Included studies metabolic syndrome surveillance

Year	Bibliography
2021	Lopez, R., et al. (2021). “Testosterone deficiency in men surviving childhood acute leukemia after treatment with hematopoietic stem cell transplantation or testicular radiation: an L.E.A. study.” Bone Marrow Transplant 56(6): 1422-1425.
2021	Netterlid, A., et al. (2021). “Premature ovarian failure after childhood cancer and risk of metabolic syndrome: a cross-sectional analysis.” Eur J Endrocrinol 185(1): 67-75.
2021	Nirmal G., et al (2021). “Prevalence and Risk Factors for Metabolic Syndrome Among Childhood Acute Lymphoblastic Leukemia Survivors: Experience From South India.” J Pediatr Hematol Oncol 43(2): e154-e158.
2018	Oudin, C. et al. (2018). “Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors’ cohort: a comparison with controls from the French population.” Heamatologica 103(4): 645-654.
2017	Ariffin, H., et al. (2017). "Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging." Cancer 123(21): 4207-4214.
2017	Bandak, M., et al. (2017). "Leydig cell dysfunction, systemic inflammation and metabolic syndrome in long-term testicular cancer survivors." Eur J Cancer 84: 9-17.
2017	Friedman, D. N., et al. (2017). "Cardiovascular Risk Factors in Survivors of Childhood Hematopoietic Cell Transplantation Treated with Total Body Irradiation: A Longitudinal Analysis." Biol Blood Marrow Transplant 23(3): 475-482.
2016	Saultier, P. et al. (2016). “Metabolic syndrome in long-term sur vivors of childhood acute leukemia treated without hematopoietic stem cell transplantation: an L.E.A. study.” Haematologica 101(12):1603-1610.
2015	Oudin, C., et al. (2015). "Metabolic syndrome in adults who received hematopoietic stem cell transplantation for acute childhood leukemia: an LEA study." Bone Marrow Transplant 50(11): 1438-1444.
2014	Nottage, K. A., et al. (2014). "Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia - From the St. Jude Lifetime Cohort." Br J Haematol 165(3): 364-374.
2014	Smith, W. A., et al. (2014). “Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study.”Cancer 120(17): 2742–2750.
2013	Blijdorp, K., et al. (2013). "Endocrine sequelae and metabolic syndrome in adult long-term survivors of childhood acute myeloid leukemia." Leuk Res 37(4): 367-371.
2013	Tonorezos, E. S., et al. (2013). “Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia.” Cancer Causes Control 24(2): 313–321.
2012	Van Waas, M., et al. (2012). “Abdominal radiotherapy: a major determinant of metabolic syndrome in nephroblastoma and neuroblastoma survivors." PLoS One 7(12): e52237.
2011	Oudin, C., et al. (2011). "Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia." Blood 117(17): 4442-4448.
2010	Chow, E. J., et al. (2010). "Increased cardiometabolic traits in pediatric survivors of acute lymphoblastic leukemia treated with total body irradiation." Biol Blood Marrow Transplant 16(12): 1674-1681.

2010	Meacham, L. R., et al. (2010). "Cardiovascular risk factors in adult survivors of pediatric cancer--a report from the childhood cancer survivor study." Cancer Epidemiol Biomarkers Prev 19(1): 170-181.
2006	Gurney, J. G., et al. (2006). "Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia." Cancer 107(6): 1303-1312.
2005	Kourti, M., et al. (2005). "Metabolic syndrome in children and adolescents with acute lymphoblastic leukemia after the completion of chemotherapy." J Pediatr Hematol Oncol 27(9): 499-501.
1996	Talvensaari, K. K., et al. (1996). “Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome.” J. Clin. Endocrinol. Metab 81(8): 3051-3055.

Evidence tables metabolic syndrome surveillance

Who needs surveillance?				
Arrifin et al. Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia Show Evidence of Chronic Inflammation and Cellular Aging. *Cancer* 2017; 123:4207-14				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Cross-sectional Country of origin Malaysia Treatment era 1985-2010 Follow-up Median 18 (IQR 14-22) yrs. after cessation of treatment	Type and number of participants Inclusion: 87 ALL survivors age 18-35 and ≥ 5 years from treatment completion Excluded: HSCT survivors, pregnant, vaccinated in the preceding 6 months. 76 also participants in an earlier study of immune senescence. Diagnoses ALL Age at diagnosis Mean 5 yrs (IQR 3-8) Age at follow-up Mean 25 yrs, range 18-35 yrs (IQR 22-29) Ethnicity Not stated but all recruited from University Malaya	Chemotherapy Anthracyclines N=64 (73.6%) Cumlative dose=240 mg/m^2 (0-240) [reported as median and IQR] Anthracylcines were doxorubicin and daunorubicin. Frequencies receiving each one or both not reported. Dose equivalency not reported. Cyclophosphamide N=66 (75.9%), cumulative dose 2500 (IQR 1000-3000) Radiotherapy Radiotherapy N=42 (48.3%) [not specified in Table 1 but in text these were all cranial RT] Surgery N/A HSCT Excluded	Outcome definitions Metabolic syndrome was defined as the presence of at least 3 of the following metabolic risk factors: fasting blood Glucose >6.1 mmol/L, hypertension (systolic blood pressure >130mm Hg or diastolic blood pressure >85mm Hg), hypertriglyceridemia (serum triglycerides >1.7 mmol/L), low high-density lipoprotein (men, <1.03 mmol/L; women, <1.29 mmol/L), and a large waistline (men, >102 cm; women, >88 cm). Results 16 survivors (18.4%) and 4 controls (4.6%) met criteria for metabolic syndrome.	**Risk of bias** A. Selection bias: Unclear Reason: Convenience cohort of ALL survivors attending an academic annual follow-up clinic. Source population not described. B. Attrition bias: Low Reason: no attrition among survivor or controls C. Detection bias: Unclear Reason: blinding not mentioned D. Confounding: Low Reason: adjustments for age, sex, smoking

	Medical Center in Kuala Lumpur, Malaysia <u>Controls (if applicable)</u> 87 age- and sex-matched controls, same inclusion criteria as for survivors, except for history of cancer. Attempted to recruit from a diverse socio-economic background/lifestyle. Recruited from family members of participants, university students, nurses, and general hospital workers (demographic breakdown of controls not provided).			

Who needs surveillance?				
Bandak M. et al. Leydig cell dysfunction, systemic inflammation and metabolic syndrome in long-term testicular cancer survivors. *European Journal of Cancer* 2017; 84: 9-17.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Longitudinal study, single centre Country of origin Denmark Treatment era 1984-2012 Follow-up VISIT 2: 9.7 yrs (4.1-17.1 yrs)	Type and number of participants Testicular cancer survivors (TCS) (Seminoma and non seminoma patients), selected on the basis of visit 1 (during their first 5-year follow up) according the following 3 groups (a,b,c) and recruited (n° 158) in the period from Aug 2014-March 2016 (FOLLOW UP VISIT 2) with : a) Uncompensated Leydig cell (LC) dysfunction (n= 28) b) Compensated Uncompensated Leydig cell dysfunction (n= 59) c) Normal Leydig cell function (N= 71 (controls) Primary Cancer Diagnoses Testicular cancer (Seminoma and non seminoma patients) 100%, treated from 1984 to 2012 at Copenhagen Univ hospital (age > 18 yrs and <	Chemotherapy In disseminated disease Cisplatin Based Chemotherapy (41%) or abdominal radiotherapy (15%) Surgery: 100% Orchiectomy and contralateral biopsy in all patients. Orchiectomy alone in stage I. (31%) In case of contralateral germ cell in situ neoplasia Radiotherapy was applied to the contralateral testicle.(13%) HSCT: None	Outcome definitions MetS, defined and analysed using both the NCEP ATP III criteria and IDF criteria. Results a) Using IDF criteria the prevalence of MetS and Follow up visit 2 was 33% in uncompensated LC dysfunction, 12% in compensated LC dysfunction and 27% in controls. The difference statistically significant (p=0.04) was between compensated LC dysfunction and controls. Moreover there was no evidence of increases systemic inflammation compared to controls. b) Using the NCEP ATP III criteria the prevalence of MetS and Follow up visit 2 was 11% in uncompensated LC dysfunction, 7% in compensated LC dysfunction and 17% in controls. There were no statistically significant differences between groups. c) TCS with MetS (IDF criteria) were older at follow up, had decreased levels of testosterone, total and free: total testosterone METS vs no METS, OR 0.80 95% CI 0.71-0.90, P = 0.0002 Age adjusted OR 0.81 95% CI 0.72-0.91, P=0.001, Free testosterone METS vs no METS OR 0.994, 95% CI 0.989-0.999, P = 0.02, Age adjusted	- The number of patients with MetS is too small to evaluate some differences. No differences between those treated with CT and RT versus surgery only. This is in contrast with data of literature. - 13% of the series had RT on the contralateral testis but testosterone substitution was an exclusion criteria - Other limitations are listed in the paper. **Risk of bias** A. Selection bias: Unclear Reason: There are no data about the total number of patients treated from 1984 to 2012 and no data about reason for not participating (lost to follow up, refusal, exclusion criteria). B. Attrition bias: Low risk Reason: The follow up is adequate. C. Detection bias: Unclear Reason: Blinding is not mentioned. D. Confounding: Low risk Reason: Adequate controlling for confounding variables.

	65 yrs) ; total cohort number not available Age at diagnosis 31.2 (25.8-36.7) Age at follow-up At Follow up VISIT 2: 43.4 yrs (37.5-50.4) Ethnicity Not specified in the text (Caucasian) Controls (if applicable) Testicualr cancer survivors with normal Leydig cell function (N° 79)		OR 0.995, 95% CI 0.990-1.000, P = 0.08, and SHBG, an increased level of leptin compared with TCS without MetS.	

Who needs surveillance?

