemotherapy (n =28); Surgery only (n = 23) as a control group	Hyperconnectivity in areas involved in attention, working memory, executive functions, psychomotor speed. Differences in hair cortisol levels were not found. No differences in cognitive change. (i.e., change between 3-years post-treatment and 14-years) were found between the two groups.	2

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Manhães 2019	Brazil	To determine the main biopsychosocial needs reported by survivors of testicular cancer and to translate and to evaluate the evidence of validation of a brief version of the CAYA-T scale.	Cross-sectional study Quantitative: subjective scales (distress, anxiety, cognition)	Testicular survivors (n = 29) - surgery + chemotherapy No sample distribution	It was observed a high prevalence of distress and low prevalence of anxiety, depression and a moderate impact on quality of life and cognition. Self-image and sexual function were the most prevalent problems.	1
Nowe 2019	Germany	To assess cancer-related fatigue and associated factors in young adult cancer patients.	Type of study Quantitative: subjective scales (EORTC QLQ-FA12, subscale on cognitive fatigue; Financial problems from the disease/treatment = 23 item of EORTC QLQ-C30)	Mixed oncological patients (n = 577) Testicular patients (50)	Testicular patients had the lowest levels of cognitive fatigue in every dimension, but they also had the most uneven distribution - they were either on one or the other side of the spectrum.	1
Whitford 2020	Australia & New Zealand	To study testicular cancer patients' objective and subjective cognitive function longitudinally, comparing a surgery group with a chemotherapy and only surgery group	Comparative study Quantitative: objective and biological tests (blood, hormone – testosterone), subjective scales (cognition, anxiety...)	Testicular patients (n =102) Surgery and chemotherapy (n = 41); Surgery only (n = 41)	Only one subtest showed significant cognitive decline - DET (detention task - psychomotor function). However, psychomotor function (controlling for age- the older patients) and physical well-being were significantly worse for the chemotherapy versus the surgery group at baseline, with groups converging by follow-up. The chemotherapy group showed higher anxiety, poorer functional well-being and worse fatigue compared to the surgery-only group at baseline, but not by follow-up. For both groups, emotional well-being, functional well-being and anxiety significantly improved over time. High level of testosterone and less fatigue to led better performance.	2
Buskbjerg 2021	Denmark	To assessed changes in cognitive functions and structural brain connectomes in newly orchiectomized testicular patients with health group from a baseline assessment to 6 months later and explored the associations between cognitive changes and endocrine status and hypothesized risk genotypes (APOE, COMT, and BDNF).	Longitudinal study Quantitative: objective and biological tests (MRI, blood – testosterone), subjective scales (anxiety, depression, fatigue, stress, sleep difficulties)	Testicular patients after surgery (n = 38) and Healthy control group (n = 21)	At 6-month follow-up, group of testicular patients showed decline in processing speed, visuospatial ability, verbal recall, and visuospatial learning. Patients showed signs of cognitive impairment when compared with health control group. While some patients showed overall decline, some also showed overall improvement. No changes in the brain were demonstrated, and none of the biological variables (genes, testosterone level) was related to cognitive decline.	3

Table 2: Overview of reviewed articles

First author and year	Study location	Aim	Design	Sample	Main findings	Quality, rating
Stelwagen 2021	Netherlands	To objectify long-term cognitive impairment after and identify treatment compared to results with stage I TC survivors and controls) associated factors related to the development of late effects.	Longitudinal study Quantitative: objective and biological tests, subjective scales	Testicular survivors (n = 184); Chemotherapy (n = 66); Radiation therapy (n =53) and Surgery group (n = 65) and Healthy control group (n = 70)	TC survivors had a lower combined score of the cognitive tests compare to control group. No differences in mean Z-scores between treatment groups of TC survivors. No significant differences between TC survivors and the controls in age, level of education, current rate of employment, smoking behavior, blood pressure, total cholesterol, serum glucose, HbA1c levels and score of depressive symptoms on the HADS questionnaire. The CT group experienced more anxiety symptoms than the RT or orchiectomy only groups. Level of testosterone was lower compared to controls. CT was the only predicting treatment modality for cognitive function - factors—such as having received chemotherapy, the presence of hypogonadism, and lower biologically available testosterone levels—were associated with worse cumulative Z-scores on cognitive tests. RT was not associated with poorer performance on cognitive function.	2
Buskbjerg 2022	Denmark	To compare cognitive performance in newly orchiectomized TC patients with age and education matched HCs, 2) to compare structural brain network properties in TCPs and HCs and explore associations with cognitive performance; and 3) to explore the possible associations of cognitive performance with endocrine status indicators, in particular testosterone levels, and selected genotypes.	Comparative study Quantitative: objective and biological tests, subjective scales	Newly Testicular patients (n = 40) and Healthy group (n = 22)	Testicular patients scored statistically significantly lower than demographically comparable health group on 6 out of 15 neuropsychological tests and overall cognitive performance. WAIS-IV Coding was associated with more self-reported cognitive impairment. Self-reported cognitive impairment was positively correlated with anxiety and depression. In brain network analysis, there were not differences between group.	2

