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Original Research

Clinical characteristics of subsequent histologically confirmed meningiomas in long-term childhood cancer survivors: A Dutch LATER study

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KEYWORDS
Subsequent meningioma;
Childhood adolescent young adult (CAYA) cancer survivors;
Cranial radiotherapy

Abstract ***Background:*** Meningiomas are the most frequent brain tumours occurring after pediatric cranial radiotherapy (CrRT). Data on course of disease, to inform clinical management of meningiomas, are sparse. This study reports the clinical characteristics of histologically confirmed meningiomas in childhood cancer survivors (CCS) in the Netherlands.
Methods: In total, 6015 CCS from the Dutch Long-Term Effects After Childhood Cancer (LATER) cohort were eligible, including 1551 with prior CrRT. These CCS were diagnosed with cancer age <18 y (between 1963 and 2002) and are not subject to brain tumour screening. We identified histologically confirmed meningiomas by record linkage with the Dutch Pathology Registry (PALGA; 1991–2018), and in the Dutch LATER registry. We extracted details regarding diagnosis, treatment, and follow-up from medical records.
Results: We described 93 CCS with meningioma, of whom 89 (95.7%) were treated with CrRT (5.7% of 1551 with prior CrRT; OR = 68). Median age at diagnosis was 31.8 y (range: 13.2–50.5). Thirty survivors (32.3%) had synchronous meningiomas; 84 (90.3%) presented with symptoms. Only 16.1% of meningioma was detected at late effects clinics. Over time, all survivors had surgery; one-third also received radiotherapy. During follow-up 38 (40.9%), survivors developed new meningiomas, 22(23.7%) recurrences and at least four died due to the meningioma.
Conclusions: Histologically confirmed meningiomas after childhood cancer are mostly diagnosed with symptoms and not during routine follow-up at late effects clinics. The meningiomas occur at a median of 20–25 y younger age than incidental meningiomas, are frequently multiple and recurrence after treatment is high. It is crucial to inform CCS and healthcare providers about risk and symptoms of subsequent meningiomas.

1. Introduction

Advanced treatment regimens have led to a rise in the number of childhood cancer survivors (CCSs). Concomitantly, an increased number of CCS is at risk of late adverse events after treatment. A concern among CCS treated with cranial radiotherapy (CrRT) is the manifestation of subsequent neoplasms in the central nervous system (CNS). The most frequent subsequent benign neoplasms in this context are meningiomas [1–3].

Although the vast majority of meningiomas (97–99% [4,5]) are histologically classified as low-grade, they can increase morbidity and severely impact daily life [6], with symptoms including seizures [7], visual changes, loss of hearing or smell, mental status changes, memory loss, extremity weakness, or severe headaches [8–11]. In the general population, meningioma incidence increases with age (most cases diagnosed > age 50 years) [8,9,12,13] and the male:female ratio is 1:2 to 3 [8,12]. The overall survival 4 to 5 years after treatment for benign, atypical, and malignant meningiomas are 100%, 59–83% and 0–59%, respectively [13]. In CT and MRI series, synchronous meningiomas are found in 1–10% [14–17].

Some studies suggest that radiation-induced meningiomas may be more aggressive than meningioma in general, including a higher likelihood to be atypical or malignant meningiomas, and with a higher tendency to be multiple, and to recur [18–21]. In CCS, subsequent low-grade meningiomas have a prognosis with 5-year survival rates exceeding 80%, while patients with high-grade meningiomas (WHO grade III) have a worse prognosis with a 5-year survival rate of 57.3% [6,22].

CrRT is the most important risk factor for a subsequent meningioma among CCS, in particular after doses of more than 18 Gy [1,3,6,23–25]. In a previous study of the Dutch LATER cohort, a population not subject to systematic surveillance for new brain tumours, we found that 1 in 8 CCS developed a benign meningioma 40 years after treatment with CrRT [24]. An MRI screening study detected meningiomas in more than 20% of asymptomatic childhood leukaemia survivors treated with CrRT [18].

Decision-making regarding management of subsequent meningiomas in CCS may differ from that in the general population owing to several circumstances. More aggressive meningiomas might require a different treatment policy. In contrast, in some situations, a less aggressive management strategy may be appropriate among CCS. Previous exposure to CrRT might lead to a reluctancy to reirradiate. Targeted radiologic surveillance of asymptomatic CCS with a history of CrRT has been suggested in research [18] and clinical settings [26]. Moreover, CCS with a history of a brain tumour and/or a history of CrRT are more likely to receive diagnostic

or follow-up brain imaging in view of primary tumour follow-up or other neurologic sequelae. In these situations, generally small and asymptomatic tumours are found among young individuals, which raise a different set of management questions.

