

Guidelines for Off-Treatment Surveillance: Frequency and Modality

Foreword

Although routinely undertaken, the efficacy of disease surveillance after completion of anti-cancer therapy is almost devoid of evidence. Salient information that applies specifically to paediatric oncology:

- 75-86% of recurrences are suspected on history/physical examination rather than detected by routine imaging¹
- In order to detect one instance of recurrent childhood cancer, 42 MRIs, 129 CTs and 257 CXRs are performed. However, there is some evidence that routine imaging is efficacious in monitoring brain tumours^{2,3}
- In Hodgkin Lymphoma, 1080 CT scans were performed to detect 4 late recurrences none of which resulted in the child succumbing to their illness⁴
- Scanning consumes resources, in particular MRI which is often done under general anaesthetic
- Scanning with x-rays is not innocent! Measurement of exposure is in milliSieverts (mSv; 1mSV=0.01Gy), a composite of radiation dose and biological radiosensitivity of the exposed tissue(s). Average annual background exposure is 3mSv. Estimates exposure relating to particular investigations is shown below⁵:

TABLE I. Estimated Effective Radiation Dose for Various Diagnostic Imaging Studies

| Imaging study | Estimated dose (mSv) |
|---------------------------------------|----------------------|
| CT chest | 6 |
| CT abdomen | 7 |
| CT pelvis | 6 |
| CT head | 2 |
| PET scan ¹⁸ FFDG* | 10 (adult) |
| | 15.3 (age 5) |
| PET/CT** | 25 |
| Bone scan ^{99m} Tc phosphate | 4.9 (age 1) |
| | 4.2 (age 5) |
| | 4.1 (age 10) |
| MIBG scan | 10.1 (age 1) |
| | 8.8 (age 5) |
| Gallium scan | 27.9 (age 1) |
| | 22.8 (age 10) |
| CXR (2 views) | .08 |
| X-ray, T-spine (2 views) | .52 |
| X-ray, extremity (2 views) | .06 |

Children with a range of cancers are exposed to a median of 61mSv, with some disease groups receiving considerably greater exposure than others²:

TABLE I. Median Cumulative Effective Dose Estimates in a Cohort of Pediatric Oncology Patients

| Diagnostic group | Median cumulative effective dose (mSv) |
|-----------------------|--|
| Leukemia | 5 |
| Lymphoma | 190 |
| Neuroblastoma | 214 |
| Brain tumors | 12 |
| Assorted solid tumors | 90 |
| Total cohort | 61 |

Exposure to 100mSv is estimated to result in one cancer in 100 individuals, quite possibly higher when exposure occurs in childhood. A single abdominal CT scan is estimated to result in cancer in 1:550 individuals⁵. “Take home” messages:

1. If possible, avoid or limit surveillance using CT, PET or other forms of radionuclides
2. If CT is strongly recommended, then ensure that paediatric scanning protocols are adhered to, in order to minimize radiation exposure

Using the Guidelines

The Guidelines are *adapted from* the various reference protocols identified at the end of this document – in general, there is release from the frequency of surveillance stringently mandated in clinical trials. Of course, if your patient is entered on a clinical trial, then that surveillance regimen must be adhered to – these guidelines apply to those patients (the majority, in fact) not entered onto a clinical trial. Apart from Hodgkin Lymphoma, and to a lesser degree, brain tumours, there is no *evidence* to guide these recommendations. For those patients under follow-up in shared care centres, an attempt has been made to divide this responsibility between the shared care paediatrician and visiting paediatric oncologist – there are obvious advantages (1) our colleague is engaged in the process, chasing and checking surveillance and other results (2) familiarity with local services, particularly community-based, enhance holistic patient/family care (3) frequency of paediatric oncologist follow-up is reduced with beneficial impacts on clinic frequency and travel. There are some glaring potential disadvantages not least of which is loss of frequent contribution from a child cancer specialist – this may be offset by excellent communication, and holding joint visiting paediatric oncology-shared care paediatrician clinics.

While these guidelines recommend the frequency of follow-up visits with increasing time from end of treatment, the decision about whether the visit will be with the oncologist or shared-care paediatrician will depend on several factors. Individual patient and family characteristics, disease and late effect aspects and the frequency of outreach clinics to a particular centre will all need to be taken into account.

Finally, these are guidelines - they should not replace accurate clinical judgment in specific cases. The individual clinician is responsible for their patients’ care and the author(s) of this guideline cannot be held responsible for their adoption.

| Acute Lymphoblastic Leukaemia (B-precursor) * | | |
|--|------------------------|--|
| Year off-treatment | Modality | Frequency |
| 1 st | PE, CBC/diff/platelets | Q4 weeks until count recovery, then at least Q3 months |
| 2 nd | PE, CBC/diff/platelets | At least Q3 months |
| 3 rd | PE, CBC/diff/platelets | Q4 - 6 months |
| 4 th | PE, CBC/diff/platelets | Q6 - 12 months |
| 5 th | PE, CBC/diff/platelets | Q6 - 12 months |