Blijdorp K, et al (2013). Endocrine sequelae and metabolic syndrome in adult long-term survivors of childhood acute myeloid leukemia. *Leuk Res* 2013; 37: 367-371

Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design:</u> Observational, cross-sectional <u>Country of origin:</u> The Netherlands <u>Treatment era:</u> 1961-2004 <u>Follow-up:</u> Chemo-only group: median 21.6 yrs since end of treatment (range, 9.1-30.7) HSCT group: median 19 yrs since end of treatment (range, 11.6-30.0)	<u>Type and number of participants</u> Five-year adult survivors: 1. Chemo-only group: treated with chemo-only (n=12) 2. HSCT group: treated with HSCT including TBI in conditioning regimen (n=9) 47 survivors were eligible, 21 survivors participated in total in the study. <u>Diagnoses</u> Chemo-only group: AML (n=12, 100%) HSCT group: AML (n=7, 78%) CML (n=1, 11%) MDS (n=1, 11%) <u>Age at diagnosis</u> Chemo-only group: median 5.1 yrs (range, 0.1-15.8) HSCT group: median11.5 yrs (range, 1.1-15.0) <u>Age at follow-up</u>	<u>Radiation therapy:</u> N=9, $43\%_{total}$ 1. Chemo-only group: n=0. 2. HSCT group: N=9 ($100\%_{total\ group}$), field: TBI: median cumulative dose: 8 Gy (range, 4-12) <u>Chemotherapy agents:</u> N=21, $100\%_{total}$. All BFM-based AML protocols 1. Chemo-only group ($n/n_{total\ group}$, cumulative dose, range): • IV Prednisone (9/12, 1235 mg/m^2, 560-4000) • IT Prednisone (2/12, 36 mg/m^2) • Vincristine (9/12, 6 mg/m^2, 3-10) • Anthracyclines (11/12, 320 mg/m^2, 80-520) • Cyclophosphamide (9/12, 500 mg/m^2, 400-8800) • Ifosfamide (1/12, 32100 mg/m^2) • Cytarabine (11/12, 20300 mg/m^2, 10690-62000) • Etoposide (11/12, 1200 mg/m^2, 400-3600)	<u>Outcome definition:</u> METS was defined per ATPIII criteria. <u>Results:</u> **METS**: 1/12 chemo-only survivors (8%) and 1/8 HSCT survivors (13%) met criteria for METS. No difference was found compared to controls (3/48, 6%, P=1.000 controls vs chemo-only, P=0.507 controls vs SCT). After adjustment for age, gender, smoking and BMI, no difference between chemo-only survivors and controls (OR=1.31, p=0.687). After adjustment, HSCT survivors had more METS components compared to controls (OR=24.1, p<0.001). Chemo-only treatment not associated with METS or with individual components. HSCT with TBI conditioning is associated with higher risk for METS.	<u>Limitations</u> • Very small cohort size resulting in limited power to detect difference in METS prevalence and risk factors. Risk of over-adjustment. • Over half of eligible survivors not included in study. Higher % of survivors not included were allo (none were auto) and higher % were recurrence or 2nd malignancy. Therefore, survivors not included may have been more morbid. <u>Strengths</u> • Comparison of chemo-only treatment with HSCT based treatment. • Healthy control group. • Detailed treatment exposure data. • Extended long-term follow-up post treatment. • MV analysis for METS with adjustment for age, gender, and smoking status. **<u>Risk of bias</u>** <u>A. Selection bias:</u> High risk Reason: 55% of eligible original cohort not included or excluded. Reasons for not participating: • 20 lost to follow-up, of which 16 went to another outpatient clinic • 2 refusal • 2 treated with CRT or abdominal irradiation • 1 Down syndrome • 1 paralyzed clinical + sociodemographic info is given of those excluded, except for 4 survivors lost to follow-up.

	Chemo-only group: median 27.4 yrs (range, 22.0-39.2) HSCT group: median 32.4 yrs (range, 23.4-44.5) <u>Ethnicity</u> not mentioned <u>Controls (if applicable)</u> 60 NL adults median aged 32.1 (range: 18.0-61.7), cross-sectional recruited from siblings, friends or neighbors of the same sex and within an age range of 5 yrs of the related survivor	• IV Methotrexate (4/12, 150 mg/m^2, 150-225) • IT Methotrexate (3/12, 36 mg/m^2, 36-66) • Thioguanine (5/12, not determined) ▪ Mercaptopurine (3/12, not determined) 2. HSCT group (n/n$_{total\ group}$, cumulative dose, range): • IV Prednisone (5/9, 1230 mg/m^2, 1225-4000) • Vincristine (5/9, 6 mg/m^2, 5-8) • Anthracyclines (7/9, 176 mg/m2, 80-356) • Cyclophosphamide (9/9, 3600 mg/m^2, 1000-6000) • Ifosfamide (1/9, 21400 mg/m^2) • Cytarabine (8/9, 28730 mg/m^2, 3500-71160) • Busulfan (1/9, 300 mg/m^2) • Etoposide (4/9, 1925 mg/m^2, 1350-2450) • IV Methotrexate (1/9, 150 mg/m^2) • IT Methotrexate (2/9, 33 mg/m^2, 30-36) • Thioguanine (6/9, not determined) • Mercaptopurine (2/9, not determined) <u>HSCT:</u> N=9, 43% 1. Chemo-only group: n=0 2. HSCT group: all (n=9)		<u>B. Attrition bias:</u> Low risk Reason: Cross-sectional design. Outcome (METS) assessed for most of participants: chemo only: 100%, HSCT group: 89%, controls: 80% <u>C. Detection bias: Unclear</u> Reason: Outcomes were well-defined. Most were lab values. Blinding not mentioned. <u>D. Confounding:</u> Low risk Reason: • for METS, MV models adjusted for age and sex, smoking history, and BMI were used. Other confounders such as socio-economic status, physical activity, use of oral contraceptives were explored using backward regression modeling and probably (not mentioned explicitly) not included in final model. • Matched controls on sex and age.

		• Allo: n=6 (29%$_{total}$) • Auto: n=3 (14%$_{total}$)		

Abbreviations: ALT, alanine transaminase; BMD, bone mineral density; FSH, follicle stimulating hormone; fT4, free thyroxine; GH, growth hormone; HOMA-IR, homeostatic model assessment insulin resistance; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; MV, multivariable; SDS, standard deviation score; TBI, total body irradiation; TSH, thyroid stimulating hormone; WC, waist circumference; yrs, years.

Who needs surveillance?				
Chow EJ, et al (2010). Increased Cardiometabolic Traits in Pediatric Survivors of Acute Lymphoblastic Leukemia Treated With Total Body Irradiation. Biol Blood Marrow Transplant; *16(12):1674-81.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Observational (Cross-sectional) Country of origin USA (Seattle, Fred Hutch, Vanderbilt) Treatment era 1990-2008 Follow-up HSCT survivors: median 10.5 yrs since dx (1-15); median 6 yrs post BMT (1-13) Non-HSCT survivors: median 10 yrs since dx (3-18)	Type and number of participants One-year ALL survivors: -HSCT survivors treated with TBI, in remission, off all GVHD meds (n=26) -Survivors in first CR after conventional chemotherapy (n=48) Diagnoses ALL (100%) Age at diagnosis <22 yrs Age at follow-up HSCT survivors: median 15 yrs (range, 8-21) Non-HSCT survivors: median 14 yrs (range, 8-21) Ethnicity Nonwhite race/ethnicity: HSCT survivors: N=8 (30.8%) Non-HSCT survivors: N=10 (20.8%) Controls (if applicable) N/A	Chemotherapy Presumably 100% but not explicitly stated HSCT group: 26 (100%) cyclophosphamide Radiotherapy HCT group: 100% • 26 (100%) received TBI (median 1320 cGy, range: 1200-1575) • 10 (38.5%) received cranial RT (median 1000 cGy, range, 600-2400) Non-HSCT group • 5 (10.4%) received cranial RT, all 1800 cGy Surgery Not stated HSCT N=26 had TBI-based HSCT; no one had more than one HSCT *14 patients developed GH deficiency (13 treated with HSCT)	Outcome definitions Cardiometabolic traits defined per consensus criteria (Table 1). They were defined using the adult International Diabetes Foundation Consensus criteria for those ≥18 yrs and pediatric adapted values for those <18 yrs. Also compared to standard ATPIII criteria (sensitivity analysis) Adult: **METS:** 3/5 traits were present Results **Clustering of cardiometabolic traits** Greater proportions of HSCT survivors compared with non-HSCT had at least one criterion (84.6% vs 50%); same for those who met at least 3 criteria (23.1% vs 4.2%; global p<0.01) # of METS components per study group (IDF criteria): **HSCT group:** • none: 4 (15.4%) • 1: 8 (30.8%) • 2: 8 (30.8%) • 3-5: 6 (23.1%) **Non-HSCT group:** • none: 24 (50.0%) • 1: 14 (29.2%) • 2: 8 (16.7%) • 3-5: 2 (4.2%)	TBI and cranial RT are strongly associated with metabolic abnormalities TBI-exposed HSCT survivors associated with increased WtHR (not BMI) **Strengths:** Direct comparison of ALL survivors treated with and without TBI-based HSCT in the contemporary era; Assesses novel markers of inflammation, metabolic dysregulation – not possible in larger cohort studies; Provides hypothesis-generating data for other mechanistic studies on inflammation, fat profiles, etc; MV analyses and linear regression models with adjustment for appropriate factors, includes lifestyle factors (diet, PA); Compared two classification schemes (ATPIII and consensus criteria) with consistent findings **Limitations:** Small cohort (considering that recruitment occurred from three large centers) with limited power; No control group of untreated patients/population-based controls; No comment on aGVHD; definition of GH deficiency unclear – patients were not prospectively tested

			Multivariable analysis Individuals with history of HSCT were at increased risk for: -Having ≥ 2 cardiometabolic traits (OR 5.13; 95% CI, 1.54-17.15), compared to non-HSCT survivors -METS (≥ 3 cardiometabolic traits, OR 16.72, 95% CI, 1.66-168.80), compared to non-HSCT survivors Risk was also significantly increased when using ATPIII criteria: for ≥ 2 criteria OR 4.16, 95% CI 1.07-16.10 and for ≥3 criteria OR 22.99, 95% CI 1.41-373.65 Compared to those with no history of cranial RT, individuals treated with cranial RT/TBI alone and cranial RT + TBI had similar risk of having 2-3 cardiometabolic traits (ORs ranged 5-6) +FH was significantly associated with ≥ 2 cardiometabolic traits independent of HSCT status (OR 3.65; 95% CI, 1.15-11.57)	Individuals with cGVHD excluded – limits ability to explore association between GVHD and metabolic dysfunction - **S** **Risk of bias** A. Selection bias: High risk Reason: Total number of eligible patients not stated; 41 HSCT and 83 non-HSCT patients were approached (63.4% and 66.3% enrolled, reasons for not enrollment unknown); 7 survivors were excluded: -3 Down syndrome -4 incomplete data Unclear whether this cohort is representative of all ALL survivors seen in the three clinics B. Attrition bias: Low risk Reason: Cross-sectional study; attrition not an issue C. Detection bias: Unclear Reason: Unclear if outcome assessors were blinded; laboratory procedures well defined, GH deficiency clinician-reported D. Confounding: Low risk Reason: MV models with appropriate adjustment for age, sex, participating institution, race/ethnicity, and family history of CVD/diabetes