Our recent international survey among healthcare professionals showed that the choice of treating thus detected subsequent asymptomatic meningioma with surgery or radiation therapy is largely driven by clinical characteristics, of which location, size and growth are the most important [27]. There are no specific guidelines for management of meningiomas in CCS; however it is likely that management of subsequent symptomatic meningiomas in CCS is also influenced by clinical characteristics. Until now, limited information is available regarding the clinical characteristics, course of disease and treatment of subsequent meningiomas in CCS [6]. The present study aims to describe these characteristics for a Dutch cohort of CCS with histologically confirmed subsequent meningiomas.

2. Materials and methods

2.1. Design and eligible study population

This retrospective clinical case-series describes histologically confirmed subsequent meningiomas diagnosed in CCS from the multi-center Dutch Long-Term Effects After Childhood Cancer (LATER) cohort. The source cohort (n = 6165) includes all CCS who survived at least five years after diagnosis. They were diagnosed before the age of 18 years and treated in a pediatric oncology center in the Netherlands between January 1 1963 and December 31 2001. The methodology and study design of the Dutch LATER study have been described elsewhere [28]. Information concerning diagnosis, treatment and clinical course of the primary childhood cancer was obtained from the Dutch LATER registry. We included CCS with a subsequent meningioma diagnosed during 1991–2018.

2.2. Ascertainment of meningiomas

In the Netherlands, there is no active surveillance for brain tumours among asymptomatic CCS with a history of CrRT. We confirmed histological diagnosis in two ways:

Our main source was linkage of the Dutch LATER cohort with the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) [29]. PALGA contains excerpts of all Dutch pathology reports since 1991. A previous linkage of the Dutch LATER cohort with PALGA (described in detail elsewhere [24]) was updated through July 18, 2018. We excluded cohort members who declined use of healthcare data (n = 150) and those who declined approval for record linkages (n = 876). The linkage was based on the first eight letters of the family name, date of birth and sex. The search included all meningiomas, both benign and malignant, in the PALGA database 1991–2018 [30].

Further cases were identified from subsequent tumours reported to the Dutch LATER registry, based on information from medical records. For this study 6015 CCS were eligible, including 1551 survivors treated with CrRT.

We excluded meningioma cases when the tumour was not surgically resected or in case clinical information about meningioma diagnosis, treatment and follow-up were unavailable. The flow chart showing the inclusion of the survivors with meningioma for this case-series is available in Appendix A.

2.3. Identification of the clinical characteristics

Medical records with pathology reports, treatment reports and letters documenting follow-up visits at the late effects' outpatient clinics, were retrospectively reviewed in six academic medical centers. A case report form was designed for this study to capture information of interest. We registered information on meningioma diagnosis, size, location, Simpson grade, WHO grade, follow-up and cause of death. If a patient had multiple meningiomas or recurrences, we reviewed characteristics of the meningioma that was treated first. We considered a period of more than six months after radiologic diagnosis without treatment as a watchful waiting policy. We collected information about treatment of the meningioma (including timing of first surgery and the first period of radiation therapy), recurrences, and development of new meningiomas. Progression was defined as the development of recurrent meningioma (at the same location of the first meningioma) or development of new meningiomas (on different locations from the first meningioma). We based our conclusions regarding 'progression' on the imaging reports. Synchronous meningiomas were distinguished as two or more meningiomas identified simultaneously at first presentation, whereas metachronous meningiomas represent the identification of multiple meningiomas during follow-up after diagnosis of the first meningioma. Data from medical records were registered in Castor Electronic Data Capture [31].

2.4. Statistics

We used descriptive statistics to describe the diagnostic pathway, characteristics of the meningioma at diagnosis,

course of disease, and treatment of the meningioma. Mean and standard deviations (SDs) or counts and percentages were used for normally distributed data and the median and range for data with skewed distributions. Cause-specific survival time was calculated from the time of histologic diagnosis of the meningioma to time of death or to the last date of follow-up, with death due to other causes as competing risk. With univariable and multivariable Cox proportional hazard models we assessed explanatory factors for survival rates concerning meningioma-related deaths. The model included sex, age at histological confirmation of the meningioma and multiplicity at diagnosis. A factor with a P value ≤ 0.05 was considered significant. Analyses were carried out with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp. [32]) and R (version 3.5.1; The R Foundation for Statistical Computing, Vienna, Austria).

