Conclusions of evidence from the systematic literature search for subsequent CNS neoplasm surveillance for CAYA cancer survivors

What is the prognosis for subsequent CNS neoplasms and does early diagnosis result in better outcomes?	
Prognosis of <u>subsequent CNS neoplasms</u> in CAYA cancer survivors	**Quality of evidence**
5-year survival rate of subsequent *glioma* ranges from 0% (high-grade glioma) to 38·9% (low-grade glioma)	LOW[10,28-30]
5-year survival rate of subsequent *meningioma* ranges from 57·3% to 100%	LOW[6,10,12,28-33,49]
5-year survival rate of *subsequent CNS neoplasms (different types)** ranges from 16·6% to 69·9%	LOW[8,25-27]
Early detection of <u>subsequent CNS neoplasms</u> in CAYA cancer survivors	**Quality of evidence**
Small, but non-significant differences between screened versus unscreened CAYA cancer survivors related to meningioma size, extent of resection and persistent morbidity	VERY LOW[24]
Unknown recurrence rate, mortality rate, survival rate and quality of life when CNS neoplasm detected in smaller size or asymptomatic stage	No studies
Who needs surveillance for subsequent CNS neoplasms?	
Risk of subsequent <u>glioma</u> in CAYA cancer survivors	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	HIGH[7,10,27,34]
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	HIGH[7,10,27]
No significant effect of *alkylating agents* vs. no alkylating agents	MODERATE [7,27]
No significant effect of *antimetabolites* vs. no antimetabolites	MODERATE[7,27]
No significant effect of *intrathecal methotrexate* vs. no intrathecal methotrexate	LOW[27]
No significant effect of *6-mercaptopurine or 6-thioguanine* vs. no 6-mercaptopurine or 6-thioguanine	LOW[7]
No significant effect of *epipodophyllotoxins* vs. no epipodophyllotoxins	VERY LOW[7]
No significant effect of *anthracyclines* vs. no anthracyclines	LOW[7]
No significant effect of *platinum agents* vs. no platinum agents	VERY LOW[7]
No significant effect of *chemotherapy (not further specified)* vs. no chemotherapy	MODERATE[10,34]
Increased risk after *younger age at primary cancer treatment* vs. older age	LOW[7,10,27,34]
No significant effect of gender	MODERATE[7,10,27,34]
No significant effect of *hormonal replacement therapy* vs. no hormonal replacement therapy	LOW[27]
Unknown risk in patients with *genetic syndromes*	No studies
Risk of subsequent <u>meningioma</u> in CAYA cancer survivors	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	HIGH[7,12,27,35-41]
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	HIGH[7,10,12,27,35,37,38,41,48-50]
No increased risk after *alkylating agents* vs. no alkylating agents	LOW[7,27,36,38]
Increased risk after *intrathecal methotrexate* vs. no intrathecal methotrexate	VERY LOW[10,27,37]
No significant effect of *6-mercaptopurine or 6-thioguanine* vs. no 6-mercaptopurine or 6-thioguanine	VERY LOW[7]
No significant effect of *epipodophyllotoxins* vs. no epipodophyllotoxins	MODERATE[7,36,38]
No significant effect of *anthracyclines* vs. no anthracyclines	MODERATE [7,36,38]
Increased risk after *platinum agents* vs. no platinum agents	VERY LOW[7,36-38]

No significant effect of *chemotherapy (not further specified)* vs. no chemotherapy	LOW[35]
Increased risk after *younger age at primary cancer treatment* vs. older age	LOW[12,27,35-38,49]
Increased risk in *females* vs. males	MODERATE[12,27,35-38,49]
No significant effect of *growth hormone replacement therapy* vs. no hormonal replacement therapy	LOW[27,40]
Unknown risk in patients with *genetic syndromes*	No studies
Risk of subsequent CNS neoplasms (different types)* in CAYA cancer survivors	**Quality of evidence**
Increased risk after *cranial radiotherapy* vs. no cranial radiotherapy	HIGH[7-10,25,27,29,42-47]
Increased risk after *higher doses of cranial radiotherapy* vs. lower doses	HIGH[8,25,27,42]
No significant effect of *alkylating agents* vs. no alkylating agents	MODERATE[8,27]
No significant effect of *intrathecal methotrexate* vs. no intrathecal methotrexate	LOW[27]
No significant effect of *anthracyclines* vs. no anthracyclines	LOW[8]
Unknown risk after *epipodophyllotoxins*	No studies
Unknown risk after *platinum agents*	No studies
No significant effect of *chemotherapy (not further specified)* vs. no chemotherapy	VERY LOW[9]
Increased risk after *younger age at primary cancer treatment* vs. older age	LOW[8,25,27,29,45]
Increased risk in *females* vs. males	LOW [8,27,45]
No significant effect of *hormonal replacement therapy* vs. no hormonal replacement therapy	LOW[27]
Increased risk in patients with *neurofibromatosis* vs. no fibromatosis	VERY LOW[9]
No significant effect of *hereditary cancer predisposition syndromes other than neurofibromatosis* vs. no genetic syndrome	VERY LOW[9]
At what age or time from exposure should surveillance for subsequent CNS neoplasms be initiated?	
Latency time of subsequent CNS neoplasms in CAYA cancer survivors	**Quality of evidence**
Latency time of *glioma* ranges from median 7 to 17 years after primary cancer diagnosis, ranging from minimal 4 years to at least 25·5 years	MODERATE[7,10,28,29,32,36,43,53,55]
Latency time of *meningioma* ranges from median 11 to 27 years after primary cancer diagnosis, ranging from minimal 5 years to at least 44·5 years	MODERATE[6,7,10,12,28,29,32,33,36,37,42,43,47,49,50,52,53,57]
Latency time of *subsequent CNS neoplasms (different types)** ranges from median 7 to 25 years after primary cancer diagnosis, ranging from minimal 1 year to at least 33 years	MODERATE[8,25,29,30,38,42,43,45-47,52-55]
At what frequency should surveillance for subsequent CNS neoplasms be performed?	
Risk of subsequent CNS neoplasms over time in CAYA cancer survivors	**Quality of evidence**
Cumulative incidence of *high-grade glioma* increased over time and reaches a plateau 14 years after primary cancer diagnosis	VERY LOW[29]
Standardized incidence ratio of *glioma* decreases over time	MODERATE[7,10]
Cumulative incidence of *meningioma* increases over time which does not seem to plateau	MODERATE[12,27,29,37,43,48,50,57]
Standardized incidence ratio of *meningioma* increases over time which does not seem to plateau	LOW [35]
Cumulative incidence increases of *subsequent CNS neoplasms (different types)** over time which does not seem to plateau	MODERATE[8,25,32,36,45,47]

Standardized incidence ratio of *subsequent CNS neoplasms (different types)**; presence of plateau cannot be assessed	LOW[8,45,46,56]
Unknown growth rate of *glioma, meningioma and other CNS neoplasms*	No studies
What surveillance modality should be used for the detection of subsequent CNS neoplasms?	
Diagnostic value of imaging techniques to detect <u>subsequent CNS neoplasms</u> in CAYA cancer survivors	**Quality of evidence**
Unknown diagnostic value computed tomography (CT) scan compared to magnetic resonance imaging (MRI) and neurological exam compared to MRI	No studies
MRI with and without contrast preferable to CT	Guidelines[58-65]

CAYA, childhood, adolescent and young adult, CNS, central nervous system.
* Studies including different types of subsequent CNS neoplasms, not making a distinction between glioma, meningioma and other types.