Conclusions and quality of the evidence for bone mineral density surveillance in CAYA cancer survivors

Who needs bone mineral density surveillance?				
Risk and risk factors for low BMD, very low BMD, lower BMD Z-score, and fractures in CAYA cancer survivors diagnosed up to 25 years of age				
	Very low BMD (Z-score ≤-2)	**Low BMD (Z-score ≤-1 and ≤-2)**	**Lower BMD Z-score (continuous)**	**Fractures (all types)**
Risk				
Risk	↑⊕⊕⊕⊖ MODERATE[6,7,9,10,30–37,39–44,47–55,58–62,64,66–71]	↑⊕⊕⊕⊖ MODERATE[6,7,9–11,30–70]	↑⊕⊕⊕⊖ MODERATE[30,31,33,38,39,41,43,44,50,52–55,58,60,61,64,66,67,69–79]	↑⊕⊖⊖⊖ VERY LOW[7,8,80]
Risk after low BMD/fracture	No studies	No studies	No studies	No studies
Host factors				
Male sex	↑⊕⊕⊕⊖ MODERATE[6,41,54]	↑⊕⊕⊕⊕ HIGH[6,9,64,65,68,32,40–42,45,51,54,56]	↑⊕⊕⊖⊖ LOW[9,35,41,43,44,49,53,67,74,76]	↑⊕⊕⊕⊖ MODERATE[41,58,81]
Age at diagnosis	=⊕⊕⊕⊕ HIGH[6,54,69]	=⊕⊕⊖⊖ LOW[6,9,54,56,64,68,69]	⇳ ⊕⊖⊖⊖ VERY LOW[9,35,44,53,67,70,72]	=⊕⊕⊖⊖ LOW[80,81]
White race	↑⊕⊖⊖⊖ VERY LOW[41]	↑⊕⊕⊕⊖ MODERATE[40,41,51,65,68]	↑⊕⊕⊕⊖ MODERATE[41,43]	↑⊕⊖⊖⊖ VERY LOW[80]
Low BMI/weight/lean mass	↑⊕⊕⊕⊕ HIGH[6,54,69]	↑⊕⊕⊕⊕ HIGH[6,9,40,42,51,54,56,64,68,69]	↑⊕⊕⊕⊖ MODERATE[9,33,35,36,43,52,53,72,74,126]	No studies
Certain SNPs	=⊕⊖⊖⊖ VERY LOW[66]	=⊕⊖⊖⊖ VERY LOW[66]	↑⊕⊕⊖⊖ LOW[9,73,74,78]	↑⊕⊖⊖⊖ VERY LOW[127]
Family history of OP/#	No studies	No studies	No studies	No studies
Treatment factors				
Corticosteroids (y/n)	=⊕⊕⊕⊖ MODERATE[6,54]	↑⊕⊕⊕⊖ MODERATE[6,9,51,54,68]	↑⊕⊖⊖⊖ VERY LOW[9,38,44]	=⊕⊖⊖⊖ VERY LOW[80,127]
Higher corticosteroid dose	↑⊕⊖⊖⊖ VERY LOW[69]	↑⊕⊕⊕⊖ MODERATE[32,46,69]	↑⊕⊕⊕⊖ MODERATE[41,67,70,72,74]	↑⊕⊕⊖⊖ LOW[81]
DEXA vs. PRED	No studies	No studies	=⊕⊖⊖⊖ VERY LOW[79]	No studies
Methotrexate (y/n)	=⊕⊕⊕⊖ MODERATE[6,54]	=⊕⊕⊕⊖ MODERATE[6,9,54,68]	=⊕⊕⊖⊖ LOW[9,38]	↑⊕⊖⊖⊖ VERY LOW[80,81]
Higher methotrexate dose	No studies	=⊕⊕⊖⊖ LOW[32]	=⊕⊖⊖⊖ VERY LOW[70]	↑⊕⊖⊖⊖ VERY LOW[127]
Ifosfamide (y/n)	=⊕⊕⊕⊖ MODERATE[6]	=⊕⊕⊕⊖ MODERATE[6,9]	=⊕⊕⊖⊖ LOW[9]	=⊕⊖⊖⊖ VERY LOW[80]
Higher ifosfamide dose	No studies	No studies	No studies	No studies
Cyclophosphamide (y/n)	=⊕⊕⊕⊖ MODERATE[6]	=⊕⊕⊕⊖ MODERATE[6,9,68]	=⊕⊕⊖⊖ LOW[9]	=⊕⊖⊖⊖ VERY LOW[80]
Higher cyclo dose	No studies	No studies	=⊕⊕⊖⊖ LOW[68,70]	No studies
Cisplatin (y/n)	No studies	No studies	No studies	No studies
Higher cisplatin dose	No studies	No studies	No studies	No studies
6-MP (y/n)	No studies	No studies	No studies	No studies
Higher 6-MP dose	No studies	No studies	=⊕⊖⊖⊖ VERY LOW[70]	No studies
Cyclosporine (y/n)	No studies	No studies	No studies	No studies