2.5. Ethics

Ethical approval was not required as per the Medical Research Involving Human Subjects Act because only retrospective care data were used. In accordance with the Dutch law, survivors who opposed use of their healthcare data for research purposes were excluded from the eligible study cohort (n = 150).

3. Results

Linkage with PALGA yielded 102 potentially eligible cases of subsequent meningiomas diagnosed between January 01, 1991 and July 18, 2018 (Appendix A). In addition, we found six survivors in the Dutch LATER registry with a subsequent meningioma which was surgically removed. Another six cases had a radiologically suspected meningioma without surgery up to the study ascertainment period, and were not included in this series. Fifteen cases of meningioma were excluded because of missing information on meningioma diagnosis, treatment and follow-up. The analysis sample in this study therefore includes 93 eligible cases with ≥1 histologically confirmed meningioma (1.5% of n = 6015).

3.1. Baseline characteristics

Table 1 gives a summary of the patient characteristics. Subsequent meningiomas occurred in 49 women and 44 men. The majority of survivors (76.0%) were diagnosed with a pediatric cancer at an age of younger than 10 years, with a median age of 5.3 years. Most meningiomas occurred after childhood leukaemia (n = 57) and after CNS-tumours (n = 25). Ninety-two were diagnosed with a cranial meningioma and 1 had a spinal meningioma. Four survivors had a genetic disorder of neurofibromatosis type 1, neurofibromatosis type 2 or Gorlin syndrome. Eighty-nine patients (95.7%) had CrRT in the past (5.8% of 1551 CCS with prior CrRT, OR = 68) and 87.0% received a dose of ≥20 Gy. Four patients did not have prior CrRT (n = 4); however one of them developed a spinal meningioma after previous abdominal/pelvic and spinal radiotherapy for a nephroblastoma.

3.2. Diagnostic characteristics meningioma

Table 2 shows the diagnostic characteristics of survivors with subsequent meningiomas. The average time between childhood cancer diagnosis and radiologic diagnosis of the subsequent meningioma was 25.2 years (SD: 7.7). We observed that in 15 CCS (19.2%), the radiologic diagnosis was made before the age of 25 years (Appendix B) (median: 31.8, range: 13.2–50.5, Table 2). A graphical representation of time after diagnosis with childhood cancer versus number of survivors with meningioma is available in Appendix C.

The majority of meningioma cases presented with clinical symptoms (90.3%), of which headaches or feeling of pressure in the head (48.3%) were most common. Among a large variety of settings, the most frequent mode of detection was after a visit at the general practitioner (19.4%), followed by a visit to a late effects clinic (16.1%). In some cases (n = 9, 9.7%), the meningioma was an incidental finding during imaging for other medical reasons, such as trauma or for other lesions.

Meningioma location was most frequently reported as frontal (51.6%), followed by temporal/parietal (44.1%). Synchronous meningiomas were found at first presentation in 30 survivors (32.3%). Pathology showed 43 WHO grade I (46.2%) and 15 WHO grade II (16.1%) meningiomas. However, in 35 (37.6%) patients with meningioma, the WHO grade was not explicitly stated in the medical record. Simpson grade was not consistently enough reported in surgical reports to allow for analyses. The reported size of the largest dimension of meningiomas at first diagnosis ranged between 0.5 and 8.5 cm, with a median of 3.2 cm.

3.3. Course of disease

In Table 3 the course of disease is presented. For 44.1%, a watchful waiting policy was initially followed after diagnosis. Owing to our inclusion criteria, all survivors included in this study (n = 93) were eventually treated with surgical resection. The median interval between radiologic diagnosis and first surgery was 2 months, but ranged widely (0–14.4 years). Twelve survivors had ≥3 surgeries for growth of residual tumour, recurrences, and new meningiomas (Appendix B). The most frequently reported indications for the first surgical resection were growth (n = 26) and symptoms (n = 22) of the meningioma (Table 3). Furthermore, tumour size

Table 1
Baseline characteristics of 93 childhood cancer survivors with subsequent meningiomas in the Dutch LATER cohort.

