Prevalence of leukoencephalopathy and its potential cognitive sequelae in cancer patients

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ABSTRACT

Due to the rising use of chemotherapy in cancer patients and growing survival rates, therapy-induced neurotoxic side effects are increasingly reported. Given the ambiguity about the prevalence and severity of leukoencephalopathy, one of such toxic side effects, in non-central nervous system (CNS) cancer patients, we performed a systematic literature search using the PubMed/Medline database to summarize existing literature regarding leukoencephalopathy epidemiology in non-CNS cancer patients and its potential cognitive sequelae. The search was based on the following terms: ('MRI' OR 'T2-weighted MRI' OR 'FLAIR') AND ('cancer' OR 'tumor' OR 'leukemia' OR 'neoplasms') AND ('chemotherapy' OR 'radiotherapy') AND ('posterior reversible encephalopathy' OR 'leukoencephalopathy' OR 'cerebral ischemia' OR 'stroke'). Thirty-two studies discussing the occurrence of leukoencephalopathy in cancer patients were included, of which the majority investigated Acute Lymphoblastic Leukemia (ALL) patients (n=22).

Regularly scanned ALL patients showed a prevalence of leukoencephalopathy between 17 - 87%, and 15 - 83% of patients presented with leukoencephalopathy when only scanned after a CNS event. When diagnosed with posterior reversible encephalopathy syndrome, 100% of patients showed leukoencephalopathy because its diagnosis is based in part on observable lesions. An increased prevalence was observed in ALL patients treated with higher doses of methotrexate (5 g/m² MTX, 42 - 87%) when compared to lower doses (< 5 g/m², 32 - 67%). By contrast, in breast cancer patients, white matter lesions were mainly detected in case of neurological symptoms, but not (yet) clearly associated with chemotherapy administration in general. However, chemotherapy treatment was associated with more infratentorial microbleeds in breast cancer patients. Up to 50% of other (neurologically asymptomatic) solid tumor patients presented white matter lesions, even years after treatment. When cognitive data were investigated, lesioned patients showed lower scores on neurocognitive tests in 50% of studies, years after ending therapy.

In conclusion, leukoencephalopathy is well-documented for ALL patients (with a focus on methotrexate), but there is a lack of knowledge for other intravenous chemotherapeutics, other oncological populations, wider age ranges and risk factors (e.g. history of CNS event). Furthermore, the long-term neuropsychological impact and potential risk for neurodegenerative processes due to leukoencephalopathy remains inconclusive. Hence, large international databanks, epidemiological and prospective case-control studies are necessary to stratify risk groups for CNS-related side effects.

Keywords: leukoencephalopathy; cancer; chemotherapy; structural; imaging; review

Highlights:

- Prevalence of leukoencephalopathy in asymptomatic ALL patients ranges from 17 to 87%
- Increased prevalence seen in patients treated with higher doses of methotrexate
- Lower scores on neurocognitive tests after chemotherapy-induced leukoencephalopathy

1 INTRODUCTION

With rising survival rates after cancer treatment, it is becoming increasingly important to assess long-term side effects and consequently ensure quality of life of cancer survivors. Cancer treatment is known to affect both tumor and healthy tissue. Consequently, acute toxic side effects can arise such as cardiotoxicity, neurotoxicity, etc., affecting long-term quality of life. As neurotoxicity can affect brain development throughout the lifespan, neuropsychological research has been conducted increasingly to investigate long-term psychological functioning and accelerated neurodegeneration ¹. Cognitive decline can occur after chemotherapy with a wide spectrum of clinical manifestations, ranging from very subtle to more severe symptoms, including memory, processing speed, attention etc. being affected ². Previous research has shown that cognitive side effects can persist up until 10 to 20 years after treatment ^{3,4}. The number of studies investigating this so-called “*chemobrain*” keeps expanding ⁵⁻⁷. However, it remains uncertain to which extent such observed cognitive impairments are reversible ⁸, as well as what the exact underlying mechanisms are.

Multiple hypotheses of (in)direct pathways of neurotoxicity have been proposed, including inflammation, direct neurotoxicity, oxidative stress, hormonal dysregulation and genetic predisposition⁹. When the developing brain of a child is exposed to such toxicity, these mechanisms have high potential to alter crucial developmental events (e.g. myelination, synaptogenesis, neurogenesis, cortical thinning, and formation of neuronal networks) and cause brain injury ¹⁰.

Due to easier access to magnetic resonance imaging (MRI) and the use of higher chemotherapy doses, leukoencephalopathy, defined as a neurological disease affecting the white matter, is an increasingly observed complication. Leukoencephalopathy is often identified as a symptom of the acute phase of posterior reversible encephalopathy syndrome (PRES), which sometimes recovers ^{11,12}. The most common clinical features of PRES are seizures with headaches, altered mental status, neurological deterioration and visual impairment. Other possible acute chemotherapy-related neurological complications are dysarthria, hemiplegia, stroke-like episodes, intracranial hemorrhages and cerebellar syndromes ^{8,11-13}. Such

neurological complications (e.g. stroke, epilepsy) are associated with white matter damage ¹⁴ and in turn increase the risk for cognitive decline ^{15–19}.

Generally, white matter lesions are observed as transient hyperintense regions on a T2-weighted MRI, predominantly localized in the subcortical posterior temporal, parietal and occipital white matter, but they can also affect the basal ganglia, cerebellar hemispheres or brainstem. In some cases, additional diffusion-weighted MR imaging is needed for diagnosis because of the high signal intensity in the deep white matter ¹¹. Moreover, diffusion-weighted MR helps to distinguish cytotoxic edema from vasogenic edema. In contrast to cytotoxic edema, vasogenic edema is typically the case in PRES and suggests a reversible process with favorable prognosis ¹³. Ultimately, longitudinal acquisition of MR images are preferred for long-term follow-up of leukoencephalopathy. Given that advanced neuroimaging studies (including microstructural white matter and cortical analyses) are increasingly performed in oncological populations by cognitive neuroscientists ^{20,21}, the clinical radiological abnormalities (of which leukoencephalopathy is most well-known in non-central nervous system cancer patients) are highly important to bear in mind for these studies. Recently, a growing body of literature investigating radiological abnormalities in oncology, such as leukoencephalopathy, has been published. However, most studies investigated childhood Acute Lymphoblastic Leukemia (ALL) ²², while only few studies focused on other cancer patients. For ALL patients, treatments consistently include methotrexate (MTX), administered both intravenously (IV) and intrathecally (IT). This agent may be a causal factor in the development of encephalopathy ^{23,24}. In addition to the well-documented neurotoxicity of MTX, neurotoxic effects of other cytostatics, administered intravenously, such as alkylating substances (i.e. ifosfamide, cyclophosphamide, cisplatin) or vincristine have also been reported ^{23,25,26}. Therefore, we aimed to (1) summarize the existing evidence on the prevalence of leukoencephalopathy in both adult and pediatric non-central nervous system (CNS) cancer patients treated with chemotherapy; (2) stratify these ratios according to age and acute CNS-related adverse events; (3) summarize the evidence on neurocognitive outcomes after leukoencephalopathy.