Abbreviations: CR, complete remission; GH, growth hormone; PA, physical activity; FH, family history; MV, multivariable; WtHR, waist-to-hip ratio; Dx, diagnosis; yrs, years; aGVHD, acute GVHD; cGVHD, chronic GVHD

Who needs surveillance?				
Friedman et al. (2017). Cardiovascular Risk Factors in Survivors of Childhood Hematopoietic Cell Transplantation Treated with Total Body Irradiation: A Longitudinal Analysis. *Biol Blood Marrow Transplant 23(3): 475-482.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Country of origin US Treatment era April 1987-May 2011 Follow-up Median time since TBI 8.0 (range 1.01-24.6) y	Type and number of participants 123 childhood HCT survivors treated with TBI with a primary diagnosis of Leukemia or Lymphoma, who survived at least a year relapse-free from HCT and who were ≤ 21 y at the time of TBI Diagnoses ALL/NHL: N=77 (62.6%) AML/CML: N=46 (37.4%) Age at diagnosis Not reported Age at TBI Median age 11.8 (range 1.6-21.9) y Age at follow-up Median age 20.1 (range 4.0-41.4) y Ethnicity White, non-Hispanic: N=96 (78.0 %) Other: N=23 (18.6 %) Missing: N=4 (0.03 %) Controls (if applicable) A random sample of National Health and Nutrition Examination Survey (NHANES). For each visit an HCT survivors had, 3 sex, ethnicity and age-at	Pre-Transplant Therapy Anthracyclines: N=115 (93.5%) Glucocorticoids: N=100 (81.3%) Cranial radiation: N=38 (30.9%) HCT Autologous: N=5 (4.1%) Allogenic: N=118 (95.9 %) TBI Range: 12-15 Gy ≤ 1410 cGy: N=54 (43.9 %) > 1410 cGy: N=69 (56.1 %)	Outcome definitions CVRF cluster - a surrogate for METS - was defined as occurrence of 3 or more of the 5 CVRFs defined below. These definitions are based on Adult International Diabetes Foundation Consensus. Pediatric-adapted values were used when needed. Obesity Adult: BMI≥ 30 kg/m2 Pediatric: BMI≥ 95th percentile for age and sex Elevated blood pressure Adult: ≥ 130/85 mmHg Pediatric: ≥ 90th percentile for age, sex, and height Elevated glucose Adult: Fasting glucose ≥ 100 mg/dl Pediatric: Fasting glucose ≥ 100 mg/dl Low HDL-cholesterol Adult: Males < 40 mg/dl and females < 50 mg/dl Pediatric: ≤ 40 mg/dl Hypertriglyceridemia Adult: ≥ 150 mg/dl Pediatric: ≥ 110 mg/dl Events and estimated cumulative incidence CVRF cluster Events: N=35 5-year cumulative incidence: 10.6 (5.6-17.5) 10-year cumulative incidence: 28.4 (18.8-38.7) Factors associated with CVRF and CVRF cluster	Survivors with multiple HCTs, active GVHD, or glucocorticoid use within 3 months of first assessment time were excluded. Limitations 1. Single center study 2. Using BMI instead of waist circumference 3. GH stimulation was performed only for those with evidence of poor growth, so it may be underestimated 4.Information provided for treatment history is limited Strengths 1. Relatively large sample size 2. Multivariate models with appropriate adjustment **Risk of bias** A. Selection bias: Unclear B. Attrition bias: Low risk Reason: This is a longitudinal study, so per design all participants were followed C. Detection bias: Unclear Reason: Blinding not mentioned D. Confounding: Low risk Reason: analyses were adjusted for age at TBI and treatment era. Survivors and controls were matched on age at assessment, sex and ethnicity.

	assessment matched controls from NHANES were selected and used for comparing prevalence of CVRF in HCT survivors and the general population.		CVRF cluster Cranial radiation: HR 4.0 (1.7-9.6), p=0.002 GH deficiency: HR 8.6 (2.1-34.4), p=0.002 History of grade II-IV GVHD: HR 4.2 (1.5-12.2), p=0.008 Prevalence of CVRF and CRRF cluster in survivors vs general population by era CVRF cluster 1991-2000: 5.5% in NHANES vs 5.9% in survivors 2001-2006: 8.0% in NHANES vs 6.3% in survivors 2007-2013: 12.1% in NHANES vs 14.4% in survivors P=0.70	

Who needs surveillance?				
Gurney et al. (2006). Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. *Cancer 107(6): 1303-1312.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design:</u> Retrospective cohort study <u>Country of origin:</u> US <u>Treatment era:</u> 1970-1986 <u>Follow-up:</u> Mean 24.6 (± 4.8) yrs since diagnosis	75 long-term childhood ALL survivors treated at age ≤20 yrs 207 survivors were eligible participants, 75 survivors participated in the study <u>Primary cancer diagnosis:</u> ALL (100%) <u>Age at primary cancer diagnosis:</u> Mean 5.6 (± 4.3) yrs <u>Age at follow-up:</u> Mean 30.2 (± 7.1) yrs <u>Ethnicity:</u> White N=74, 98.7% Nonwhite N=1, 1.3% <u>Controls:</u> 730 US adults aged 18-45 yrs from the the National Health and Nutrition Examination Study (NHANES)	<u>Radiation therapy:</u> N=50, 66.6% **Dose:** **<24 Gy** N=25, 33.3% **24+ Gy** N=25, 33.3% **Body areas:** **Brain** N=50, 66.7% **Spine** N=17, 22.7% **Pelvis or testis** N=11, 14.7% **Total body** N=5, 6.7% <u>Chemotherapy agents:</u> N=29, 38.7% **Actinomycin** N=1, 1.3% **Cytoxan** N=33, 44.0% **Ara-C** N=33, 44.0% **Daunorubicin** N=21, 28.0% **Dexamethasone** N=11, 14.7% **Doxorubicin** N=21, 28.0% **Isofosfomide** N=1, 1.3% **L-aspariginase** N=72, 96.0% **6-mercaptopurine** N=69, 92.0% **Methotrexate** N=75, 100% **Prednisone** N=74, 98.7% **6-thioguanine** N=18, 24.0% **Vincristine** N=75, 100% **Teniposide** N=2, 2.7% **Allopurinol** N=2, 2.7% **Anthracycline dose mg/m^2** **None** N=46, 61.3% **1-100** N=10, 13.3% **101-300** N=11, 14.7% **301+** N=8, 10.7%	<u>Outcome defition:</u> METS was defined using the revisions of the NCEP ATP III criteria;Participants with 3 or more of the following criteria were considered positive for metabolic syndrome: 1) waist circumference >102 cm in men or >88 cm in women 2) triglyceride levels ≥150mg/dL 3) HDL-C <40 mg/dL in men or <50 mg/dL in women or on current treatment for high cholesterol 4) blood pressure ≥130/85 mmHg or on current treatment for hypertension 5) glucose ≥100 mg/dL. <u>Prevalence of METS in study cohort:</u> **Total group** N=11, 14.67% **Cranial radiation** N=9, 18.0% **No cranial radiation** N=2, 8.0% <u>Weighted* prevalence of METS in survivors vs. controls:</u> 16.59% (SE 4.74) vs. 17.45% (SE 3.02) P=0.87 <u>No. of METS components:</u> **None** N=16, 21.33% **1** N=24, 32.00% **2** N=24, 32.00% **3-5** N=11, 14.67%	Survivors with GH levels <9 µg/L were considered growth hormone deficient and with GH levels 9-16.5 µg/L growth hormone insufficient. <u>Limitations</u> - GHRH/ARG stimulation tests may underdiagnose GH deficiency in early years after cranial irradiation. - Nowadays less reliance on irradiation therapy, thus results have less contemporary relevance. - These data are not sufficient to draw etiologic conclusions, as the study was not designed to evaluate etiologic mechanisms - Small study population (for METS yes, N=11) <u>Strengths</u> - Data from this study were compared with data from a population-based comparison group (N=730). **Risk of bias:** - <u>Selection bias:</u> 75 of 207 eligible survivors participated in the study (=36.2%) > <u>high risk</u>, reasons for not participating: - Refusal - Lost to follow-up - Never scheduled because accruel was met - Random number of survivor not reached from sampling scheme - <u>Attrition bias:</u> low risk, outcome was assessed for >75% of participants. - <u>Detection bias:</u> unclear if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> low risk, cases and controls were stratified by age and gender.