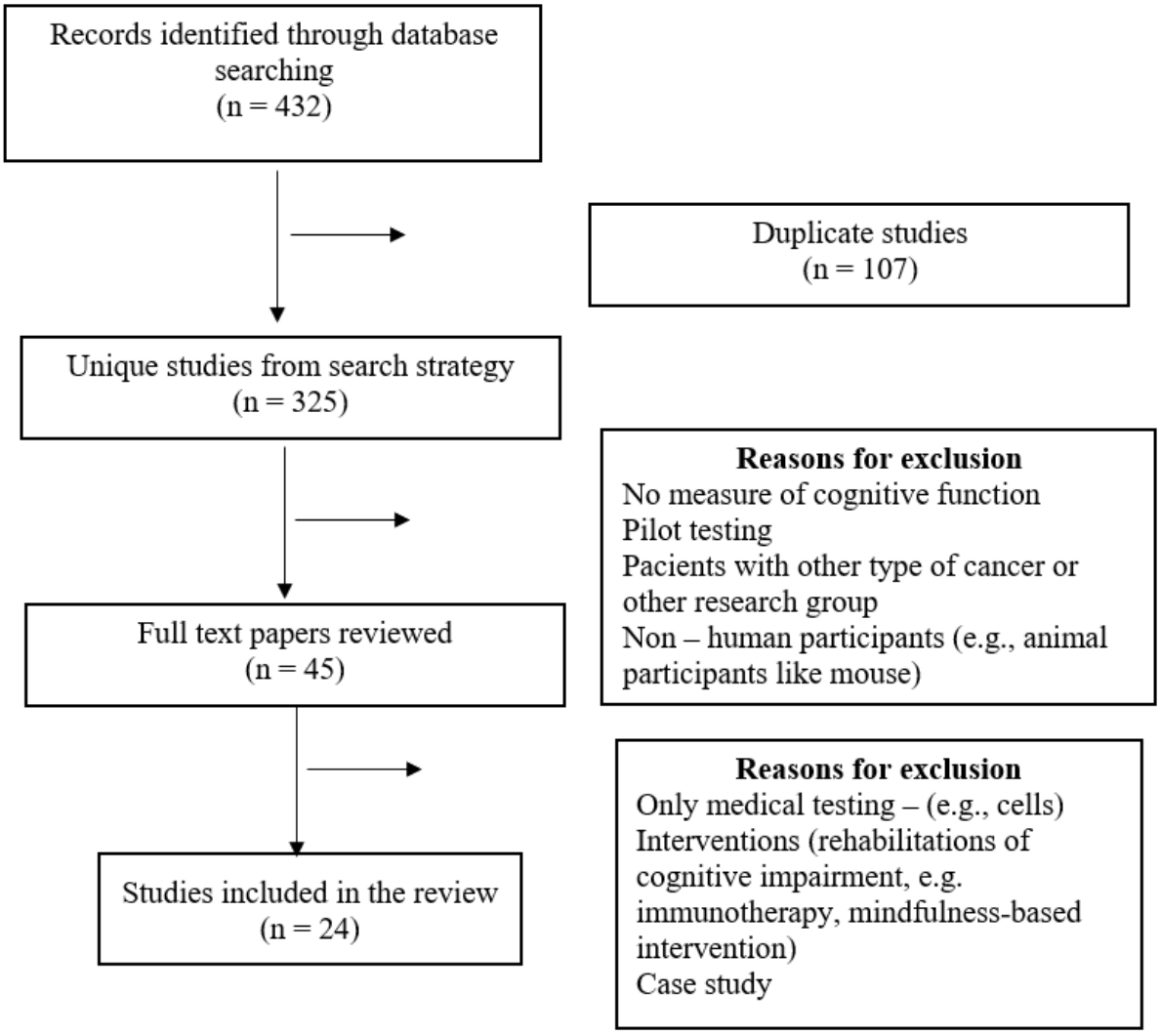

Figure 1: PRISMA flow diagram of the review process.