Baseline characteristics	Women	Men	Total
Sex n (%)	49 (52.7)	44 (47.3)	**93 (100)**
Age at diagnosis of childhood cancer in years n (%)			
<5	23 (46.9)	21 (47.7)	**44 (47.3)**
5 < 10	14 (28.6)	13 (29.5)	**27 (29.0)**
10 < 15	10 (20.4)	7 (15.9)	**17 (18.3)**
15 < 18	2 (4.1)	3 (6.8)	**5 (5.4)**
Primary childhood cancer diagnosis n (%)			
Leukaemia	31 (63.3)	26 (59.1)	**57 (61.3)**
Medulloblastoma	8 (16.3)	7 (15.9)	**15 (16.1)**
CNS non-medulloblastoma	5 (10.2)	5 (11.4)	**10 (10.8)**
Non-Hodgkin lymphoma	3 (6.1)	3 (6.8)	**6 (6.5)**
Soft-tissue tumour	1 (2.0)	1 (2.3)	**2 (2.2)**
Germ cell tumour	0 (0)	2 (4.5)	**2 (2.2)**
Renal tumour	1 (2.0)	0 (0)	**1 (1.1)**
Neurofibromatosis type 1[a] n (%)	2 (4.1)	0 (0)	**2 (2.2)**
Neurofibromatosis type 2[a] n (%)	1 (2.0)	0 (0)	**1 (1.1)**
Gorlin syndrome n (%)	0 (0)	1 (2.3)	**1 (1.1)**
Cranial radiotherapy for childhood cancer n (%)			
Cranial radiotherapy	46 (49.5)	43 (46.2)	**89 (95.7)**
• Whole brain volume[c]	44 (89.8)	41 (93.2)	**85 (91.4)**
• Partial brain volume	2 (4.1)	2 (4.5)	**4 (4.3)**
No cranial radiotherapy[b]	3 (6.1)	1 (2.3)	**4 (4.3)**
Radiation dose to the head n (%)			
No radiation therapy to the head[b]	3 (6.1)	1 (2.3)	**4 (4.3)**
>0–<20 Gy	4 (8.2)	3 (6.8)	**7 (7.5)**
≥20 < 40 Gy	28 (57.1)	26 (59.1)	**54 (58.1)**
≥40 Gy	14 (28.6)	13 (29.5)	**27 (29.0)**
Dose missing	0 (0)	1 (2.3)	**1 (1.1)**
Chemotherapy for childhood cancer n (%)			
No	6 (12.2)	4 (9.1)	**10 (10.8)**
Yes	43 (87.8)	40 (90.9)	**83 (89.2)**

[a] Here we only report the syndromes that were confirmed and explicitly documented in the medical records.
[b] Includes one patient with a spinal meningioma after a nephroblastoma treated with abdominal/pelvic and spinal radiotherapy, one patient with a non-Hodgkin lymphoma and two patients with a soft tissue tumour.
[c] Including two patients with total body irradiation and two patients with a combination of cranial radiation therapy and total body irradiation.

(n = 11) and patients' (young) age (n = 8) were frequently mentioned reasons to initiate surgery. One-third of the survivors also received radiotherapy during follow-up after surgical resection for a residual tumour, recurrence or new meningioma. In only one case (with neurofibromatosis type 2), radiotherapy preceded surgery. In the other cases, surgery preceded radiotherapy, with a median interval of 18 months between first surgery and first radiation therapy (Appendix B). The following reasons were mentioned as indications to intervene with radiotherapy in a residual tumour, recurrence, or new meningioma: growth of the meningioma (n = 5), the fact that surgery was not a good treatment option (n = 5), location of the meningioma (n = 4) and symptoms (n = 3) (Table 3).

For 78 survivors (84.0%), information was available from the first radiologic meningioma diagnosis until the 18th of July 2018 or date of death and for 100% until 31st of May 2015. In our study sample, median follow-up time after radiologic meningioma diagnosis spanned 10.5 years (range: 0.2–24.3 years). During follow-up 38 (40.9%), survivors developed new meningiomas and 22 (23.7%) developed meningioma recurrences after surgery, with a median latency time from radiologic diagnosis of the first meningioma to the occurrence of a new meningioma or post-surgical recurrence of 3.5 years (range: 0.4–18.3 years). During follow-up in 36 survivors (38.7%), metachronous meningiomas were detected. At the end of the study, 16 (17%) survivors were deceased; meningioma was assigned as the underlying cause of death in four of these. In Table 4, the characteristics of the four deceased patients are described. For five survivors the cause of death was not described in the medical record. The meningioma-related mortality since histologic diagnosis of the meningioma was 1.3%, 3.2% and 9.3% after 5, 10 and 15 years, respectively (Appendix D). Univariable and multivariable analyses did not identify variables significantly associated with an increased risk of death related to meningioma (Appendix E).