Given that cranial irradiation can induce substantial cognitive and neurological damage as well ²⁷, patients receiving such treatment were excluded from this review to disentangle chemotherapy effects, differentiating this manuscript from previous reviews ²².

2 METHODS

2.1 Search strategy

A comprehensive systematic literature search was performed by investigating the PubMed/Medline database with date restrictions from 1995-2019. Subject categories 'MRI', 'cancer', 'therapy' and 'leukoencephalopathy' were searched, by using the following search terms: ('MRI' OR 'T2-weighted MRI' OR 'FLAIR') AND ('cancer' OR 'tumor' OR 'leukemia' OR 'neoplasms') AND ('chemotherapy' OR 'radiotherapy') AND ('posterior reversible encephalopathy' OR 'leukoencephalopathy' OR 'cerebral ischemia' OR 'stroke'). Both studies in children and adults were accepted. Extracted data included patient characteristics, type of cancer, leukoencephalopathy prevalence and cognitive measurements (when investigated).

2.2 Study selection

The screening procedure consisted of three different stages. First, potential articles were screened, based on titles. Second, studies were selected by abstract. Third, if the abstract was eligible, full texts were screened. The systematic selection of studies was supplemented with the manual selection of cited references from retrieved articles or other relevant articles. Included in the review were studies (1) with adult or childhood non-CNS cancer patients/survivors, (2) which reported the prevalence of leukoencephalopathy, defined as PRES, ischemia, demyelination, hyperintensities on MR images, white matter lesions or vascular damage, and (3) used at least one post-treatment T2-weighted or Fluid-attenuated Inversion Recovery (FLAIR) MR scan.

Exclusion criteria were: (1) studies published before 1995 (which was indicated in the PubMed/Medline database selection), (2) animal or cell culture studies, (3) case reports with less than 5 cases, (4) studies with patients who received cranial irradiation, (5) pharmacological studies which focused on survival and success rates of new products, (6) studies focusing on diseases other than cancer, (7) studies with MR scans which were not of main interest (e.g. only T1-weighted), (8) studies in which patients did not receive

chemotherapy,(9) studies with patients diagnosed with CNS tumors and (10) studies with no full English written text available.

3 RESULTS

The literature search of the PubMed/Medline database provided 1094 articles. After screening of titles, 1055 articles were removed because they did not meet inclusion criteria. Due to (non-English) language, lack of full-text and duplicate data, 7 articles were additionally excluded after full text screening. A total of 32 articles published between 1997 – 2019 were included in this review (Figure 1). An overview of these articles is provided in Table 1.

3.1 Prevalence of leukoencephalopathy

3.1.1 Leukemia patients

The majority of the included studies in this review investigated ALL patients, i.e. 22/32 studies (69%)^{12,24,36–42,28–35}. The age at inclusion of ALL patients varied between 1 and 19 years old. No data were available for adult ALL patients. All patients received MTX, both intrathecal (IT) and intravenous (IV). Two studies did not describe the used treatment protocol^{12,37}. Depending on the chemotherapy regime, children received either monotherapy with IT-MTX or, as described more recently, triple intrathecal therapy (TIT), which consists of a combination of MTX, cytarabine and prednisolone. The dose of MTX varied between 2 g/m² and 5 g/m². Only Mahoney et al. (1998) used a lower dose protocol with 1 g/m² MTX⁴². Additional therapy also varied; most frequent additional drugs were oral corticosteroids, vincristine, L-asparaginase, daunorubicin, cyclophosphamide and 6-mercaptopurine.

Some studies scheduled brain imaging of cancer patients on a regular basis, to allow follow-up of leukoencephalopathy. These were planned for example after induction, consolidation, re-induction or at end of therapy. The prevalence in these regularly scanned patients ranged from 17 to 87%, largely depending on

the sample size and time since diagnosis^{30,32,34,36,39}. Long-term follow-up studies reported a decrease in prevalence of leukoencephalopathy from 79 to 27%, assessing ALL patients from 2.6 years to over 15 years after ending therapy^{30,31,33,40,41,43} (see Figure 2).

Eleven out of the 32 studies only described MR images if patients were diagnosed with PRES, and thus 100% of these cases demonstrated leukoencephalopathy (see Table 1)^{44,45,54,46–53}. When such patients received a follow-up MR scan, the lesions remained observable in 20% after two weeks⁵⁰ and in 49% of patients after two months⁵¹.

A third population of patients was only scanned during therapy at time of a CNS event (eg an epileptic seizure, stroke, visual disturbances, headache, aphasia, changed behavior). This group showed leukoencephalopathy in 26 to 83% of patients^{12,24,28,29,35,38,42}. These hyperintensities were persistent in 36% of patients 6 months after presenting with PRES, stroke or epilepsy (8 out of 22)³⁵ and in all 5 patients investigated 2 – 39 months after a stroke-like episode²⁴. One study reported radiological normalization of high intensity areas in *all* ALL patients (6 patients) 1-7 months after ending therapy, who presented with seizures, affective disturbance or other neurological deficits³⁹.

Since dose regimens and a combination of multiple cytostatic agents were used across studies, specific agent dose effects are difficult to disentangle. However, two studies did compare low- to high-risk patient populations. Low-risk patients received 2 g/m² or 2.5 g/m² IV-MTX, while 5 g/m² IV-MTX was administered in standard- or high risk groups^{29–31,34–37}. Patients in the standard- and high-risk groups had a higher prevalence of leukoencephalopathy (42 to 87%) than patients in the group with a lower dose of IV-MTX (32 to 67%)^{36,38}. Reddick et al. (2005) concluded that higher doses and more courses of IV-MTX placed patients at higher risk for leukoencephalopathy during treatment³⁶. However, Cheung et al. (2016) compared the cumulative doses of agents between patients with and without persistent leukoencephalopathy and found no statistical differences³⁰. This discrepancy may be attributed to a threshold effect, since all patients received a cumulative dose of 15g/m² of IV-MTX on average. No difference was found between patients who were treated with TIT versus monotherapy IT-MTX (22 - 76% versus 37 - 83%, respectively)^{12,24,36,38–41,28–35}. By contrast, Mahoney et al. (1998) showed a significantly higher prevalence of leukoencephalopathy in patients treated with TIT versus mono IT-MTX shortly after a CNS event⁴².