* Case data weighted for sampling distribution and response rates, NHANES data weighted for sampling probabilities, strata, and primary sampling units
Abbreviations: GH, growth hormone; METS, metabolic syndrome; SE, standard error; yrs, years

Who needs surveillance?				
Kourti M et al. Metabolic Syndrome in Children and Adolescents With Acute Lymphoblastic Leukemia After the Completion of Chemotherapy. *J Pediatr Hematol Oncol 2005;27(9):499-501.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Prospective cohort study Country of origin Greece Treatment era Not reported Follow-up Median 37 months since completion of therapy (range 13–121 months).	Type and number of participants 52 survivors of childhood and adolescent ALL in the initial years after treatment. Unclear how many survivors were eligible for the study; 52 were evaluated. Diagnoses ALL n=52 (100%) Age at diagnosis Not reported Age at follow-up Median 15.2 years (range 6.1-22.6) Ethnicity Not reported Controls (if applicable) Not applicable Additional study characteristics: Gender: 29 males (56%) and 23 females (44%)	Chemotherapy N= 52 (100%) treated with chemotherapy only. According to the ALL-BFM 90 chemotherapy protocol; Most were treated with prednisone alone. No further info provided	Outcome definitions Participants were classified as having METS if they met three or more of the following abnormalities: • hypertriglyceridemia (ATPIII or equivalent pediatric percentiles): adults: >=146.61 mg/dL 75th percentile for males and 85th percentile for females; pediatric population: >=97.34 mg/dL • low levels of HDL (ATPIII or equivalent pediatric percentiles): adults: <40.1 mg/dL in males and < 50.19 mg/dL in females (40th percentile); pediatric population: < 50.19 mg/dL in males and < 45.17 mg/dL in females • high fasting glucose levels (ATPIII): adults: >=110 mg/dL); pediatric population >=6.1 mg/dL • obesity: BMI (kg/m2) using z-scores, calculated by using normative data from the U.S. National Health and Nutrition Examination survey II, adjusted for age and sex: overweight: z-score threshold 1.5 obesity: z-score threshold 2.0 moderately obese: z-score of 2.0 to 2.5 severely obese: z-score above 2.5 • hypertension: elevated systolic or diastolic blood pressure defined as a value > 95th percentile for age, gender, and height according to the U.S. National Heart, Lung and Blood Institute. But elsewhere in the manuscript: Adults: systolic >=130 mmHg and diastolic >=80 mmHg; Pediatric population: >90th for age, gender and height	Limitations • Small study population • No controls (they did use established reliable norms from widely accepted population-based studies) • No risk analyses • Lots of relevant information not reported • Different definitions of abnormalities reported throughout the manuscript Risk of bias A. Selection bias: Unclear Reason: unclear how many survivors were eligible for the study. B. Attrition bias: Low risk Reason: all 52 patients evaluated C. Detection bias: Unclear Reason: unclear if the outcome assessors were blinded for important determinants related to the outcome. D. Confounding: Not applicable Additional information: In the discussion the authors stated that the prevalence of the syndrome (as defined by Cook) was estimated at about 4% in US adolescents; this was not significantly different from our results.

			<u>Results</u> <u>Prevalence of METS:</u> 3/52 (5.76%) All 3 had high triglyceride levels, glucose intolerance, and obesity. No risk analyses were reported.	

Who needs surveillance?				
Lopez et al. (2021). Testosterone deficiency in men surviving childhood acute leukemia after treatment with hematopoietic stem cell transplantation or testicular radiation: an L.E.A. *Bone Marrow Transplantation 2021 56, 1422–1425.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Retrospective cohort study Country of origin: France Treatment era: Since 1980 Follow-up: Not reported	255 childhood leukemia survivors treated with HCST and/or testicular radiation 279 survivors were eligible participants, 255 (91.4%) survivors participated in the study. Primary cancer diagnosis: Leukemia N=255 (100%), of which 75.7% with lymphoblastic leukemia Age at primary cancer diagnosis: Mean 8.8 ± 5.1 yrs Age at follow-up/evaluation: Mean 25.6 ± 6.3 yrs Ethnicity: Not reported. Controls: N/A.	HSCT: **HSCT yes** N = 234 Conditioning regimen before HSCT: **Myeloablative TBI or Bu-conditioning regimen** N = 53 Radiotherapy: **TBI yes** N=178 **12 Gy** (6 fractions/3 days) N=155/178 **No additional TR** N=137/178 **Additional TR** N=41 **4-6 Gy testicular boost at TBI** N=24 **18-24 Gy TR** N=15 **Both** N=2 **TR (24 Gy) without HSCT or TBI** N=21	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2005 modified version). **Results:** Prevalence of METS in study cohort: 25% in 130 patients with total testosterone deficiency (N~33). 12.1% in 42 patients with partial testosterone deficiency (N~5). 8.8% in 83 patients with normal Leydig cell function (N~7). Risk of METS in multivariable analysis Testosterone deficiency vs normal Leydig cell function OR = 2.909, P=0.05. Partial testosterone deficiency vs normal Leydig cell function not significant (data not shown).	Limitations - possible underevaluation of METS due to young age of included survivors. - unclear which factors are included in the multivariable model Strengths - multivariate analyses - homogenous cohort **Risk of bias:** - Unclear: size of original cohort not reported, reasons for not participating not reported. - Attrition bias: low risk, 255 (91.4%) had sufficient data available. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, multivariate model including type of leukemia, relapse, age at HSCT and CNS irradiation were included as covariates.

Who needs surveillance?				
Meacham L et al. (2010) Cardiovascular Risk Factors in Adult Survivors of Pediatric Cancer – a report from the Childhood Cancer Survivors Study. *Cancer Epidemiol Biomarkers Prev. 2010 January; 19(1): 170-181*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective cohort study Country of origin US Treatment era 1970-1986 Follow-up >5 yrs.	Type and number of participants 8599 survivors of childhood cancer (52% male) and 2936 matched siblings (46% male) Diagnoses ALL N=2581 (30.0%) AML N=217 (2.5%) Other leukemia N=170 (2.0%) Astrocytomas N=649 (7.5%) Medulloblastoma, PNET N=234 (2.7%) Other CNS tumors N=167 (1.9%) Hodgkin lymphoma N=1006 (11.7%) Non-Hodgkin lymphoma N=673 (7.8%) Kidney tumors N=849 (9.9%) Neuroblastoma N=596 (6.9%) Soft tissue sarcoma N=755 (8.8%) Ewing sarcoma N=216 (2.5%) Osteosarcoma N=454 (5.3%) Other bone tumors N=32 (0.5%) Age at diagnosis <5 yrs, N=3573 (41.6%)5- 9 yrs, N=1940 (22.6%) 10-14 yrs, N=1690 (19.7%) 15-20 yrs, N=1396 (16.2%) Age at follow-up < 19 yrs, N=122 (1.4%) 19-29 yrs, N=3729 (43.4%)	Chemotherapy Anthracyclines None n=4779 (62.6%) < 100 mg/m2 n=296 (3.9%) 100-299 mg/m2 n=1223 (16%) >300 mg/m2 n=336 (17.5%) Platinum n=367 (4.7%) Radiotherapy None n=2740 (31.9%) MR unavailable n=763 (8.9%) TBI n=99 (1.2%) Abd w/o chest n=566 (6.6%) Abd w/ chest n=734 (8.5%) Chest w/o abd n=610 (7.1%) Cranial w/ spinal n=427 (5.0%) Cranial w/o spinal n=2075 (24.0%) Other n=585 (6.8%) Surgery n/a HSCT n/a Current steroid use (N=96 (1.1%))	Outcome definitions Clustering of cardiovascular risk factors (CVRFC) – parallel definition for MetS (having at least 3 of the following 4 risk factors – obesity, hypertension, dyslipidemia, and diabetes mellitus or impaired glucose tolerance). - Self-report of medications from Follow-up 2003 survey used - Looked at responses regarding medicines taken regularly in the last 2 year period - Questions included in analysis: - 1) Pills for diabetes - 2) Insulin injections for diabetes - 3) Medications for high blood pressure or HTN - 4) Medications to lower cholesterol or triglycerides - 5) Other prescribed drugs - Obesity determined by calculating BMI Results **Cardiovascular disease risk factors among survivors and siblings** - Survivors and siblings were equally likely to meet criteria for CVRFC (survivors with CVRFC N=113, (1.3%), controls N=34 (1.2%)) OR: 1.3, 95% CI 0.9–1.9) **Association between demographics, lifestyle, treatment and cardiovascular risk factors** - Older age at the time of questionnaire was associated with CVRFC p<0.001.	**Strengths:** Large sample size **Limitations:** MetS definition was created from the data that was available All information provided was self-reported – thus survivors and siblings may have untreated or unrecognized CVRFC Weight and height were self-reported (to calculate BMI) **Risk of bias** A. Selection bias: Low risk/High risk/Unclear Reason: High risk less than 75% of the original cohort completed the survey at follow-up 2003. B. Attrition bias: Low risk/High risk/Unclear Reason: Low risk (outcome was assessed for > 75% of those in cohort) C. Detection bias: Low risk/High risk/Unclear Reason: Unclear (Study not blinded) D. Confounding: Low risk/High risk/Unclear Reason: Low risk (age at diagnosis, follow-up and treatment modalities were all taken into account)

	30-39 yrs, N=3510 (40.8%) 40-49 yrs, N=1190 (13.8%) 50+ yrs, N=48 (0.6%) Ethnicity White N=7338 (85.3%) Black N=327 (3.8%) Hispanic N=349 (4.1%) Other/missing N=585 (6.8%) Smoking status Never smoker N=5859 (69.6%) Former smoker N=1156 (13.7%) Current smoker N=1402 (16.7%) Sedentary lifestyle Yes N=1950 (22.7%) No N=6616 (77.0%) Unknown N=33 (0.3%) Controls (if applicable) 2936 matched siblings Age at follow-up < 19 yrs, N=126 (4.3%) 19-29 yrs, N=995 (33.9%) 30-39 yrs, N=1078 (36.7%) 40-49 yrs, N=647 22.0%) 50+ yrs, N=90 (3.1%) Ethnicity White N=2536 (86.4%) Black N=64 (2.2%) Hispanic N=82 (2.8%) Other/missing N=254 (8.6%) Smoking status Never smoker N=1711 (59.7%) Former smoker N=572 (20.0%) Current smoker N=583 (20.3%)		- Gender was not associated with CVRFC: female vs male OR 0.8 95% CI 0.5-1.2. - Black ethnicity was not associated with CVRFC: black vs white OR 2.6 95% CI 1.0-5.6. - Hispanic ethnicity was not associated with CVRFC: Hispanic vs white OR 1.7 95% CI 0.6-4.0. - Other ethnicity was not associated with CVRFC: other vs white OR 0.8 95% CI 0.3-1.9. - Age at follow up (questionnaire) was associated with CVRFC: 30-39 yrs vs <30 yrs OR 2.6 95% CI 1.3-5.3, 40+ yrs vs <30yrs OR 8.2 95% CI 3.5-19.9. - Age at diagnosis was not associated with CVRFC: <5yrs vs 15-20 yrs OR 1.3 95% CI 0.6-3.0, 5-9 yrs vs 15-20 yrs OR 1.3 95% CI 0.6-2.6, 10-14 yrs vs 15-20 yrs OR 1.2 95% CI 0.7-2.2. - Sedentary lifestyle was associated with CVRFC (OR 1.7 95% CI 1.1-1.6) and each CVRF except dyslipidemia. - Smoking status was not associated with CVRFC. Former smoker vs never smoker OR 0.9 95% CI 0.5-1.6, current smoker vs never smoker OR 1.1 95% CI 0.6-1.9. - Current steroid use was not associated with CVRFC OR 2.8 95% CI 0.7-8.1. **Effect of Treatment modalities** - Exposure to any dose of anthracyclines was not associated with CVRFC: <100 mg/m2 OR 1.6 95% CI 0.5-4.2, 100-299 mg/m2 OR 0.9 95% CI 0.5-1.7, >300 mg/m2 OR 1.0 95% CI 0.6-1.8. - Exposure to platinum agents was not associated with CVRFC: OR 0.9 95% CI 0.2-2.7.	