Table 2
Diagnostic characteristics of 93 childhood cancer survivors with subsequent meningiomas.

Diagnostic characteristics	Total
Age at radiologic diagnosis meningioma in years[a] median (range)	**31.8 (13.2–50.5)**
Latency between childhood cancer diagnosis and radiologic meningioma diagnosis median (SD)	**25.2 (7.7)**
Mode of detection n (%)	
After a general practitioner visit	**18 (19.4)**
At late effects outpatient clinic	**15 (16.1)**
Hospital admission	**11 (11.8)**
During medical check-up because of medical history[b]	**10 (10.8)**
At the neurologist	**9 (9.7)**
Incidental finding	**9 (9.7)**
Referring specialist not specified	**2 (2.2)**
At the optician	**1 (1.1)**
Not documented	**18 (19.4)**
Clinical symptoms at presentation n (%)	
Yes	**84 (90.3)**
No	**9 (9.6)**
Symptoms at presentation[c] n (%)	
Headache/feelings of pressure in the head	**43 (48.3)**
Visual changes	**18 (20.2)**
Epileptic insults	**16 (18.0)**
Hearing loss/tinnitus/dizziness	**13 (14.6)**
Speech disorders	**11 (12.4)**
Neurocognitive complaints	**11 (12.4)**
Symptoms of paralysis	**9 (10.1)**
Sensation disorders/neurological pain	**9 (10.1)**
Vomiting/nausea	**9 (10.1)**
Gait disturbance	**7 (7.9)**
Other	**24 (26.9)**
None	**9 (10.1)**
Localisation meningioma[d] n (%)	
Frontal	**48 (51.6)**
Temporal/parietal	**41 (44.1)**
Skull base	**21 (22.6)**
Falx	**17 (18.3)**
Occipital	**7 (7.5)**
Tentorium	**5 (5.4)**
Other	**8 (8.6)**
Not documented	**1 (1.1)**
Multiplicity at diagnosis n (%)	
Solitary meningioma	**56 (60.2)**
Synchronous meningiomas	**30 (32.3)**
Not documented	**7 (7.5)**
Size in cm (median, range)	**3.2 (0.5–8.5)**

[a] Based on n = 78; for n = 15 the exact date of radiologic diagnosis was not available in the medical record.
[b] Although there is no active surveillance in the Netherlands, some survivors are followed up with routine MRI because of other lesions or their specific medical history.
[c] Patients presented with several combinations of symptoms.
[d] In the medical records of 44 survivors more than one of the location categories was reported and therefore numbers and percentages add up to more than 100%.

Table 3
Course of disease of 93 childhood cancer survivors with subsequent meningiomas.

Characteristics	Total
Age at histologic diagnosis of meningioma in years median (range)	**32.8 (15.5–54.0)**
Interval between diagnosis with imaging and first surgery in months[a] median (range)	**2 (0–173)**
Treatment policy n (%)	
Watchful waiting (no treatment within 6 months), followed by surgery	**41 (44.1)**
Immediate surgery	**52 (55.9)**
Pre-surgical radiotherapy	**1 (1.08)**
Post-surgical radiotherapy	**30 (32.3)**
Reason for surgery as choice of treatment[b] n (%)	
Symptoms	**22 (23.7)**
Growth of the meningioma	**26 (28.0)**
Size	**11 (11.8)**
(Young) Age	**8 (8.6)**
Location of the meningioma	**3 (3.2)**
Other[c]	**14 (15.1)**
Not documented	**33 (35.5)**
Reason for radiation therapy as choice of treatment n = 31[b] n (%)	
Symptoms	**3 (9.4)**
Growth of the meningioma	**5 (15.6)**
Location of the meningioma	**4 (12.5)**
Resection (for a new meningioma/recurrence) not a good option	**5 (15.6)**
Other[d]	**8 (25.0)**
Not documented	**12 (37.5)**
Follow-up time since radiologic diagnosis meningioma in years[a] median (range)	**10.5 (0.2–24.3)**
Follow-up time since first surgery in years median (range)	**9 (0–24.0)**
Progression n (%)	
New meningioma during follow-up	**38 (40.9)**
Recurrence during follow-up	**22 (23.7)**
• Multiple new meningiomas or recurrences (metachronous meningiomas)	**36 (38.7)**
No new meningioma or recurrence during follow-up	**33 (35.5)**
Vital status at the end of follow-up n (%)	
Alive, without meningioma	**25 (26.9)**
Alive, with meningioma (either recurrence or incomplete resection)	**52 (55.9)**
Deceased	**16 (17.2)**
• Meningioma-related cause of death	**4**
• Other cause of death than meningioma[e]	**7**
• Cause of death unknown	**5**