When evaluating age effects in leukemia patients, Bhojwani et al. (2014) revealed that patients older than 10 years at time of treatment were at a higher risk for neurotoxic events than patients younger than 10 years ²⁹.

White matter lesions appeared widespread across the brain; predominantly frontal, parietal and occipital regions were affected by encephalopathy ^{12,24,28,35,39,46,50,53}. Such lesions were also reported in the temporal lobe, semioval nucleus, hippocampus and the thalamus ^{12,28,35,39}. Uniquely reported lesions are located in the fasciculi or corona radiata ³⁰ callosal splenium ²⁴ or in the cerebellum ³⁹.

3.1.2 Other cancers

Eight studies included patients who were diagnosed with other cancers than ALL ^{12,37,39,43,54–57}. First, Koppelmans et al. (2015) described the prevalence of leukoencephalopathy in 187 breast cancer survivors (aged 50-80) 20 years after they had received chemo- (combination of cyclophosphamide, 5-fluorouracil and oral MTX) and radiotherapy ⁵⁵. When compared to age-matched healthy controls, patients showed a higher prevalence of both total cerebral and deep infratentorial microbleeds (MBs), but no increased risk of infarctions or white matter lesions. Additionally, patients with cerebral MBs in deep or infratentorial regions, performed worse on tests of verbal memory and processing speed. Menning et al. (2017) confirmed these results in breast cancer patients (aged <70), 6 months after treatment with anthracycline-based chemotherapy, identifying no significant FLAIR white matter abnormalities. However, they did observe a clear shift from Fazekas score 0 to 1 in all breast cancer patient groups ⁵⁶. In contrast, Choi et al. (2001) reviewed clinical records of breast cancer patients treated with a 5-fluorouracil derivative or a combination with 5-fluorouracil, cyclophosphamide and epirubicin, and they encountered six patients who developed leukoencephalopathy during chemotherapy on MR images ⁴⁴.

Second, childhood Hodgkin lymphoma (HL) patients were investigated in two reports ^{37,43}. Krull et al. (2012) performed MR imaging in 62 survivors (18-35 years) more than 15 years after diagnosis. The prevalence of leukoencephalopathy was 35% in the frontal lobe, 13% in the parietal lobe and 30% in the centrum semiovale ⁴³. Suzuki et al. (2014) similarly investigated the development of PRES in a population of 161 children with hematological malignancies, including two cases of Hodgkin lymphoma ³⁷. The two cases were not diagnosed

with PRES. Given that only PRES patients were summarized in the manuscript, radiographic presentation of white matter lesions alone was not reported.

Third, childhood non-Hodgkin lymphoma (NHL) patients were described in three studies. However, none made any distinction in the used chemotherapy agents ^{12,37,39}. Zierissen et al. (2005) studied twelve NHL patients and showed that six patients developed abnormal MR findings ³⁹. By contrast, none of the fifteen NHL cases studied by Suzuki et al. (2014) did develop PRES ³⁷.

Lastly, Lim et al. (2011) evaluated MR images after a CNS event (not specified which neurological event) in chronic myeloid leukemia, NHL and solid tumors such as osteosarcomas, germ cell tumors and rhabdomyosarcoma. In 6 of these 12 patients (i.e. 50%), MR images were positive for white matter injuries ¹². A more recent study by Sleurs et al. (2019) , solely investigating asymptomatic sarcoma survivors at least 2 years after diagnosis, also demonstrated 27% of survivors showing leukoencephalopathy ⁵⁷. Additionally, a higher prevalence (40%) of white matter lesions was found in patients treated with high dose (HD) MTX IV.

3.2 Neurocognitive outcome of leukoencephalopathy

Since leukoencephalopathy affects the white matter, its possible impact on neurocognitive functioning should not be neglected. Eight out of the 32 studies included objective neurocognitive assessments ^{23,30,31,33,34,40,43,55}.

Compared to population-matched controls ^{30,31,33,34,40,43,55} or population norms ³³, all studies concluded that patients had lower scores on neurocognitive tests or had more neurobehavioral problems. Neurocognitive outcome was mostly evaluated using measures of intelligence, attention, executive functioning and memory. Neurobehavioral problems observed after cancer therapy included problems with working memory; initiation, planning and organizing; memory span; executive functions, fine motor functioning and processing speed ^{30,31,33,34,40,43,55,57}. Only one report described a clear association between higher exposures to IV-MTX and neurocognitive outcomes (executive functioning) in long-term ALL survivors ³⁰.

All reports but two investigated the relationship between leukoencephalopathy and cognition ^{30,31,33,40,43,57}. Duffner and colleagues ³³ reported an association between leukoencephalopathy and poorer performance

on tests of attention and intelligence in a group of ALL survivors 3 years after diagnosis. There were significant differences in specific measures of attention based on presence of leukoencephalopathy, with patients having leukoencephalopathy performing significantly worse on these subtests ($p < 0.05$). Scores more than one standard deviation from the mean of a norm population were considered cognitively impaired. For the different IQ measurements, 64-100% of the cognitively impaired patients presented with leukoencephalopathy. Additionally, Cheung et al (2016) showed ALL survivors with a history of acute leukoencephalopathy displayed more problems in organization and initiation five years after diagnosis (population norms: $T=50$, $SD=10$; adjusted T-scores patients: 52.2–56.2, $p < 0.05$)³⁰. Lastly, Nassar et al. (2017) found significant differences in rates of leukoencephalopathy on MRI between ALL patients divided in a seizure and control cohort during (56 % vs. 13%, $p < .01$) and at the end of therapy (39% vs. 6%, $p = .01$). By contrast, Sabin et al. (2018)³¹ and Kingma et al. (2001)⁴⁰ did not encounter lesion-related outcomes in ALL survivors >5 years after completing therapy. However, Sabin et al. (2018)³¹ did find diffusion-weighted imaging parameters (mean diffusivity) in the genu of the corpus callosum ($p = 0.04$), corona radiata ($p = 0.02$), and superior fronto-occipital fasciculi ($p = 0.02$) to be associated with neurocognitive impairment.

Hodgkin lymphoma survivors showing white matter lesions (53%) also demonstrated a reduced cognitive fluency, more than 15 years after diagnosis compared to population norms ($p = 0.001$)⁴³.