	<u>Sedentary lifestyle</u> <u>Yes N=407 (13.9%)</u> <u>No N=2518 (85.7%)</u> <u>Unknown N=11 (0.4%)</u>		- CVRFC was associated with TBI (OR 5.5 95% CI 1.5–15.8) and combined abdominal-chest radiation (OR 2.3 95% CI 1.2–2.4). - CVRFC was not associated with abdominal radiation only (no chest) (OR 1.9 95% CI 0.7-4.2). - CVRFC was not associated with chest radiation only (no abdomen) (OR 1.2 95% CI 0.5-2.7). - CVRFC was not associated with cranial with combined cranial-spinal radiation (OR 1.5 95% CI 0.5-3.8). - CVRFC was not associated with cranial radiation only (no spinal) (OR 1.2 95% CI 0.6-2.3) - CVRFC was not associated with other radiation (OR 1.2 95% CI 0.4-2.6). **Association between previously reported cardiovascular events and CVRFC** - All of these previously reported cardiac events, except for stroke, were associated with an increased risk of reporting CVRFC (3 or 4 CVRFs) subsequently at second follow-up (p= 0.003).	

Who needs surveillance?

Netterlid et al. (2021). "Premature ovarian failure after childhood cancer and risk of metabolic syndrome: a cross-sectional analysis" European Journal of Endocrinology (2021) 185(1): 67–75.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design:</u> Cross-sectional <u>Country of origin:</u> Sweden <u>Treatment era:</u> 1964-2008 <u>Follow-up:</u> Median 30 (12–39) yrs	167 female childhood cancer survivors 331 survivors were eligible participants, 167 survivors participated in the study <u>Primary cancer diagnosis:</u> **Leukemia** N=51 (30%) **Brain tumor** N=39 (23%) **Lymphoma** N=21 (13%) **Sarcoma** N=18 (11%) **Wilms tumor** N=19 (11%) **Ovarian tumor** N=11 (7%) **Other** N=8 (5%) <u>Age at primary cancer diagnosis:</u> Median 11.7 (0.4–17.9) yrs <u>Age at follow-up/evaluation:</u> Median 39 (21–55) yrs <u>Ethnicity:</u> Not reported. <u>Controls:</u> 164 matched controls (three dropouts). Controls were matched on age, sex, ethnicity, area of residency and smoking habits.	<u>Radiotherapy:</u> **All radiotherapy** N=87 (52%) **Cranial RT** N=53 (32%) **Abdominal RT** N=34 (20%) **Both cranial and abdominal RT** N=16 (10%) **TBI** N=7 (4%) <u>Chemotherapy:</u> **All chemotherapies** N=126 (75%) **Alkylating agents** N=81 (49%) <u>HSCT:</u> N = 11 (7%) <u>Surgery only:</u> N=19 (11%)	<u>Outcome definition:</u> METS was defined using the revisions of the NCEP ATP III criteria and IDF criteria. IDF criteria were used for the analyses. **<u>Results:</u>** <u>Prevalence of METS in CCS study cohort:</u> **NCEP all CCS** N=16 (10%) **IDF all CCS** N=24 (14%) **NCEP POI** N=4 (18%) **IDF POI** N=5 (23%) **NCEP no POI** N=12 (8%) **IDF no POI** N=19 (13%) <u>Prevalence of METS in controls study cohort:</u> **NCEP** N=3 (2%) **IDF** N=6 (4%) **NCEP** all CCS vs controls (ref) P = 0.002 **IDF** all CCS vs controls (ref) P = 0.001 All CCS vs controls (ref) OR 4.4, 95% CI 1.8-11.1 P = 0.002 (IDF criteria) <u>Univariable analyses:</u> <u>POI and MetS:</u> POI vs controls (ref) OR 7.7, 95% CI 2.1-28.1 P = 0.002 No POI vs controls (ref) OR 4.0, 95% CI 1.5-10.2 P = 0.004 CCS with POI vs CCS without POI (ref) OR 1.9, 95% CI 0.7-5.4 P = 0.210	<u>Limitations</u> - small number of POI and MetS cases, only 16/24 out of 167 - analyses for treatment only controls used as reference, not CCS without the treatment - difficult to distinguish what is the most crucial cause for MetS; a direct effect of irradiation and chemotherapy or an indirect effect of ovarian failure and subsequent estrogen deficiency <u>Strengths</u> - Long FU time **Risk of bias:** - <u>Selection bias:</u> 167 out of 331 eligible survivors participated in the study (=50.4% > <u>high risk</u>, reasons for not participating (129 refusals, 28 drop-outs due to lack of time, 4 excluded due to severe disabilities, three excluded due to pregnancy) - <u>Attrition bias:</u> <u>low risk</u>, outcome was assessed for all included participants. - <u>Detection bias:</u> <u>unclear</u> if the outcome assessors were blinded for important determinants related to the outcome. - <u>Confounding:</u> <u>high risk</u>, no multivariable analyses.

			<u>Radiotherapy and MetS:</u> All radiotherapy vs controls (ref) OR 5.5, 95% CI 2.0-14.7 P = 0.001 CRT (also including alkylating agents) vs controls (ref) OR 6.1, 95% CI 2.1-17.8 P = 0.001 CRT (without alkylating agents) vs controls (ref) OR 6.0, 95% CI 1.7- 21.3 P = 0.006 Abdominal RT vs controls (Ref) OR 4.5, 95% CI 1.3-15.9 P = 0.018 <u>Chemotherapy and MetS:</u> All chemotherapy vs controls (ref) OR 4.4, 95% CI 1.7-11.4 P = 0.002 Alkylating agents vs controls (ref) OR 5.0, 95% CI 1.8-13.8 P = 0.002 <u>Surgery only and MetS:</u> CCS with surgery only vs controls (ref) OR 3.1, 95% CI 0.6-16.6 P = 0.186 *AMH levels per se were not associated with MetS (data not shown).*	

Who needs surveillance?				
Nirmal et al. (2021). Prevalence and risk factors for metabolic syndrome among childhood acute lymphoblastic leukemia survivors: experience from South India. *J Pediatr Hematol Oncol (2021); 43(2): 154-158.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Country of origin: India Treatment era: Not reported Follow-up: 5.4 years (2.1 to 18.5 y) from treatment completion	277 childhood ALL survivors (56.7% male) Unknown number of eligible participants, 277 participated Primary cancer diagnosis: **B-ALL** N=221 (79.8%) **T-ALL** N=47 (17%) **MPAL** N=9 (3.2%) Age at primary cancer diagnosis: Mean 5.2 ±3.2 yrs Age at follow-up/evaluation: Mean 13.1 ± 3.9 Ethnicity: Not reported Controls: N/A	Cranial radiotherapy: **None** N=117 (42.2%) **18 Gy** N=127 (45.8%) **15 Gy** N=28 (10.2%) **12 Gy** N=4 (1.4%) **24 Gy** N=1 (0.4%) Chemotherapy per modified BMF ALL protocol: **Standard-risk protocol** N=120 (43.3%) **High-risk protocol** N=157 (56.7%)	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria and IDF criteria. NCEP ATP III criteria were used for multivariable analyses. **Results:** Prevalence of METS: **NCEP all CCS** N=14 (8.7%) **IDF in 214 CCS*** N=13 (6%) *IDF N/A in CCS <10 yrs **1 or more components METS** N =138 (49.8%) **2 or more components of METS** N=54 (19.5%) Risk factors for METS in multivariable analysis: **Overweight/obesity at evaluation** OR ~17, 95% CI=6.2-50.1, P=0.001 1 s.d. higher BMI-z score at ALL diagnosis Not significant, data not reported Sex, age at diagnosis, age at follow-up and cranial radiotherapy were not significantly associated with METS in univariable analysis and therefore not included in the multivariable model.	Limitations - small cohort, only 13 survivors developed METS - few multivariate analyses performed - multivariate analyses not corrected for age, sex and treatment, because not significant in univariate analysis, but show a strong trend - possible underevaluation of METS due to young age of included survivors Strengths - Multivariable analysis performed **Risk of bias:** - Selection bias: unknown (because unknown number of eligible participants) - Attrition bias: low risk, outcome was assessed for all included participants. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, multivariate analysis, but did not include parameters that indeed were not significant in univariate analysis, but show a strong trend.

Who needs surveillance?				
Nottage et al. Metabolic syndrome and cardiovascular risk among long-term survivors of acute lymphoblastic leukaemia – from the St. Jude Lifetime Cohort. *Br J Haematol. 2014;165:364-374*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design Retrospective single-center cohort study Country of origin US Treatment era 1962-2002 Follow-up Median 26.1 (range 11-45.3) survival time	Type and number of participants 784 childhood acute lymphoblastic leukemia survivors ≥5 years from diagnosis and ≥18 y/o at study entry Diagnoses ALL Age at diagnosis Median 5 (0.2-19.5) years Age at follow-up Median 31.7 (19.9-59.1) years Ethnicity White N=720 (91.8%) Non-white N=64 (8.2%) Controls (if applicable) 777 US adult controls selected from NHANES (2005-2010), age- (5-year categories), sex-, and race-matched 1:1 to ALL survivors	Chemotherapy Cumulative doses of: Anthracyclines median 42.4 (0-607.5) mg/m2 Cyclophosphamide median 6000 (0-38487) mg/m2 L-asparaginase median 59091 (0-999247) units/m2 Prednisone median 9020 (200-27360) mg/m2 Vincristine median 37 (2-148) mg/m2 Methotrexate median 5112 (0-37473) mg/m2 Cytarabine median 3469 (0-72923) mg/m2 6-MP median 37800 (0-74550) mg/m2 Dichotomous exposure to: Oral methotrexate N=288 (36.7%) Epipodophyllotoxins N=536 (68.4%) Radiotherapy No CRT N=277 (35.3%) CRT with CSI N=411 (52.4%) CRT without CSI N=96 (12.2%) CRT dose 0 Gy N=277 (35.3%) 1-23 Gy N=223 (28.4%) 24+ Gy N=284 (36.2%) Surgery N/A	Outcome definitions Primary Metabolic syndrome (MetS) – defined by NCEP-ATP III ≥ 3 of: - Waist circumference ≥102 cm in men and ≥88 cm in women - Hypertriglyceridemia ≥1.69 mmol/l or on drug treatment - Low high-density lipoprotein <1.04 mmol/l in men and <1.3 mmol/l in women - Hypertension with syst≥130 mmHg or diastolic ≥85 mmHg or on treatment - Hyperglycemia ≥5.5 mmol/l or on treatment Results SJLIFE ALL survivors were significantly more likely to have MetS (N=259, 33.6%, RR 1.43, 95%CI, 1.22–1.69) than age-, sex- and race-matched controls (descriptives not provided). - Current age (5-year increments) RR 1.13 (1.06-1.19) - Prior CRT without CSI vs no CRT RR 1.88 (1.32-2.67) - Prior CRT with CSI vs no CRT RR 1.67 (1.26-2.23) - Oral MTX (y/n) RR 1.24 (1.02-1.52) - Cumulative prescribed prednisone-equivalent dose (100 mg/m2) RR 0.99 (0.97-1.01) - Cumulative anthracycline dose (100 mg/m2) RR 0.89 (0.78-1.01)	**Risk of bias** A. Selection bias: High risk Reason: 61.5% of eligible survivors participated, however the direction of bias is impossible to determine B. Attrition bias: Low risk Reason: 770/777 (99%) assessed for primary outcome (Table II) C. Detection bias: Unclear Reason: Blinding is not mentioned D. Confounding: Low risk Reason: Potentially confounding variables are adjusted for