[a] Based on n = 78; for n = 15 the exact date of radiologic diagnosis was not available in the medical record.
[b] In some cases more than one reason for treatment was given.
[c] Other reasons included amongst others: the possibility of atypical meningioma after CrRT, to increase the chance of achieving cure, to obtain a histologic diagnosis, patient preferences, and resection would have been more difficult in the future.
[d] Other reasons included amongst others: At this moment the therapeutically consequences are limited, the possibility of atypical meningioma after CrRT, and adjuvant radiotherapy.
[e] Other causes of death included: Myocardial infarction; Cerebral infarction; Klebsiella pneumonia meningitis; Subsequent malignant neoplasm; Aspiration pneumonia; Complex neurologic status with post irradiation encephalopathy and endocrine dysfunction.

4. Discussion

In the present study, we described the clinical characteristics of 93 CCS with a histologically confirmed subsequent meningioma. Our study shows that subsequent meningiomas in CCS are detected at a younger age (median: 31.8), with symptoms at

Table 4
Characteristics of four deceased CCS with meningioma as cause of death.

Characteristics	Total n
Sex	
Male	**3**
Female	**1**
Primary childhood cancer diagnosis	
Leukaemia	**4**
Neurofibromatosis type 2	**1**
Cranial radiation therapy for childhood cancer	
Whole brain volume	**3**
Total body irradiation	**1**
Chemotherapy for childhood cancer	
No	**0**
Yes	**4**
WHO grade after first surgical resection	
WHO grade I	**2**
WHO grade II	**2**
Histology	
Meningothelial meningioma	**2**
Atypical meningioma	**2**

presentation like headaches and visual changes, and diagnosed in medical settings other than the late effects clinics. The presence of multiple synchronous and metachronous meningiomas is common, and despite surgical resection, recurrences are frequently observed.

In the current case-series, the median age at radiologic diagnosis was 31.8 years. Other studies among CCS showed a lower median age (between 25.5 and 30 years) at diagnosis [23,33,34]. This is on average 20–25 years younger than in patients with meningioma in the general population (with mean/median ages ranging between 56 and 66 years [9,12,13]). An explanation for the occurrence at young age can be the exposure to CrRT, with the consequence of possible DNA damage to healthy meningeal tissue. In our study, 91.4% had whole-brain radiotherapy. Importantly, the median attained age among CCS in our cohort was 35.6 years; therefore possibly the majority of subsequent meningiomas in our cohort is still to come. It will be of great interest to follow this cohort beyond the 6th decade to ascertain the patterns of brain tumour risk across the lifetime [35].

Unlike the sex ratio in incidental meningiomas, with a propensity of meningioma in women, we found no significant difference in proportions of meningiomas between men (47.3%) and women (52.7%). This is in concordance with two other studies on meningiomas in CCS [18,23]. In contrast, Bowers *et al.* identified female sex as a risk factor for subsequent meningioma. In the same study, only 20% of the CCS reported a new neurologic sequela (including seizures, auditory-vestibular-visuals sensory deficits, focal neurological dysfunction and severe headaches) within 6 months before or subsequent to meningioma diagnosis [6]. The great majority of cases in our study presented with symptoms (90.3%); however it was not always clear whether the symptoms were caused by the meningioma; symptoms from a meningioma may be non-specific and many CCS suffer from other (neurologic) late effects as well. Notably, our study only includes histologically confirmed meningiomas and symptoms were confirmed by medical records, whereas Bowers *et al.* identified meningioma and neurologic symptoms through initial self-report or via proxy report. Another explanation for the difference might be that the threshold for imaging in the USA is lower than in the Netherlands, resulting in the diagnosis of more asymptomatic lesions [26]. Diagnosis of multiple meningiomas is rare in incidental meningiomas (1–10%) [14–17]. In the Childhood Cancer Survivor Study (CCSS) 14.8% of the CCS with subsequent meningioma reported two or more meningiomas [6]. In our series, we frequently observed synchronous meningiomas at first presentation (32.3%) and metachronous meningiomas during follow-up (38%). This difference from the results of the CCSS might be explained by the method of data collection. We retrieved our information from the patient record including imaging reports. The use of self-report or proxy report by the CCSS might have introduced some bias. It is possible that the survivors were not aware of the number of meningiomas that are diagnosed. The difference could also be related to the follow-up time. Median follow-up time since diagnosis of childhood cancer until linkage with PALGA was 28.2 year (min. 16.6 years; max. 55.5 years) in our study. The CCSS reported a follow-up time of 22.8 years for survivors with meningioma and 25.7 years for survivors without meningioma (min. 5.5; max. 39 years). Possibly, the results of the CCSS with same study group changes over time and would show a higher percentage of multiplicity with a longer follow-up time.