While Koppelmans et al. (2015) did not encounter more leukoencephalopathy in chemotherapy-treated breast cancer patients, they did report a lower than expected cognitive performance or cognitive decline in these survivors, 20 years after ending treatment when compared to age-matched controls ($p < 0.03$; odds ratio 1.79 – 2.25)⁵⁵.

Unfortunately, cognitive outcomes in other types of cancer treated with intensive chemotherapy regimens, i.e. neuroblastoma tumors, bone tumors, soft tissue tumors, ... are not investigated thoroughly yet. However, the increasing attention might lead to more small sample studies. For instance, Sleurs et al. (2019) demonstrated that higher Fazekas levels in childhood sarcoma survivors 9 years after diagnosis was associated with longer reaction times during attention tasks ($p < 0.05$, $F > 2.9$)⁵⁷.

4 DISCUSSION

Our study was the first systematic review to describe the prevalence of chemotherapy-induced leukoencephalopathy in all types of cancer throughout the lifespan of patients. Our review shows a high prevalence of leukoencephalopathy after chemotherapy, up to several years after termination of active treatment. Neurocognitive decline was observed in most of studied patients, and lesioned patients scored lower on cognitive tests.

4.1 Prevalence of leukoencephalopathy

Leukoencephalopathy is a well-known neurological adverse side effect of chemotherapy. Most studies reviewed here (69%) were performed in childhood ALL, which is the most common childhood cancer. This is probably due to the fact that ALL is treated with CNS-directed chemotherapy, resulting in an increased risk of CNS complications. Across all types of cancer, we conclude a large variation in prevalence of leukoencephalopathy in patients with (26-83% of cases) or without (0-87% of cases) an acute CNS event or presentation of PRES (100%).

Since multiple CNS events were often investigated together in studies, it is difficult to disentangle which CNS events has the most detrimental and permanent effects. However, leukoencephalopathy persisted months after stroke(-like) episodes ²⁴, PRES or temporal lobe epilepsy ³⁵, but not in case of acute seizures, affective disturbance or focal neurological deficits ³⁹. These results demonstrate that acute neurologic complications can both co-exist with an acute presentation of leukoencephalopathy (and recovery) or permanent presentation of white matter abnormalities, with possible additional neurotoxicity, such as cerebral small vessel disease. In breast cancer patients for instance, cerebral small vessel disease has been reported, with the absence (or recovery) of white matter lesions ⁵⁵.

The location of white matter hyperintensities varied between studies. Lesions appeared across the entire brain including frontal, parietal and occipital regions that were affected by encephalopathy^{12,24,28,35,39,46,50,53}.

In most of the reported studies, IV- and IT-MTX administration was considered as the most important risk factor for developing leukoencephalopathy. Some authors reported higher rates of leukoencephalopathy in ALL patients who were treated with more intensive MTX treatments (i.e. higher number of cycles including MTX or higher doses of IV-MTX or TIT MTX)^{31,33,36,38,42}. In the study population of Cole et al. (2006) HD-MTX was not included in the treatment protocol, which could explain the lower prevalence of leukoencephalopathy in this specific study³². A threshold effect could explain why other studies did not observe this dose-related prevalence. More specifically, once a specific dose intensity or cumulative dose is reached, the effect of treatment on neurological outcomes might be equal³⁰. Besides such dose-response relationships, the toxic effects of chemotherapeutic agents might be moderated by neurobiological responses to the treatment (e.g. biomarkers of oxidative stress and inflammation), which also affects the severity of white matter changes³⁰. In addition, older age at treatment is an additional risk factor in adult (breast) cancer patients, given the decreased neural integrity and cognitive reserves^{58,59}. To which extent these mechanisms play a role in specific oncological populations or treatments, remains inconclusive. In order to address the patient- and treatment-specific risk factors more specifically, large international databanks, epidemiological and case-control studies are highly recommended, comparing the occurrence and degree of leukoencephalopathy in different treatment arms and across a wide age range.

Cancer treatment could also indirectly lead to the development of leukoencephalopathy. Several studies describe the possible side effect of arterial hypertension, due to a corticosteroid treatment or to renal complications¹³. As a result of a higher blood pressure, endothelial damage of the blood brain barrier can cause capillary hypoperfusion and consequent vasogenic edema. This process has been proposed as candidate mechanism for the pathogenesis for PRES³⁵. However, the exact sequence of such mechanisms remains unclear^{12,13,60}. Furthermore, it needs to be stressed that a rise in blood pressure is not obligatory for the development of PRES¹². Finally, renal complications or acute renal failure were reported in several

studies to coincide with the presence of some or all symptoms of PRES ^{12,13,35}. More specifically, renal complications could delay methotrexate clearance and contribute to neurotoxicity as such ⁶¹.

4.2 Neurocognitive outcome of leukoencephalopathy

Almost all reports described patients with lower scores on neurocognitive tests after treatment with chemotherapy (see Table 2). Most reported problems covered tasks that require working memory, initiation, planning and organizing, memory span, executive functions, fine motor functioning and processing speed ^{30,31,33,34,40,43,55,57}.

While half of the included studies did not find ^{31,34,40} (or did not investigate ⁵⁵) a relationship between cognitive function (during therapy until >5 years after ending chemo) and the presence of leukoencephalopathy, four studies did. Survivors of childhood ALL ^{30,33}, childhood sarcoma ⁵⁷ and Hodgkin lymphoma ⁴³ treated with chemotherapy demonstrated a relationship between more neurobehavioral problems and the presence of leukoencephalopathy when studied 2.6 years ³⁰, >5 years ³³, >9 years ⁵⁷ and >15 years after therapy ⁴³. This suggests the presence of leukoencephalopathy, or concomitant neurological events, to be indicative for risk of long-term cognitive functioning. In non-cancer populations, neurological insults (and their resulting brain damage) are known to impact cognition; epilepsy (inducing abnormal electrophysiological brain activity), loss of blood supply (inducing ischemic damage), stroke (with vascular damage, microbleeds and possible necrosis)^{16–19}. In older individuals, this interplay of cardiovascular diseases, CNS pathology and cognitive impairment becomes even more apparent ⁶². Interestingly, only Nassar et al. (2017) ³⁴ investigated possible CNS events as indicator for cognitive profiles, by dividing patients based on presentation of seizures during therapy. As expected, patients with a history of seizures scored lower on several cognitive tests. Still, future studies are required to unravel the role of CNS events in a patients' susceptibility for cognitive decline, since patients with different neurological profiles (history of stroke, small vessel disease or epilepsy) are also expected to have different cognitive profiles ^{16–19,62}.