		HSCT States they were included, but no details provided		

Who needs surveillance?				
Oudin C et al: Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia. *Blood 2011; 117:4442-4448*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
<u>Study design</u> Cross-sectional study <u>Country of origin</u> France <u>Treatment era</u> 1980 – present <u>Follow-up</u> Mean 15.4 years (3.4 – 30.2)	<u>Type and number of participants</u> 184 adults included in a prospective multicentric cohort of leukemia survivors 220 survivors were eligible participants, 184 survivors participated in the investigation <u>Diagnoses</u> ALL (n= 150; 81.5%) and AML (n= 34 (18.5%) <u>Age at diagnosis</u> Mean 7.9 years (0.5-18) <u>Age at follow-up</u> Mean 21.2 years (15.9 – 39.1) <u>Ethnicity</u> Not specified <u>Controls (if applicable)</u> Not applicable	<u>Chemotherapy only</u> N=97, 52.7% <u>Chemotherapy and CNS irradiation</u> N=27, 14.7% **Involved fields** **Cranial irradiation** n=22, 81.5% **Craniospinal irradiation** n=5, 12.5% **Irradiation dose** **18 Gy** n=20, 74.1% **24 Gy** n= 5 18.5% **unknown** n= 2, 7.4% <u>Surgery</u> Not specified <u>HSCT</u> n= 60, 32.6% allogenic SCT n= 39, 65% - MSD n=27 - MUD n=4 - Mismatched SD n=2 - Cord blood n=6 acute GVHD grade >=2 or chronic GVHD n=18(46.2%) post transplant steroids n=32(82.1%) autologous SCT n=21, 35.0% **Total body irradiation (TBI)** n=43, 71.7% **Previous CNS irradiation** n=0	<u>Outcome definitions</u> METS was defined according to the NCEP ATP III revised in 2005. Patients were defined as having the MS when they met at least 3 of 5 criteria 1) elevated waist circumference (>=102 cm in men, >=88 cm in women) 2) elevated blood pressure (systolic blood pressure ≥130 mmHG and/or diastolic blood pressure 85 mmHg and/or treatment 3) reduced high-density lipoprotein (HDL) cholesterol (< 40mg/dL in men, <50 mg/dL in women) 4) elevated fasting glucose (≥1g/dL or drug treatment for elevated glucose) 5) elevated triglycerides (≥150mg/dL or drug treatment for elevated triglyceride) <u>Results</u> <u>Prevalence and risk factors of METS in study cohort:</u> **Total group N=17, 9.2%** Variables associated with higher risk of MS: - history of TBI (18.6% vs. 6.4%, p=.015) - older age at time of evaluation (mean 22.2 years with MS vs. 21.1. years in unaffected subjects, p=0.05) multivariate logistic regression analysis: **Chemotherapy only (n=5/97, 5.2%, reference)** **Chemotherapy and cranial irradiation** (n=3/27,11.1%) adjusted OR 1.7 (0.3 – 9.0), P=.51 **HSCT without TBI (**n=1/17, 5.9%) adjusted OR 1.1. (0.1 – 14.1), P=.96	<u>Limitations</u> cohort may be too small to detect weaker effects, data are not sufficient to draw etiologic conclusions <u>Strengths</u> multivariable linear regression analysis with appropriate adjustment for confounding variables **<u>Risk of bias</u>** <u>A. Selection bias:</u> Unclear Reason: assessment was proposed systemically to all patients with a new health status evaluation during two years. Certain selection effect is always present in follow-up cohorts as more health conscious patients are always more likely to participate <u>B. Attrition bias:</u> low risk Reason: possible due to a multicenter setting, but on the other hand > 80% of the cohort was included <u>C. Detection bias: Unclear</u> Reason: no controls, homogenous cohort <u>D. Confounding:</u> low risk Reason: stratification according to treatment

		Steroids and Asparaginase N=150 (all ALL-patients) Steroid therapy (any time) N=162 (88%)	**HSCT with TBI** (**n= 8/43, 18.6%, adjusted OR 3.9 (1.1. – 13.3), P=.03** METS in males (N=8 (8.4%)) vs females (N=9 (10.1%)): OR 0.7 95% CI 0.2-2.0, P=0.48. Frequency and risk factors for the components of MS Elevated waist circumference n=22/184, 15.5% Elevated blood pressure n=41/184, 25.3% Low HDL-cholesterol n=55/184, 31.8% Elevated trigycerides n=level 24/184, 13.0% Elevated fasting glucose n=10/184, 5.7%	

Who needs surveillance?				
Oudin et al. (2015). Metabolic syndrome in adults who received hematopoietic stem cell transplantation for acute leukemia: an LEA study. *Bone Marrow Transplantation (2015) 50, 1438–1444*				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Country of origin: France Treatment era: 1980-2012 Follow-up: Mean post-HSCT follow-up duration was 14.5 years (±6.1).	170 childhood ALL survivors (female N=78 (45.9%) and male N=92 (54.1%)). 228 survivors were eligible participants, 170 survivors participated in the study Primary cancer diagnosis: ALL N=119 (70%) AML N=46 (27.1%) Age at primary cancer diagnosis: Mean 8.6 (±4.9) yrs Age at follow-up/evaluation: Mean 24.8 (± 5.4) yrs Ethnicity: Not reported. Controls: N/A	Radiation therapy: **None** N=39 (22.9%) **CNS irr or TBI** N=131 (77.1%) **Pre-transplant CNS irradiation** N=16 (9.4%) **Cranial irradiation** N=9 (56.3%) **Cranio spinal irradiation** N=6 (37.5%) **Unknown** N=1 (6.2%) Conditioning regimen **TBI** N=124 (72.9%) **Bu-cy** N=30 (17.6%) **Others** N=16 (9.4%) HSCT: **Allogeneic** N=124 (72.9%) **Autologous** N=46 (27.1%) Steroids dose **Post-transplantation total dose of steroids** 1488.6 (±2702.3) mg/m2 **Total dose of steroids** 5313.6 (±4366.3) mg/m2	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2005 modified version). **Results:** Prevalence of METS in study cohort: N=29 (17.1%), 95% CI 11.7–23.6 Cumulative incidence of METS in cohort increases with age. Gender and METS: Female vs male (ref) OR 1.95, 95% CI 0.8–4.89, P = 0.15 (1 s.d. higher) BMI-z score at HSCT and METS OR 1.57, 95% CI 1.18–2.08, P = 0.002 HSCT type and METS Allogeneic vs autologous (ref) OR 1.2, 95% CI 0.395–3.639, P = 0.749 TBI and METS TBI vs no TBI (ref) OR 1.47, 95% CI 0.50–4.27, P = 0.48 Post HSCT steroid dose OR 0.99, 95% CI 0.97–1.01 (per each additional 500 mg/m2 dose) P = 0.44 Follow-up since HSCT and METS OR 1.02, 95% CI 0.95–1.10 (per each additional year of follow-up) P = 0.59 Univariable analyses: GH deficiency and METS	Limitations - small cohort, only 29 survivors developed METS - possible underevaluation of METS due to young age of included survivors - limited number of evaluations per patient (1.38) - Only TBI/cyclo and Bu/Cy regimes commented on. - uncertain about cranial radiation impact (did any have before TBI?) Strengths - multivariate analyses - prospective study - homogenous cohort **Risk of bias:** - Selection bias: unclear - Attrition bias: low risk, the outcome of 170 out of 228 eligible survivors was assessed (=74.6%). - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, multivariable analysis included all variables that were significant in univariable analysis (gender, BMI at time of HSCT, type of transplantation (allogeneic versus autologous), conditioning regimen with or without TBI, follow-up duration (from the HSCT) and total dose of steroids post-HSCT

			METS and GH deficiency N=10 (35.7%) METS but no GH deficiency N=3 (8.3%) P = 0.011 <u>Hypogonadism and METS</u> METS and hypogonadism N=19 (22.6%) METS but no hypogonadism N=8 (12.3 P = 0.1 <u>Hypothyroidism and METS</u> METS and hypothyroidism N=16 (23.2%) METS but no hypothyroidism N=13 (13.3%) P = 0.1 *Leukemia type (ALL or AML), age at transplantation, central nervous system irradiation and acute or chronic GvHD showed significant impact neither on METS nor its components (data not shown).*	