We also observed a high recurrence rate compatible with a previous small series in CCS [25]. Although the majority of meningiomas are of benign histology and its behaviour is comparatively benign compared to many other CNS tumours, we found more often WHO grade II meningiomas (n = 15, which is 25.9% of those with a reported WHO grade) than previously described in sporadic meningioma series [4,5,12]. The British Childhood Cancer Survivor Study (BCCSS) reported 137 subsequent meningiomas in their cohort, of which 42 died at the end of follow-up [22]. Most of those deaths were caused by the meningioma. In our series in at least four of sixteen deaths the underlying cause of death was meningioma-related, a proportion quite similar to that reported in the series of the CCSS [6]. Other causes of death in our series included amongst others cerebrovascular disease and subsequent malignancies. It is plausible that all deaths were late adverse events of treatment with CrRT. This underlines the importance of the acknowledgement of CCS with treatment of CrRT as high risk group with increased risk of premature death.

Previously, our research group identified 261 subsequent malignant neoplasms (excluding basal cell carcinoma of the skin) in this cohort after a median follow-up of 20.7 years (range: 5.0–49.8 years), of which 24 occurred in the CNS [28]. Another report on risk and risk factors of benign meningioma in the Dutch LATER cohort showed that one in eight CCS treated with CrRT develops a subsequent meningioma by age 40 years [24]. Few studies described clinical characteristics of subsequent meningiomas in CCS so far [6,25]. This study provides an overview of the clinical characteristics of histologically confirmed subsequent meningiomas. As PALGA contains all pathology reports in the Netherlands since 1991, the chance that we may have missed histologically confirmed meningiomas is small. In the Netherlands, survivors are followed as per clinical surveillance guidelines for late effects in a nationwide network of late effect outpatient clinics. Hence, we were able to analyse high-quality data concerning previous childhood cancer diagnosis and treatment retrieved in a nationwide cohort. Owing to extensive research of medical records in academic hospitals, we can provide a detailed and longitudinal description of the clinical characteristics of 86% of all subsequent meningiomas, including diagnosis, treatment and follow-up of subsequent meningioma.

The study has several limitations. Unlike pathology data, radiological reports are not centrally registered, and European privacy legislation demands destructions of radiology imaging after 10 years. We excluded patients with meningiomas that were radiologically confirmed but not resected yet, to maximise completeness of case ascertainment and to avoid inclusion of other brain tumours. It is likely that there are more radiologically identified subsequent meningiomas which are not resected yet, for which a watchful waiting policy exists. It is not possible to identify these through linkage with a registry yet. Moreover, since meningiomas are usually benign tumours, meningiomas are not systematically registered in the Dutch LATER database by all centers and thus this is an incomplete source. In addition, meningiomas diagnosed before 1991 were not captured by the linkage with PALGA. Based on the long latency of subsequent meningiomas and the fact that we supplemented data collection with information from the LATER registry, we expect that the level of potential under-ascertainment is of a small degree. Finally, for 15 eligible cases, the medical record search did not yield sufficient detail on the meningioma diagnosis, interventions and follow-up.