Higher cyclosporine dose	No studies	No studies	No studies	No studies
TKIs (y/n)	No studies	No studies	No studies	No studies
TKI dose	No studies	No studies	No studies	No studies
Tacrolimus (y/n)	No studies	No studies	No studies	No studies
Higher tacrolimus dose	No studies	No studies	No studies	No studies
C(S)RT (y/n)	↑⊕⊕⊕⊕ HIGH[6,54]	↑⊕⊕⊕⊕ HIGH[6,9,32,38,51,54,64,68]	↑⊕⊕⊖⊖ LOW[9,33,38,50,52,67,72,79]	=⊕⊕⊖⊖ LOW[81]
Higher C(S)RT dose	No studies	↑⊕⊕⊖⊖ LOW[32]	No studies	=⊕⊖⊖⊖ VERY LOW[127]
HSCT (y/n)	=⊕⊕⊖⊖ LOW[54]	=⊕⊕⊖⊖ LOW[9,54]	↑⊕⊖⊖⊖ VERY LOW[9,44]	No studies
TBI (y/n)	No studies	↑⊕⊕⊕⊕ HIGH[9,45,54,64,65]	↑⊕⊕⊖⊖ LOW[9,44,67,75]	No studies
Higher TBI dose	No studies	No studies	No studies	No studies
Abdominal/pelvic RT (y/n)	↑⊕⊕⊕⊖ MODERATE[6]	↑⊕⊕⊖⊖ LOW[6,9]	=⊕⊕⊖⊖ LOW[9]	=⊕⊖⊖⊖ VERY LOW[80]
Higher abd./pelvic RT dose	No studies	No studies	No studies	No studies
Medical conditions				
GHD (y/n)	↑⊕⊕⊖⊖ LOW[10,54,82,83]	↑⊕⊕⊕⊖ MODERATE[10,54,61,68,82,83]	=⊕⊕⊖⊖ LOW[67,75]	No studies
Hypogonadism (y/n)	↑⊕⊕⊕⊖ MODERATE[10,54]	↑⊕⊕⊖⊖ LOW[10,38,51,54,61,68,82,84]	↑⊕⊖⊖⊖ VERY LOW[38,67]	No studies
Vitamin D deficiency (y/n)	No studies	No studies	No studies	No studies
Hyperthyroidism (y/n)	No studies	No studies	No studies	No studies
Endocrine dysfunction* (y/n)	No studies	↑⊕⊖⊖⊖ VERY LOW[62]	No studies	No studies
Health behaviors				
Inadequate vit. D intake (y/n)	No studies	=⊕⊕⊕⊖ MODERATE[51]	No studies	No studies
Vitamin D deficiency (y/n)	No studies	↑⊕⊕⊖⊖ LOW[65]	No studies	No studies
Inadequate Ca intake (y/n)	No studies	=⊕⊕⊕⊖ MODERATE[51]	↑⊕⊖⊖⊖ VERY LOW[33]	No studies
Inadequate vit. B intake (y/n)	No studies	No studies	No studies	No studies
Lack of exercise (y/n)	No studies	↑⊕⊕⊕⊖ MODERATE[11,40,51,56]	↑⊕⊕⊖⊖ LOW[39,63]	=⊕⊕⊖⊖ LOW[11,80]
Current/prior smoking (y/n)	=⊕⊕⊕⊖ MODERATE[6]	↑⊕⊕⊕⊖ MODERATE[6,9,56,61]	=⊕⊕⊖⊖ LOW[9]	↑⊕⊖⊖⊖ VERY LOW[80]
Alcohol consumption (y/n)	No studies	⇕⊕⊖⊖⊖ VERY LOW[61]	No studies	No studies
Carbonated beverages (y/n)	No studies	No studies	No studies	No studies
What surveillance modality should be used?				
Diagnostic value to detect (very) low BMD in CAYA cancer survivors diagnosed up to 25 years of age				
Variable			**Outcome**	**Quality of evidence**
Diagnostic value of *QCT* vs. DXA			Unknown	No studies
Correlation between *QCT and DXA derived BM(A)D and BMD Z-scores*			Significant (r 0.33-0.64)	⊕⊕⊖⊖ LOW[41,85]
Diagnostic value of *QUS* vs. DXA			Moderate	⊕⊖⊖⊖ VERY LOW[86]
Diagnostic value of *QUS* vs. QCT			Unknown	No studies
Diagnostic value of *pQCT* vs. QCT			Unknown	No studies