An important consideration, however, remains the discordance between symptoms (acute or long-term) and neuroimaging findings. Cases have been described in which patients did not have any complaints

despite positive MR images^{24,33,35}. Conversely, a number of patients presented with persistent neurological or cognitive symptoms, despite normal radiological findings. This suggests that leukoencephalopathy and cognitive outcomes do not have a one-to-one relationship, but multiple treatment- and patient-specific factors can play an additional role³³.

For example, since Hodgkin patients are more often diagnosed during adolescence (i.e. later ages than ALL), the impact on cognitive scores which develop earlier might be limited, while education and employment can be affected later in life, being under-reported to date⁴³. According to Parasole et al. (2010), PRES will persist in about 10% of patients, with potentially severe or even fatal neurological disorders³⁵. Therefore, a prolonged neurological follow-up time of at least several years is recommended. Unfortunately, the long-term impact of chemotherapy-induced leukoencephalopathy on the development of neurodegenerative diseases at an older age is under-investigated. For adult cancer survivors, a subgroup of elder solid tumor survivors consistently reported difficulties in daily life due to a change in cognitive functioning after treatment for cancer^{9,59,63}. How this is associated with the presence of leukoencephalopathy, remains to be unraveled in future research.

The cognitive results suggest that white matter changes during therapy may disrupt long-term brain development, possibly due to altered white matter integrity⁶⁴. Additionally, due to such white matter lesions, the structural connectivity between grey matter areas can be affected, which can explain the observed cognitive deficits after chemotherapy⁶⁵. However, cognitive impairment after chemotherapy is not only caused by anti-cancer drugs, but rather results from complex interactions between patient-specific susceptibility factors (age, cognitive reserve, genetics), tumor-related factors (paraneoplastic, endocrine), non-specific treatments (steroids, psychotropic drugs, anticonvulsants) and specific treatments (surgery, radiotherapy, and chemotherapy)⁸. The frequent use of corticosteroids (i.e. during breast cancer, ALL, NHL and HL chemotherapy treatment) may possibly be a contributing factor in the development of neurocognitive disturbance⁴⁰.

Given that not all studies demonstrated significant associations between leukoencephalopathy and cognitive decline, leukoencephalopathy alone appears to be insufficient to explain the cognitive decline that can be observed after cancer treatment⁹. Alternatively, other psychological domains or more subtle

deficits that are associated with acute leukoencephalopathy might not have been adequately measured by the neurocognitive tests used for the abovementioned studies. Additionally, conventional structural MRI years after diagnosis may not adequately predict the lasting neurocognitive effects of acute white matter injury, nor does it quantify microstructural changes due to injury of the myelin or axons. Other imaging approaches, such as diffusion-weighted MRI or myelin water imaging, and estimations of structural connectivity should be considered in subsequent studies to advance our understanding ⁶⁶. For example, multiple studies investigating the so-called “chemobrain” in cancer patients report cognitive decline after treatment with chemotherapy to co-exist with white matter differences (e.g. based on diffusion, myelin water and structural imaging), but did not necessarily look at the presence of white matter lesions ^{21,59,67,68}. Future research unravelling a relationship of presence of leukoencephalopathy in all cancer populations and cognitive decline remains pressing to further define vulnerable populations.

4.3 Methodological considerations and limitations

Magnetic resonance images have a fundamental role in the diagnosis and follow-up of leukoencephalopathy in cancer patients. Using T2-weighted or FLAIR scans, radiologists are able to distinguish between white matter lesions and hemorrhagic accidents. For this purpose, the low tissue contrast of CT scans makes them suboptimal, except when large vascular lesions are to be observed ³⁵. More advanced techniques increasingly receive attention in the diagnostic field, since they are able to improve insights into the development and follow-up of brain damage. For instance, one study investigated diffusion tensor imaging (DTI) parameters, which appeared associated with neurocognitive performance in chemotherapy-treated ALL survivors ³¹. Techniques such as functional MR imaging, advanced DWI models, MR spectroscopy or positron emission tomography may provide new opportunities to understand changes in neural signaling and brain functioning ⁴⁰. Additionally, new biomarkers will play an important role in future diagnostics and treatment of cancer patients. Firstly, there may be a depletion of folate in the CNS fluid after administration of MTX (both monotherapy and TIT), resulting in an accumulation of phosphorylated tau protein in CNS fluid and an increase of homocysteine in peripheral blood due to decreased remethylation ^{32,42}. Secondly, neuroinflammation caused by cytokine and interleukin production

may cause vascular damage with vasogenic edema, promoting the development of white matter lesions ³⁷. Thirdly, diagnosis-related emotional stress can have a negative influence on the development of leukoencephalopathy and cognitive problems ^{8,69}. Lastly, the detection of polymorphisms in genes responsible for neurogenesis could help clinicians to predict the patient's susceptibility to leukoencephalopathy in the future ^{29,70}. The combination of more advanced neuroimaging techniques, detection of biomarkers, identification of genes involving neurogenesis or neuronal plasticity and a universal cognitive assessment protocol, should provide more clarity about long-term effects of leukoencephalopathy in cancer patients in the future. By implementing global evaluation of patients, better follow-up and rehabilitation programs, quality of life of the growing number of survivors of cancer can be enhanced.

The large variability in leukoencephalopathy ratios across studies might partly be explained by the heterogeneity in the lesion rating scales and in sample sizes. As a consequence, it was impossible to standardize the definition or grade of leukoencephalopathy. Therefore, it will become important to investigate larger international databases which provide clearly defined criteria or ratings for leukoencephalopathy (e.g. FAERS, VigiBase, Eudravigilance, EORTC). These databases also contain more recent chemotherapeutic protocols in contrast to survivor studies included in this literature review. Secondly, most studies reported childhood ALL. Data were only minimally available for adult patients, other chemotherapeutics than MTX, other cancers than leukemia, and older ages. However, because of the large group of ALL patients included in this study, the treatment is broadly uniform allowing fair comparisons for this cancer group.

The most important implication resulting from this review is to bring awareness to clinical personnel and neuroscientists, in order to provide information to cancer patients on expected neurotoxic side effects. Although the aggressiveness of the disease and survival of patients is still the first concern of the physician, knowledge on expected sequelae after treatment can only improve clinical guidance of patients and future research improving this.

5 CONCLUSION

The central nervous system is very susceptible to complications of cancer and its systemic treatment. With the exception of childhood ALL studies, there is a lack of research concerning the prevalence of leukoencephalopathy in patients treated for other cancers, receiving other chemotherapeutics and over a spectrum of ages. Sufficiently large, prospective follow-up studies will be necessary to determine the prevalence and long-term clinical neurocognitive effects of leukoencephalopathy in cancer patients, as well as analyzing international databases for observable adverse drug effects. Earlier identification using more advanced neuroimaging techniques, detailed CNS event administration, and neurological biomarkers may allow healthcare professionals to define risk groups in more detail, which will guide the physician in patient-tailored treatment decisions. Finally, intervention techniques and preventive measures against CNS-related side effects should receive more attention in future studies.