Current surveillance guidelines for CCS in the Netherlands do not recommend active radiologic surveillance to detect CNS tumours among asymptomatic CCS [36]. Until now, there is insufficient evidence that early detection of meningiomas reduces morbidity and mortality [37,38]. Surveillance for subsequent meningiomas has both benefits and harms. It is therefore relevant to inform survivors about the consequences of surveillance for subsequent CNS tumours. Shared decision-making is an important concept when considering diagnostic and therapeutic trajectories for CCS with neurological symptoms at risk for subsequent CNS tumours. The decision to undertake MRI surveillance should be made by the survivor and healthcare provider after careful consideration of the potential harms and benefits of MRI surveillance [38]. As this and other series show, albeit based on small numbers, meningioma-related mortality among CCS with a meningioma is not uncommon. Therefore, in case of new neurologic symptoms, it is important for clinicians who take care of CCS to consider the differential diagnosis of a meningioma in an early phase, to have a window of opportunity for earlier intervention to provide a better prognosis. Several treatment policies for meningiomas exist. In the general population a wait and see policy is often preferred [17]. Management of subsequent meningiomas in CCS is, however, different from treatment of meningiomas in the general population [27]. The decision to intervene is influenced by concerns that radiation-induced meningiomas may be more aggressive. Moreover, no or a lower cumulative radiotherapy dose can be given to previously irradiated tissue. Yet, there are no specific guidelines for management of meningiomas occurring after radiotherapy. Decision-making regarding treatment of asymptomatic subsequent meningioma is largely driven by clinical characteristics [27]. In our study with a majority of symptomatic meningioma, the decision to treat with surgery was in most cases indicated by symptoms, growth and size of the meningioma. Moreover, many cases were detected with symptoms outside the late effect outpatient clinics, among others in neurology and general practice. For that reason, it is important to inform both CCS, healthcare providers at the late effect outpatient clinics, as well as other healthcare providers about the risk and symptoms of subsequent meningiomas.

Several initiatives have set out to characterise the genetic background and biologic behaviour of meningioma [39,40]. More insight in and understanding of potential differences in biological behaviour between subsequent meningiomas and incidental meningiomas is warranted to further inform tailored clinical decision-making. The patient perspective on surveillance for subsequent meningioma and quality of life after diagnosis of a subsequent meningioma remains unclear and could add valuable insights in the impact of subsequent meningiomas on the lives of affected CCS, to further improve tools that facilitate shared decision-making.

5. Conclusion

In this retrospective study, we studied the clinical characteristics of 93 histologically confirmed subsequent

meningiomas in the Dutch LATER cohort. Subsequent meningiomas in CCS were often detected at a young age, with symptoms at presentation and diagnosed outside of the late effects outpatient clinics. The presence of synchronous and metachronous meningiomas is relatively common in this group, and despite surgical resection, recurrences are frequently observed. This information enhances the knowledge on clinical characteristics of subsequent meningiomas in CCS. It is important to inform both CCS as well as health care providers about the risk of meningiomas and symptoms that might indicate a meningioma.

Author contributions

Lisanne Verbruggen: Conceptualisation, Methodology, Formal analysis, Software, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualisation, Project administration; **Judith Kok**: Conceptualisation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Visualisation; **Jop C. Teepen**: Formal analysis, Visualisation, Writing – review & editing; **Geert O. Janssens**: Writing – review & editing, Funding acquisition; **Charlotte M. de Boer**: Writing – review & editing; **Lukas J.A. Stalpers**: Writing – review & editing; **Meike W. Vernooij**: Writing – review & editing; **Eline van Dulmen-den Broeder**: Resources, Writing – review & editing; **Jacqueline J. Loonen**: Resources, Writing – review & editing; **Marry M. van den Heuvel-Eibrink**: Resources, Writing – review & editing; **Wim J.E. Tissing**: Resources, Writing – review & editing; **Margriet van der Heiden-van der Loo**: Resources, Writing – review & editing; **A. Birgitta Versluijs**: Resources, Writing – review & editing; **Sebastian J.C.M.M. Neggers**: Resources, Writing – review & editing, Funding acquisition; **Flora E. van Leeuwen**: Writing – review & editing; **Eelco W. Hoving**: Writing – review & editing; **Pieter Wesseling**: Writing – review & editing; **Leontine C.M. Kremer**: Conceptualisation, Methodology, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition; **Cécile M. Ronckers**: Conceptualisation, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition; **Helena J. H. van der Pal**: Conceptualisation, Methodology, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Funding acquisition. **Dutch LATER Consortium/collaborative authors**: Marloes Louwerens; Andrica de Vries; Monique Jaspers; Nynke Hollema; Jaap den Hartogh; Netteke Schouten - van Meeteren.

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Conflict of interest statement

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

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