Who needs surveillance?				
Oudin et al. (2018). Prevalence and characteristics of metabolic syndrome in adults from the French childhood leukemia survivors' cohort: a comparison with controls from the French population. *Haematologica 2018 Volume 103(4):645-654*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Country of origin: France Treatment era: 1980-present Follow-up: Mean follow-up duration since diagnosis was 16.32 ± 0.21 years.	1025 childhood ALL/AML survivors (female N=524 (51.1%) and male N=501 (48.9%)). 1462 survivors were eligible participants, 1025 survivors participated in the study Primary cancer diagnosis: ALL N=867 (84.6%) AML N=158 (15.4%) Age at primary cancer diagnosis: Mean 8.37 (±0.15) yrs Age at follow-up/evaluation: Mean 24.4 (± 0.2) yrs Ethnicity: Not reported. Controls: 3203 age- and sex-matched controls. Controls had significantly lower SES and education levels and higher BMI than survivors.	Chemotherapy only: N=637 (62.2%) Chemotherapy + CNS RT: N=143 (13.9%) HSCT + TBI: N=168 (16.4%) HSCT +Bu-based cond.: N=77 (7.5%) HSCT: N=245 (23.9%) **Autologous** N=65 (26.5%) **Allogeneic** N=180 (73.5%) **Matched sibling** N=105 (62.1%) **Mismatched related donor** N=9 (5.3%) **Matched unrelated donor** N=32 (18.9%) **Cord blood** N=23 (13.6%) CNS Radiation therapy: N=168 (16.4%) **18 Gy** N=128 (76.2%) **24 Gy** N=28 (16.7%) Other radiation: N=8 (4.8%) **Cranial irradiation** N=122 (72.6%) **Craniospinal irradiation** N=44 (26.2%)	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2005 modified version). **Results:** Prevalence of METS (with all criteria) in study cohort: 10.3% (n=106/1025) in survivors 4.5% (n=145/3203) in controls OR 2.49, 95% CI 1.91-3.25 P<0.001 Prevalence of METS (without hypertension criterium) in study cohort: 46 survivors (4.5%) 66 controls (2.1%) P<0.001 Gender and METS: 9.7% of female survivors 4% of female controls OR 2.56, 95% CI: 1.75-3.74 P<0.001 11% of male survivors 5% of male controls OR 2.33, 95% CI 1.63-3.34 P<0.001 *No analyses done to compare males vs females.* Cumulative incidence of MetS in survivors over time: 25 years: 7.86% (95%CI: 5.99-10.29) 30 years: 14.42% (95%CI: 11.22-18.43) HSCT and MetS vs controls:	Limitations - possible underevaluation of METS due to young age of included survivors - significant differences between survivors and controls Strengths - multivariate analyses - prospective study - large cohort **Risk of bias:** - Selection bias: unclear. - Attrition bias: high risk, outcome was assessed for 1025 (=70.2%) of eligible survivors. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, only adjusted for sex and age and not other variables significantly different between survivors and controls (SES, education level and BMI).

			Prevalence 18.8%, OR 4.87, 95%CI: 3.4-6.99 P<0.001 HSCT + TBI and MetS vs controls: All: prevalence N=39 (23.2%), OR=6.26, 95%CI: 4.17-9.36 P<0.001 Women: OR=9.25, 95%CI: 5.33-16.1) P<0.001 Men: OR=4.13, 95%CI: 2.26-7.56 P<0.001 HSCT without TBI and MetS vs controls: Prevalence N=7 (9.1%) OR=2.18, 95%CI: 0.97-4.86 P=0.057 CNS irradiation and MetS vs controls: OR= 2.32 (95%CI: 1.36-3.97) P=0.002 Chemotherapy only and MetS vs controls: OR= 1.68 (95%CI: 1.17-2.41) P=0.005	

Who needs surveillance?				
Saultier et al. (2016). Metabolic syndrome in long-term survivors of childhood acute leukemia treated without hematopoietic stem cell transplantation: an L.E.A. study. *Haematologica 2016 Volume 101(12):1603.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Country of origin: France Treatment era: Since 1980 Follow-up: Mean follow-up since diagnosis 16.00±6.79 yrs.	650 childhood ALL survivors (female N=339 (52.2%) and male N=311 (47.8%)). 870 survivors were eligible participants, 650 survivors participated in the study. Primary cancer diagnosis: ALL N=582 (89.5%) AML N=62 (9.5%) Biphenotypic N=6 (0.9%) Age at primary cancer diagnosis: Mean 8.22±4.80 yrs. Age at follow-up/evaluation: Mean 24.23±5.18 yrs. Ethnicity: Not reported. Controls: N/A.	CNS radiation: **None** N=530 (81.5%) **18 Gy** N=94 (14.5%) **24 Gy** N=21 (3.2%) **Unknown** N=5 (0.8%) Radiation type: **Cranial** N=87 (74.4%) **Craniospinal** N=29 (24.8%) **Unknown** N=1 (0.9%) Steroids dose Cumulative prednisone-equivalent dose mean 4494±2578 mg/m2	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2005 modified version). **Results:** Prevalence of METS in study cohort: N=45 (6.9%), 95% CI 5.1-9.2 No. of METS components ≥ 1 N=385 (59.2%), 95% CI 55.3-63.0 ≥ 2 N=149 (22.9%), 95% CI 19.8-26.4 Age and METS Cumultative prevalences: Cumulative prevalence increases with age: The age-specific cumulative prevalence at 20 yrs, 1.3% (95% CI 0.6-2.7). 25 yrs, 6.1% (95% CI 4.0-9.1). 30 yrs, 10.8% (95% CI 7.2-15.9). 35 yrs, 22.4% (95% CI 15.1-32.6). Age at last evaluation (multivariable): **Each additional year of follow-up** OR 1.10 95% CI 1.04-1.17, P=0.001. Gender and METS (multivariable): **Male vs female (ref)** OR 2.64; 95% CI 1.32-5.29; P=0.006. BMI and METS Mean BMI at last evaluation (univariate): **No METS** 22.9±3.7 kg/m2 (obese N=22, 3.7%) **METS** 29.5±5.8 kg/m2 (obese N=19, 45.2%) (P<0.001). BMI-z score at diagnosis (multivariable): **METS vs no METS (ref)** OR 1.15 per each	Limitations - possible underevaluation of METS due to young age of included survivors. - not accounted for potential risk factors such as genetics and behavioural factors. - lack of appropriate comparison group. Strengths - multivariate analyses - prospective study - homogenous cohort **Risk of bias:** - Selection bias: 650 out of 870 eligible survivors participated in the study (=74.7%) > low risk, reasons for not participating are quite unclear (named reason is evaluation incomplete), but no significant difference between cohorts. - Attrition bias: low risk, outcome was assessed for all included participants. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, multivariable analysis included all variables that were significant in univariate analysis (gender, age at last evaluation, BMI-z score at diagnosis, 24Gy CNS radiation).

			additional z-score unit; 95% CI 1.01-1.32; P=0.037). CNS radiation and METS (multivariable): **18 Gy vs no radiation** OR 0.92 95% CI 0.37-2.29, P =0.866. **24 Gy vs no radiation** OR 1.87 95% CI 0.56-6.27, P=0.309.	

Who needs surveillance?				
Smith et al. (2014). " Lifestyle and metabolic syndrome in adult survivors of childhood cancer: a report from the St. Jude Lifetime Cohort Study." Cancer. 2014 September 1; 120(17): 2742–2750.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Prospective cohort study Country of origin: USA Treatment era: Not reported Follow-up: Mean follow-up duration since diagnosis was 25.6 (± 7.6) years.	1639 childhood cancer survivors (female N=832(50.8%) and male N=807 (49.2%)). 2654 survivors were eligible participants, 1629 survivors participated in the study Primary cancer diagnosis: **ALL** N=809 (49.4%) **Lymphoma** N=264 (16.1%) **Sarcoma** N=180 (11.0%) **Neuroblastoma** N=70 (4.3%) **Wilms Tumor** N=74 (4.5%) **CNS tumor** N=135 (8.2%) **Other** N=107 (6.5%) Age at primary cancer diagnosis: Mean 7.9 (± 5.5) yrs Age at follow-up/evaluation: **18-29** N=604 (36.9%) **30-39** N=675 (41.2%) **40-49** N=311 (19.0%) **50-59** N=49 (3.0%) Race: **White** N=1435 (87.6) **Black** N=188 (11.5) **Other** N=16 (1.0) Educational attainment:	CRT: N=621 (37.9%) HSCT: N=45 (2.7%)	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2001). **Results:** Prevalence of METS in study cohort: 32.5 % of males 31.0% of females Adherence to WCRF/AICR guidelines and MetS: No adherence vs adherence to guidelines, males: RR 2.2, 95% CI 1.6-3.0. No adherence vs adherence to guidelines, females: RR 2.4, 95% CI 1.7-3.3. Advanced age and MetS: 30-39 years vs 18-29 years, females: RR 1.5, 95% CI 1.2-1.9. 30-39 years vs 19-29 years, males: RR 1.7, 95% CI 1.3-2.3. 40-59 years vs 18-29 years, females: RR 1.6, 95% CI 1.2-2.1. 40-59 years vs 18-29 years, males: RR 2.3, 95% CI 1.7-3.0. CRT and MetS: CRT vs no CRT, females: RR 1.4, 95% CI 1.2-1.8. CRT vs no CRT, males: RR not significant (data not shown).	Limitations - possible underevaluation of METS due to young age of included survivors - limited description of treatments received Strengths - multivariate analyses - prospective study - large cohort **Risk of bias:** - Selection bias: 1639 out of 2654 eligible survivors participated in the study (=61.8%) > high risk, reason for not participating: 46 (1.7%) lost to follow up, 707 (26.6%) who actively (n=245) or passively (n=462) chose not to participate, and 162 (6.1%) who completed the surveys butdid not complete a campus visit. An additional 41 (1.5%) had incomplete or inaccurate dietary or MetSyn status data. - Attrition bias: low risk, outcome was assessed for all included participants. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: low risk, potential confounders (current age, race, CRT, education, smoking status and age at diagnosis) included in regression model, analyses performed for females and males separately.

	<college graduate N=1002 (61.1%) **College graduate** N=597 (36.4%) **Not reported** N=40 (2.4%) Smoking status: **Current smoker** N=332 (20.3%) **None smoker** N=1307 (79.7%) BMI: **< 18.5 kg/m2** N=55 (3.4%) **18.5–24.9 kg/m2** N=497 (30.3%) **25.0–29.9 kg/m2** N=462 (28.2%) **>= 30 kg/m2** N=625 (38.1%) Controls: N/A.			