Added value of *QUS* to QCT and DXA in predicting fractures	Unknown	No studies
Location of BMD measurement (lumbar spine, total body and/or hip) that should be evaluated	Unknown	No studies
When should surveillance be initiated and at what frequency should it be performed?		
Risk over time of (very) low BMD in CAYA cancer survivors diagnosed up to 25 years of age		
Variable	**Outcome**	**Quality of evidence**
Course of BMD Z-scores over time from 2 years until at least 10 years since end of cancer treatment	Increase	⨁⨁⨁⊖ MODERATE[32,40,49,64,71,87–90]
Latency time of low BMD and fractures	Unknown	No studies
Risk of fractures for *low BMD* vs. normal BMD	Increased	⨁⨁⊖⊖ LOW[58,68]
Risk of fractures for *lower BMD* vs. higher BMD	Not significant	⨁⨁⊖⊖ LOW[81]
What should be done when abnormalities are identified?		
Use of medical interventions to improve BMD in CAYA cancer survivors diagnosed up to 25 years of age		
Variable	**Outcome**	**Quality of evidence**
Effect of *growth hormone replacement therapy* in GH deficient survivors	Significant	⨁⊖⊖⊖ VERY LOW[91–93]
Effect of *calcium and vitamin D supplementation*	Not significant	⨁⊖⊖⊖ VERY LOW[43]
Effect of *weight-bearing physical exercise*	Not significant	⨁⊖⊖⊖ VERY LOW[94]
Effect of *twice daily treatment with a vibrating plate*	Not significant (intention-to-treat analysis) Significant (per-protocol analysis)	⨁⊖⊖⊖ VERY LOW[95]
Effect of *bisphosphonates*	Unknown	No studies
Effect of *PTH*	Unknown	No studies
Effect of *Denosumab*	Unknown	No studies
Effect of *vitamin B12 supplementation*	Unknown	No studies
Effect of *sex hormone replacement therapy*	Unknown	No studies

*GHD, hypogonadism or thyroid dysfunction. ↑ indicates an increased risk, = indicates no significant effect, and ⇳ indicates conflicting evidence.

Abbreviations: BMD=bone mineral density; BMI=body mass index; CAYA=childhood, adolescent, and young adult; CRT=cranial irradiation; CSRT=craniospinal irradiation; DEXA=dexamethasone; DXA=dual-energy X-ray absorptiometry; GH=growth hormone; GHD=growth hormone deficiency; HSCT=hematopoietic stem cell transplantation; OP=osteoporosis; PRED=prednisone; PTH=parathyroid hormone; pQCT=peripheral quantitative computed tomography; QCT=quantitative computed tomography; QUS=quantitative ultrasound; RT=radiotherapy; SNP=single nucleotide polymorphism; TBI=total body irradiation; TKI=tyrosine kinase inhibitors; y/n=yes/no; 6-MP=6-mercaptopurine; #=fracture.