Figure 1. Flow diagram of the systemic review.

Figure 2. Prevalence of leukoencephalopathy on magnetic resonance images during or after cancer chemotherapy.

ALL: Acute Lymphoblastic Leukemia, CNS: central nervous system, NA: no data available about timing of MR imaging, PRES: posterior reversible encephalopathy syndrome

Table 1. Overview of included studies

Author (year)	Type cancer	Current age (mean/median years)	# patients	Chemotherapeutical			MR sequence	Timing MR scan	Regions	Prevalence
				IT	HD-MTX	Other				
Hertzberg et al. (1997)	ALL	15	39	Mono MTX	2 g/m2	NA	T2, PD	7 years after diagnosis	NA	39%
Mahoney et al. (1998)	ALL	Children	543	1x TIT and 12x IT MTX	1 g/m2	A: VCR, L-ASP, prednisolone + IM MTX	T2	after CNS event (seizure)	NA	8% of total population presented with CNS event (A: 8%, B: 4%, C: 11%)
			354		/	B: VCR, L-ASP, prednisolone + Oral MTX + IM MTX, 6-MP				B:15% if CNS event
			321		1 g/m2	C: VCR, L-ASP, prednisolone + IM MTX, 6-MP (dose less than regimen A)				C:77% if CNS event
Choi et al. (2001)	Breast cancer	46 ± 10	6	/	/	5-FU, CPM, epirubicin, carmofur	T1, T2	NA	periventricular	100% *
Kingma et al. (2001)	ALL	11	45	mono MTX + prednisolone	2 g/m2	oral MTX, cytarabine arabinoside	NA	10 years after diagnosis	NA	38% (50% definitely abnormal, 50% probably abnormal)
Rollins et al. (2004)	ALL	14 ± 1	194	Mono MTX	After IT (IV MTX)	DEXA, VCR, L-ASP, DNR, 6-MP, Ara-C, CPM and/or oral MTX	T1, T2, FLAIR, ADC map	within 17 – 23 hours after CNS event, 2 – 39 months later (stroke-like episode)	cerebral atrophy and callosal splenium - frontal and parietal lobe	3% of total population presented with CNS event, 83% if CNS event (from those, 20% at follow-up)
Reddick et al. (2005)	ALL	5	45	TIT	2.5 g/m2 or 5 g/m2	/	T1, T2, FLAIR	week 6, 7, 31 and 120 after start therapy	NA	76% (87% in high risk, 67% in low risk) ³
Ziereisen et al. (2006)	ALL	Children	90	TIT or mono MTX	5 g/m2	VCR, PRED or DEXA, DNR, L-ASP, CMP, Ara-C, 6-MP or 6-TG	T1, T2, FLAIR, ADC map (6 patients)	after therapy, after relapse and after CNS event (seizure, affective disturbance or focal neurological deficits)	frontal, parietal, occipital, supratentorial ctx, cerebellar ctx and thalamus	17% (0% after 1 – 7 months)
Baehring et al. (2008)	ALL or large cell lymphoma	14 ± 3	19	mono MTX	NA	NA	T2, FLAIR, DWI, ADC map	NA	NA	100% *
	Breast cancer	44 ± 5	4	NA		capecitabine				
	Cancer of (sigmoid-) colon, nasopharynx, pancreas	54 ± 22	4	NA		capecitabine, 5-FU, carmofur				
Lucchini et al. (2008)	ALL	5	9	NA	NA	NA	T2, FLAIR	Within 24 hours of CNS event	(sub)cortical in occipital, frontal, parietal and temporal areas	100% *

Cole et al. (2009)	ALL	Children	36	TIT	/	MTX or aminopterin per os	T1, T2, FLAIR	45 days after therapy	periventricular or subcortical white matter lesions	25%
Parasole et al. (2010)	ALL	6	253	mono MTX	none, 2 g/m2 or 5 g/m2	DEXA, VCR, DNR, L-ASP, VDS, IFO, 6-MP	T1, T2, FLAIR	at time of CNS event and 6 months after event (PRES, stroke, temporal lobe epilepsy and other)	frontal, parietal, occipital, hippocampal and semioval nucleus areas	4% of total population presented with CNS event, 37% if CNS event (from those, 36% after 6 months)
Belaramani et al. (2011)	ALL	7	4	NA	NA	MTX, DEXA, DXR, VCR, L-ASP, cytarabine	NA	within 1 week after event (seizure)	NA	100% *
	Pituitary germ cell tumor	7	1	/	/	BEP		NA		
Lim et al. (2011)	ALL, AML, CML, NHL, solid tumors	10	12	NA	NA	NA	FLAIR	after CNS event (definition not specified)	frontal, parietal, temporal, occipital	50%
Krull et al. (2012)	HL	42 ± 5	62	/	/	doxorubicin and/or anthracyclines and/or bleomycin	T1, T2, FLAIR, PD	> 15 years after diagnosis	frontal and parietal lobe and semioval nucleus	35% frontal, 13% parietal, 30% semioval nucleus
Bhojwani et al. (2014)	ALL	Children	369	TIT	2.5 g/m2 (low risk) or 5 g/m2 (high risk)	oral MTX, DEXA, VCR, CPM or cytarabine	T1, T2, FLAIR, PD	postinduction, 1 week after re-induction (cons.), 48 weeks after cont., 120 weeks after cont., during or after CNS event (seizure, stroke, behavioral changes, aphasia)	NA	23% (persisted in 74% of asymptomatic and 58% of symptomatic patients until end of therapy)
Carson et al. (2014)	HL	49 ± 2	3	/	/	BV, DXR, bleomycin, vinblastine, dacarbazine, IFO, carboplatine, ETO, methyl-PRED, cytarabine, cisplatin	NA	NA	NA	100% *
	Primary cutaneous anaplastic large cell lymphoma	38	1			BV, topical CS, MTX, bexarotene, IFN-alpha, vorinostat				
	Transformed mycosis fungoides	72	1			BV, topical CS, phototherapy, IFN-alpha, bexarotene, localized RT				
Duffner et al. (2014)	ALL	12	31	TIT and mono MTX	After IT (1a)	MP + oral MTX	T1, T2, FLAIR	> 2.6 years following end of treatment	centrum semiovale, periventricular white matter	68% mild, 3% moderate, 2% severe (2)
			23	TIT and mono MTX	Concurrent with IT (1b)	/				
Fitzgerald et al. (2014)	MM	60	12	/	/	bortezomib, DXR, thalidomide, carmustine, ETO, cytarabine, melphalan, cisplatin, (tem)sirolimus, DEXA, rituximab, adriamycin, carfilzomib or CPM	NA	NA	NA	100% *
	Other solid tumors		8			wide range of different chemotherapeutics				