Who needs surveillance?				
Talvensaari et al. (1996). Long-Term Survivors of Childhood Cancer Have an Increased Risk of Manifesting the Metabolic Syndrome. *Journal of Clinical Endocrinology and Metabolism Volume 81(8):3051-3055.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Observationals and cross-sectional Country of origin: Finland Treatment era: 1972-1982 Follow-up: Mean follow-up duration since diagnosis was 12.6 (7.9-21.3) years	50 childhood cancer survivors (female N=27 (54%) and male N=23 (46%)). 59 survivors were eligible participants, 50 survivors participated in the study Primary cancer diagnosis: ALL N=28 (56%) ANLL N=1 (2%) Lymphoma N=7 (14%) Wilms' tumor N=7 (14%) Neuroblastoma N=3 (6%) Other N=4 (8%) Age at primary cancer diagnosis: Mean 4.2 (0.1-14.9) years Age at follow-up/evaluation: Mean 18.3 (10.5-31.2) years Ethnicity: Not reported. Controls: 50 sex- and age-matched controls.	Chemotherapy only: N=6 (12%) RT only: N=2 (4%) Chemotherapy + RT: N=42 (84%) HP axis RT: *Median 25 Gy, 15-46 Gy* N=31 (64%) RT testis: *24 Gy* N=12 (24%) RT trunk: *Median 29 Gy, 2-52 Gy* N=14 (28%) CRT: *15-25 Gy* ALL patients, N=28 (56%) Current medication All participants were cancer free and off therapy at time of the study. 4 participants were on GH therapy until 3 days before the study. 8 participants received testosterone supplementation, and 2 received L-T4. One female participant took estrogen pills.	Outcome definition: METS was defined as a combination of obesity (relative weight >120%), hyperinsulinemia (fasting plasma insulin >111 pmol/L) and low HDL cholesterol (serum HDL <1.07 mmol/L). **Results:** Prevalence of METS in the study cohort: 8 survivors (16%) vs 1 control (2%), p=0.01	Limitations - possible underevaluation of METS due to young age of included survivors - small cohort Strengths - prospective study **Risk of bias:** - Selection bias: 50 out of 59 eligible survivors participated in the study (=84.7%) > low risk, reason for not participating: 2 untraceable, 1 pregnant, 3 refusals, 1 Turner's syndrome, 1 Mulibrey nanism, 1 no consent for using blood sample. - Attrition bias: low risk, outcome was assessed for all included participants. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, only adjusted for sex and age and not other variables significantly different between survivors and controls.

Who needs surveillance?				
Tonorezos et al. (2013). Contribution of diet and physical activity to metabolic parameters among survivors of childhood leukemia. *Cancer Causes Control. 2013 February ; 24(2): 313–321.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design: Cross Sectional Country of origin: USA Treatment era: 1970-2000+ Follow-up: Mean follow-up duration since treatment was 17.5 years	118 childhood ALL survivors (female N=65 (56%) and male N=52 (44%)). … survivors were eligible participants, 118 survivors participated in the study Primary cancer diagnosis: ALL N=118 (100%) Age at primary cancer diagnosis: Mean 6.7 (±4.3) years Age at follow-up/evaluation: Mean 24.3 (±4.9) years Ethnicity: **African American** N=13 (11%) **White, non-Hispanic** N=84 (72%) **Hispanic** N=15 (13%) Controls: N/A	Chemotherapy: **Anthracyclines** N=84 (72%) Radiotherapy: **CRT** N=40 (34%) Steroids: **Dexamethasone** N=13 (11%)	Outcome definition: METS was defined using the revisions of the NCEP ATP III criteria (2001). **Results:** Prevalence of METS in study cohort: N=21 (17.8%). Mediterranean diet score and METS: 4-5 vs 0-3: OR 0.9, 95% CI 0.3-2.7 6-8 vs 0-3: OR 0.1, 95% CI 0.01-0.9 P=0.04 (for trend). PAEE (physical activity energy expenditure) and MetS: Inclusion of PAEE in the logistic regression models did not alter the findings (i.e. no significant effect on development of METS).	Limitations - possible underevaluation of METS due to young age of included survivors Strengths - multivariate analyses - large cohort **Risk of bias:** - Selection bias: unclear, unclear selection of participants. - Attrition bias: low risk, outcome was assessed for all included participants. - Detection bias: unclear if the outcome assessors were blinded for important determinants related to the outcome. - Confounding: high risk, multivariate analysis but only including gender and age as confounding factors.

Who needs surveillance?				
Van Waas et al. (2012). Abdominal radiotherapy: A major determinant of metabolic syndrome in nephroblastoma and neuroblastoma survivors. *Plos One 7(12): e52237.*				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Study design - single-center - observational - cross-sectional - prospective clinical assessment - retrospective collection of exposure data Country of origin - The Netherlands Treatment era - 1961-2004 Follow-up (median) - 26.2 yrs (6.4-48.9 yrs) for nephroblastoma - 27.8 yrs (15.0-44.4 yrs) for neuroblastoma	Type and number of participants - 103 CCS - ≥5 yrs after end of Tx - ≥18 yrs at study - survivors recruited from late effects clinic (selection bias!) Diagnoses - nephroblastoma (67/103) - neuroblastoma (36/103) Age at diagnosis (median, range) - nephroblastoma: 3.3 (0.0-12.7) yrs - neuroblastoma: 0.8 (0.0-11.7) yrs Age at follow-up (median, range) - nephroblastoma: 30.2 (18.8-50.8) yrs - neuroblastoma: 29.6 (20.4-46.2) yrs Ethnicity Not mentioned Controls (if applicable) - **61 controls** - siblings, friends, neighbors ("preferably" same sex, within 5 year age range) - Age at study (median, range) 31.8 (18.0-61.8) yrs	**Chemotherapy** **N= 90** (87%), combined Agent: N, median cumulative dose 1.nephroblastoma 2.neuroblastoma Vincristin 1.N=51, 22.0 mg/m2 2.N=16, 22.8 mg/m2 Actinomycin D 1.N=18, 250 mg/m2 2.N=12, 210 mg/m2 Anthracyclines 1.N=48, 10.9 mg/m2 2.N=0 Cyclophopsphamide 1.N=2, 3825 mg/m2 2.N=29, 7350 mg/m2 Cisplatin 1.N=0 2.N=6, 450 mg/m2 Teniposide 1.N=0 2.N=6, 500 mg/m2 Dacarbazine 1.N=2, 14.7 mg/m2 2.N=0 Ifosfamide 1.N=2, 33000 mg/m2 2.N=0	**Outcome definitions** - METS was defined using the revisions of the **NCEP ATP III** criteria; participants with 3 or more of the following criteria were considered positive for metabolic syndrome: 1) waist circumference >102 cm in men or >88 cm in women 2) triglyceride levels ≥150mg/dL 3) HDL-C <40 mg/dL in men or <50 mg/dL in women or on current treatment for high cholesterol 4) blood pressure ≥130/85 mmHg or on current treatment for hypertension 5) glucose ≥100 mg/dL. - Additional outcomes: 1) single METS components 2) insulin, HOMA, LDL, FFA 3) % total body fat (Dexa): SDS ≥2 as cutoff **Explanatory variable/confounders for multivariable logistic and linear regression:** - attained age, sex - educational level (SES) (questionnaire) - physical activity (questionnaire) - smoking (questionnaire) **Exposures:** - chemotherapy y/n - surgery: nephrectomy y/n, adrenalectomy y/n - abdominal RT y/n - pancreas total y/n /partial y/n - liver total y/n /partial y/n **Results** 1) **Prevalence of single METS components** in study cohort:	**Risk of bias** A. Selection bias: High risk Reasons: 1) Eligible survivors include only those who regularly visit the late effects clinic -> maybe the healthier ones do not come to the clinic? Or survivors are somewhere else in F/U care? 2) Of eligible neuroblastoma survivors, only 66% participated (76% participation rate for neuroblastoma survivors) Also selection of controls might involve selection bias (58% participation rate) B. Attrition bias: Low risk All subjects were included in the analysis. C. Detection bias: Unclear Reason: Although blinding is not mentioned, it is probably less important for the assessment of the outcomes as they probably have been collected before setting up the study. D. Confounding: Low risk Reason: Different adjustments for different models 1-4, but always including attained age and sex. **Strengths** - homogenous study population with only nephroblastoma/ neuroblastoma - control group (but with potential selction bias) - detailed information on abdominal radiation -> stratification into partial/total liver/pancreas RT **Limitations** - single-center study - cross-sectional design - no dexa in controls

		Radiotherapy (RT) Abdominal RT N=42 (41%), categorized into fields A-D: A) spine B) left hemiabdomen C) right hemiabdomen D) total abdomen -Cumulative doses for RT (inlcuding 3 survivors with non-abdominal RT): median 20 Gy - Pancreas RT (fields A-D): partial (A+C): N=15 total (B+D): N=27 - Liver RT: Partial (A+B): N=19 total (C+D): N=23 **Surgery** - adrenalectomy, N=49 - nephrectomy, N=74 HSCT: not reported	Nephroblastoma/Neuroblastoma/Controls - high fasting glucose*: 22%/20%/14% - hypertension*: 39%/29%/14% - low HDL*: 24%/29%/20% - high triglycerides*: 27%/18%/11% - high LDL*: 31%/31%/21% - high waist circumference*: 6%/12%/10% - high % total body fat*: 15%/19%/NA *or treatment sig. difference between nephroblastoma and controls for hypertenison (p=0.002) and high triglycerides (p=0.031), other comparisons not sig. **Prevalence of METS (acc. NCEP)** not different between nephroblastoma survivors, neuroblastoma survivors, and controls (no numbers given, see Fig2) 2) **Logistic regression** (adjusting for attained age, sex, educational level and BMI) assessing association between nephroblastoma/ neuroblastoma/controls (=ref) and METS: Nephroblastoma OR 4.3 (p=0.093) Neuroblastoma OR 2.7 (p=0.38) -> no positive association between cancer dx and presence of METS **-> authors summary: abdominal RT is main determinant of metabolic syndrome**	**Others remarks** - the association between abdominal RT and different METS outcomes seems to be consistent, but there are many associations investigated which seems to be very exploratory in nature - the selection of confounders into models 1-4 is not totally clear - it is a bit confusing that for each outcome adjustment was different - why was abdominal RT and metabolic syndrome not investigated in logistic regression as this is the condition used in clinical setting? - the prevalence of METS using % total body fat positive as more than 2 SDs of reference population is not an established and validated way to score METS. Although the ratio is clear, this is not the standard and should be excluded from data analysis.