*This schedule is ultimately left to the treating Consultant's discretion. Obtain any of these studies and/or others at any time as clinically indicated.

| Acute Lymphoblastic Leukaemia (T-precursor) | | |
|---|-----------|------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; FBC | 6-8 weekly |
| 2 nd | H/PE; FBC | 2-monthly |
| 3 rd | H/PE; FBC | 3-monthly |
| 4 th | H/PE; FBC | 6-monthly |
| 5 th | H/PE; FBC | 12-monthly |

| Acute Myeloid Leukaemia | | |
|-------------------------|-----------|------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; FBC | 1-monthly |
| 2 nd | H/PE; FBC | 4-monthly |
| 3 rd | H/PE; FBC | 6-monthly |
| 4 th | H/PE; FBC | 12-monthly |

| Brain Tumour – Atypical Teratoid Rhabdoid Tumour | | |
|--|-----------------------|--------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI brain/spine | 4-monthly |
| 2 nd | H/PE; MRI brain/spine | 4-monthly |
| 3 rd | H/PE; MRI brain/spine | 6-monthly |
| 4 th | H/PE; MRI brain/spine | At 48 months |

| Brain Tumour – Choroid Plexus Tumours | | |
|---------------------------------------|-----------------------|-----------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI brain/spine | 3-monthly |
| 2 nd – 4 th | H/PE; MRI brain/spine | 6-monthly |

| Brain Tumour - Ependymoma | | |
|-----------------------------------|---------------------------------|----------------------------------|
| Year off-treatment | Modality | Frequency |
| 1 st - 2 nd | H/PE; MRI primary; MRI spine | 4-monthly At 12 and 24 months |
| 3 rd - 5 th | H/PE; MRI primary | 6-monthly |

| Brain Tumour – Germ Cell Tumour | | |
|-----------------------------------|---|------------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | Serum markers H/PE; MRI brain and spine | 3-monthly 3-monthly |
| 2 nd | H/PE; MRI brain and spine; serum markers | 4-monthly |
| 3 rd - 5 th | H/PE; MRI brain and spine; serum markers | Annual |

| Brain Tumour – Low-grade Glioma (Juvenile pilocytic astrocytoma; optic pathway glioma) | | |
|---|---|------------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; ophthalmology exam (if affecting optic pathway); MRI | 3-monthly 6-monthly |
| 2 nd - 4 th | H/PE; MRI; ophthalmology exam (if affecting optic pathway) | 6-monthly |
| 5 th onwards | H/PE; MRI; ophthalmology exam (if affecting optic pathway) | At 60 months |

| Brain Tumour – High-grade Glioma (including Diffuse Intrinsic Pontine Glioma) | | |
|---|-----------------|------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI | 4-monthly |
| 2 nd | H/PE; MRI | 6-monthly |
| 3 rd | H/PE; MRI | 6-monthly |
| 4 th | H/PE; MRI | At 48 months |
| 5 th | H/PE; MRI | At 60 months |

| Brain Tumour – Infant (not otherwise specified) | | |
|--|-----------------|------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI | 3-monthly |
| 2 nd | H/PE; MRI | 4-monthly |
| 3 rd | H/PE; MRI | 6-monthly |
| 4 th | H/PE; MRI | At 48 months |

| Brain Tumour – Medulloblastoma | | |
|---------------------------------------|-----------------------|------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI brain/spine | 3-monthly |
| 2 nd - 3 rd | H/PE; MRI brain/spine | 4monthly |
| 4 th | H/PE; MRI brain/spine | 6-monthly |
| 5 th | H/PE; MRI brain/spine | At 60 months |

| Brain Tumour – PNET | | |
|-----------------------------------|-----------------------|------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; MRI brain/spine | 3-monthly |
| 2 nd - 3 rd | H/PE; MRI brain/spine | 4-monthly |
| 4 th | H/PE; MRI brain/spine | 6-monthly |
| 5 th | H/PE; MRI brain/spine | At 60 months |

| Ewing Sarcoma | | |
|---------------------------|---|---|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE; CXR (PA & lat) Plain X-ray primary MRI (or other imaging) primary | 3-monthly 3 and 9 months 6 and 12 months |
| 2 nd | H/PE; CXR (PA & lat) Plain X-ray primary MRI (or other imaging) primary | 3-monthly 15 and 21 months 18 and 24 months |
| 3 rd | H/PE; CXR (PA & lat) Plain X-ray primary MRI (or other imaging) primary | 3-monthly 27 and 33 months 30 and 36 months |
| 4 th | H/PE; CXR (PA & lat); plain X-ray primary | 6-monthly |
| 5 th | H/PE; CXR (PA & lat); plain X-ray primary | 6-monthly |