Suzuki et al. (2014)	HL	5	2	NA	NA	steroids, VCR, CPM, THP-adriamycin, L-ASP, actinomycin D, MTX, cytarabine	T2, FLAIR	NA	NA	4%
	AML		36	NA	NA	cytarabine, ETO, mitoxantrone				
	ALL		108	/	2 g/m2 or 5 g/m2	oral MTX, DEXA, VCR, 6-MP				
	NHL		15	NA	NA	steroids, VCR, CPM, THP-adriamycin, L-ASP, actinomycin D, MTX, cytarabine				
Baytan et al. (2015)	ALL	7	323	TIT and mono MTX	5 g/m2	PRED, VCR, DNR, L-ASP, cytarabine, CPM, IFO, DEXA, ETO	T2, FLAIR	after CNS event (convulsion, blindness, aphasia, headache or facial nerve paralysis)	parietal and occipital lobe	6% of total population presented with CNS event, 83% if CNS event
Koppelmans et al. (2015)	Breast cancer	64 ± 7	187	/	/	CMP, oral MTX and 5-fluorouracil	T1, T2 GRE, FLAIR	> 20 years after end of treatment	NA	No difference in white matter lesions, cortical or lacunar infarctions and lobar microbleeds. More infratentorial microbleeds.
Li et al. (2015)	ALL, lymphoma	7	8	NA	NA	NA	T1, T2	NA	parietal, occipital, frontal, temporal regions or combinations	100% (from those, 20% after 2 weeks) *
Cheung et al. (2016)	ALL	14 ± 4	156	TIT	2.5 g/m2 (low risk) or 5 g/m2 (standard or high risk)	DEXA, L-ASP, CPM, DNR, DXR, VCR, mercaptopurine	T2, FLAIR, DWI	week 6-7 (ind.), week 1 after re-ind. (cons.), week 1 after re-ind. (cons.), week 48 (after cont.), week 120 (at end of therapy), after 5 years	NA	27% (from those, 78% after 5 years)
Kamiya-Matsuoka et al. (2016)	Leukemia and others	52	69	NA	NA	tacrolimus, DXR, VCR, DEXA, different monoclonal antibodies	T1, T2, FLAIR, DWI, ADC map	NA	parietal and occipital lobes	100% (from those, 49% after 8 weeks) *
Tang et al. (2016)	ALL	9 ± 2	11	NA	NA	MTX, cytarabine, DNR, VCR, L-ASP, prednisolone	T1, T2, FLAIR	0, 1, 3, 6 and 12 months	parietal and occipital lobe	100% *
Tsujimoto et al. (2016)	ALL	5	25	TIT	< 5 g/m2	Oral MTX	T1, T2, FLAIR	Before start of therapy and at time of CNS event (seizure, delirium, stroke-like episode)	NA	32%
			31		5 g/m2	/				42%
Kamiya-Matsuoka et al. (2017)	Primary hematological and solid tumor	50 ± 20	46	/	/	CPM, VCR, DXR (most used)	T1, T2, FLAIR, DWI, ADC map	NA	NA	100% *
Menning et al. (2017)	Breast cancer	51 ± 7	26	NA	NA	doxorubicin, cyclophosphamide, 5-fluorouracil, epirubicin, cyclophosphamide	T1, FLAIR, DWI	after surgery, 6 months after ending therapy	NA	0%

Nassar et al. (2017)	ALL	8 ± 5	57	TIT	2.5 g/m2 (low risk) or 5 g/m2 (standard and high risk)	MTX, mercaptopurine, VCR, DEXA	T1, T2, FLAIR	week 5 after ind. - week 7 after cons. - week 120 at end of therapy	NA	week 5,7,120: 0%, 56%, 39% in high risk vs 0%, 13%, 6% in low risk
Khan et al. (2018)	NHL, ALL, HL, Ewing sarcoma	7	19	TIT (n=16)	Oral MTX	carboplatin, CPM, daunorubicin, DEXA, etoposide, ifosfamide, vincristine	T2, FLAIR, T2 GRE, DWI and T1 pre- and postcontrast	At time of CNS event (seizures, visual loss or altered mental state)	bilateral symmetrical subcortical white matter involvement of the occipital and parietal lobes	100% (1.6% in total population of children with leukemia and 0.28% in those with solid tumors) *
Sabin et al. (2018)	ALL	14 ± 5	173	TIT	2.5 g/m2 (low risk) or 5 g/m2 (standard and high risk)	oral MTX, DEXA, cytarabine	T1, T2, FLAIR, PD, DWI	during therapy and >5 years after diagnosis	supra- or periventricular white matter	24% (from those, 79% after 5 years)
Sleurs et al. (2019)	Ewing, (non-) Rhabdomyosarcoma, osteosarcoma	21	34	/	0-144g/m2	alkylating agents (ifosfamide, cyclophosphamide); doxorubicin, cisplatin	FLAIR	9 years after diagnosis	NA	27%

* these studies only included patients based on clinical presentation of leukoencephalopathy and thus have a prevalence of 100%.

(1) 1a: children received standard MTX (20 mg/m² IM) weekly, 1b: received divided dose MTX (25 mg/m² PO Q 6 hours X 4 every other week)

(2) Mild: mild diffuse T2 hyperintensities in the periventricular white matter/centrum semiovale; Moderate: moderate T2 hyperintensities involving confluent deep white matter from the frontal horns to the trigone, which may extend to the subcortical U-fibers.

(3) Low risk: patients in which the plasma steady-state concentration of MTX was 33 µmol/L; High risk: patients in which the plasma steady-state concentration of MTX was 65 µmol/L.

ADC: apparent diffusion coefficient; ALL: acute lymphoblastic leukemia; Ara-C: cytosine arabinoside; B-ALL: B-lymphocyte ALL; BEP: triple chemotherapy with bleomycin, etoposide and cisplatin; BV: brentuximab vedotin (monoclonal antibody targeting CD30-positive cells); cons.: consolidation; cont.: continuation; CNS: central nerve system; CPM: cyclophosphamide; CS: corticosteroids; ctx: cortex; DEXA: dexamethasone; diff. difference; DNR: daunorubicin; DWI: diffusion weighted imaging; DTI: diffusion tensor imaging; DXR: doxorubicin; ETO: etoposide; FLAIR: fluid attenuated inversion recovery; HD-MTX: High-dose methotrexate (> 0,5 g/m²); HL: Hodgkin lymphoma; IFN- α: interferon alpha; IFO: ifosfamide; ind.: induction; IM: intramuscular; IT: Intrathecal; L-ASP: L-asparaginase; MM: multiple myeloma; MP: mercaptopurine; MR: magnetic resonance; MTX: methotrexate; NA: data not available; NHL: Non-Hodgkin lymphoma; PD: proton density weighted sequence; PRED: prednisolone; RT: radiotherapy; T-ALL: T-lymphocyte ALL; TIT: triple intrathecal therapy with MTX, cytarabine and prednisolone; T2 GRE: T2-weighted gradient recalled echo accelerated MR images; VCR: vincristine; VDS: vindesine; 5-FU: 5-fluorouracil; 6-MP: 6-mercaptopurine; 6-TG: 6-thioguanine

Table 2. Overview of included studies evaluating neurocognition/neurobehavior

Autor (year)	Cancer type	Current age (mean/median years)	# patients	Groups	Timing NPA	Function measures	Results	Correlation with MRI leukoencephalopathy?
Kingma et al. (2001)	ALL	5	45	17 chemo vs 28 chemo+CR vs 225 age-matched controls	3-6 months after cessation of chemo and 5 years later	intelligence, attention, memory, visual motor integration, fine motor functioning	After 5 years: chemo patients scored lower than controls on memory (M= 9.5 vs 10.0) and fine motor functioning (M= 9.1 vs 10.0). Chemo+CR scored lower than chemo patients on intelligence, attention and fine motor functioning. School levels differed between chemo+CR patients and siblings, but not between chemo-only patients and siblings.	No significant associations were found between MRI outcome and test scores, school placement, or education level in either group. More abnormal MRI findings in chemo+CR than chemo only (63% vs 38%).
Krull et al. (2012)	Hodgkin lymphoma	42 ± 5	62	chemo+TR vs norms	> 15 years after diagnosis	intelligence, attention, memory, processing speed and executive functioning	Compared to published norms, 12%-46% of patients showed cognitive impairments; with lower performance on sustained attention, short-term-, long-term- and working memory, naming speed and cognitive fluency (% impaired defined as 1SD below the normative mean).	Lower cognitive fluency was demonstrated in survivors with leukoencephalopathy (M Z=-0.92; SD=0.97) in the centrum semiovale compared with those without leukoencephalopathy (M Z=-0.05; SD=0.81).
Duffner et al. (2014)	ALL	13	52	chemo vs norms	> 2.6 years after end of treatment	intelligence, attention and concentration, memory, processing speed and executive functioning	Compared to published norms, 40% of patients showed deficits on intelligence scores (i.e. VIQ or PIQ scores <85) and >16% of patients had attention problems (% impaired defined as 1SD below the normative mean).	The majority (75% - 100%) of children treated with chemotherapy who scored > 1 SD worse than the normative mean on areas of specific neurocognitive function also had leukoencephalopathy.
Koppelmans et al. (2015)	Breast cancer	64 ± 7	187	chemo+ radiotherapy vs 374 age-matched controls	> 20 years after end of treatment	memory, word fluency, processing speed, executive functioning, visuospatial ability and manual dexterity	Previously published ⁴ : women exposed to chemotherapy performed significantly worse than the reference group on cognitive tests of immediate and delayed verbal memory processing speed, executive functioning and psychomotor speed (-0.40<Z<-0.05).	Association with cognition was not investigated. They did find that patients with cerebral microbleeds in deep or infratentorial regions -but not with strictly lobar cerebral microbleeds- performed worse than reference participants on tests of verbal memory and processing speed (odds ratio 1.79 – 2.25).
Cheung et al. (2016)	ALL	19 ± 4	190	190 chemo vs norms	> 5 years after diagnosis	intelligence, attention, memory, processing speed, executive functioning and fine motor dexterity	Compared to published norms, survivors were 1.6 to 3.2 times more likely to demonstrate problems across all neurobehavioral domains and demonstrated more parent-reported problems with working memory, organization, initiation and planning.	Survivors with a history of acute leukoencephalopathy displayed more neurobehavioral problems than survivors with no history on parent-reported organization (adjusted T-score 56.2 vs 52.2) and initiation (55.5 vs 52.1) (norms T=50, SD=10), while no difference was observed for neurocognitive performance.
Nassar et al. (2017)	ALL	8 ± 5	57	19 chemo on-therapy seizure children vs 38 chemo non-seizure children vs norms	week 6 induction (initial assessment), end of therapy (week 120 continuation) and two years post therapy completion	intelligence, attention, memory, processing speed and academic skills	Compared to the no-seizure patients, the seizure group performed worse on attention (M= 79.43 vs 101.17), working memory tasks (M= 6.00 vs 10.04), processing speed deficits (M= 88.57 vs 103.92) and overall intelligence (M= 88.92 vs 101).	Association with cognition was not investigated. They did find significant differences in rate of leukoencephalopathy on MRI between the seizure and the control cohort groups at week 7 (56% vs 13%) and at the end of therapy (39% vs 6%)
Sabin et al. (2018)	ALL	14 ± 5	173	chemo vs norms	> 5 years after diagnosis	intelligence, attention, memory, processing speed, executive functioning and fine motor dexterity	Compared to published norms, 10%-48% of patients showed cognitive impairments; with lower scores on measures of executive function (0.20<Z<-0.53), memory (Z=-0.42), processing speed (-0.40<Z<-1.29) and global intelligence (Z=-0.14) (% impaired defined as a score < 10 th percentile of the age-adjusted Z score)	Association with cognition was not found. They did find DTI parameters (mean diffusivity) in the genu of the corpus callosum, corona radiata, and superior fronto-occipital fasciculi to be associated with neurocognitive impairment.

Sleurs et al. (2019)	Ewing-, (non-) rhabdomyo- and osteosarcoma	21	34	chemo vs 34 controls	> 2 years after diagnosis	intelligence, attention and verbal and visual memory	Compared to controls, patients showed lower quality of life (M= 1645 vs 1913), working memory (M= 97.94 vs 109.12), processing speed (M= 99.45 vs 107.38) and visual memory.	Leukoencephalopathy prevalence was related to attentional processing speed.
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ALL: acute lymphoblastic leukemia, CR: cranial radiation, DTI: Diffusion Tensor Imaging, M: mean, non-B-ALL: non-B-lymphocyte ALL, TR: thoracic radiation

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