| Germ Cell Tumour | | |
|---------------------------|---|--|
| Year off-treatment | Modality | Frequency |
| 1 st | <u>Secreting Tumour</u> AFP/βHCG H/PE CXR (PA & lat); imaging primary <u>Non-Secreting Tumour</u> H/PE; CXR(PA & lat); image primary | Monthly 3-monthly 6-monthly 3-monthly |
| 2 nd | <u>Secreting Tumour</u> AFP/βHCG H/PE CXR(PA & lat); image primary <u>Non-Secreting Tumour</u> H/PE; CXR(PA & lat); image primary | 2-monthly 4-monthly 6-monthly 4-monthly |
| 3 rd | <u>Secreting Tumour</u> AFP/βHCG H/PE <u>Non-Secreting Tumour</u> H/PE; CXR(PA & lat); image primary | 3-monthly 6-monthly 6-monthly |

| Hepatoblastoma | | |
|---------------------------|---|-------------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | AFP H/PE; CXR(PA & lat); abdo ultrasound | 1-monthly 3-monthly |
| 2 nd | AFP H/PE; CXR(PA & lat); abdo ultrasound | 1-monthly 3-monthly |
| 3 rd | H/PE; AFP; CXR(PA & lat); abdo ultrasound | 6-monthly |
| 4 th | H/PE; AFP CXR(PA & lat); abdo ultrasound | 6-monthly 12-monthly |
| 5 th | H/PE; AFP CXR(PA & lat); abdo ultrasound | 6-monthly 12-monthly |

| Hodgkin Lymphoma | | |
|--|---|---------------------------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE/labs – FBC;ESR;LDH When possible recurrence not clinically assessable, CT initial involved sites <i>only</i> ^π | 3-monthly 6-monthly |
| 2 nd | H/PE/labs – FBC;ESR;LDH CXR (PA & lat) | 6-monthly At 24 months |
| 3 rd | H/PE/labs – FBC;ESR;LDH CXR (PA & lat) | 6-monthly At 36 months |
| ^π MRI can replace CT provided that MRI has successfully demonstrated disease at diagnosis or at early response assessment | | |

| Langerhans Cell Histiocytosis | | |
|--|---|---|
| Year off-treatment | Modality | Frequency |
| 1 st | <u>With Risk Organ Involvement</u> H/PE FBC/ESR/LFT/renal/urine osmo Bone involvement – plain X-ray Pulmonary involvement – HR CT chest; pulmonary function Liver involvement – ultrasound Diabetes insipidus/other endocrinopathy – MRI CNS “risk” lesions - MRI <u>Without Risk Organ Involvement</u> H/PE FBC/ESR/LFT/renal/urine osmo Bone involvement – plain X-ray Diabetes insipidus/other endocrinopathy – MRI CNS “risk” lesions - MRI <u>Multifocal Bone/”Special” sites</u> H/PE FBC/ESR/LFT/renal/urine osmo Bone involvement – plain X-ray Diabetes insipidus/other endocrinopathy – MRI CNS “risk” lesions - MRI | 6-weekly 3-monthly 3-monthly (until regression) 6-monthly 6-monthly At 12 months 3-monthly until regression/stable 6-weekly 3-monthly 3-monthly (until regression) At 12 months 3-monthly until regression/stable 3-monthly 6-monthly 3-monthly (until regression) At 12 months 3-monthly until regression/stable |
| 2 nd – 5 th year | <u>With Risk Organ Involvement</u> H/PE FBC/ESR/LFT/renal/urine osmo Pulmonary involvement – HR CT chest; pulmonary function Diabetes insipidus/other endocrinopathy/CNS “risk” lesion – MRI <u>Without Risk Organ Involvement</u> H/PE FBC/ESR/LFT/renal/urine osmo Diabetes insipidus/other endocrinopathy/CNS “risk” lesion – MRI <u>Multifocal Bone/”Special” sites</u> H/PE FBC/ESR/LFT/renal/urine osmo Diabetes insipidus/other endocrinopathy/CNS “risk” lesion – MRI | 6-monthly 6-monthly As clinically indicated, at least once at 5yrs Annual Annual 6-monthly 6-monthly Annual 6-monthly 6-monthly Annual |

| Neuroblastoma – low and intermediate risk | | |
|---|--|--|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE Urine catecholamines Image primary Only in case of MIBG positive <i>skeletal</i> disease at end of therapy - MIBG scan | 3-monthly Repeat 3-monthly until negative. Then perform annually. |
| 2 nd | H/PE Urine catecholamines Image primary Only in case of MIBG positive <i>skeletal</i> disease at end of therapy - MIBG scan | 3-monthly At 24 months |
| 3 rd | H/PE Urine catecholamines Image primary Only in case of MIBG positive <i>skeletal</i> disease at end of therapy - MIBG scan | 6-monthly At 36 months |

| Neuroblastoma – High Risk | | |
|-----------------------------------|---|---|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE Urine catecholamines Image primary site Only in case of MIBG positive <i>skeletal</i> disease at end of therapy - MIBG scan | 3-monthly Repeat 3-monthly until negative (or progression) |
| 2 nd - 5 th | H/PE Urine catecholamines Image primary site Only in case of MIBG positive <i>skeletal</i> disease at end of therapy - MIBG scan | 6-monthly At 24, 36, 48 and 60 months |

| Non-Hodgkin Lymphoma – Anaplastic Large Cell Lymphoma | | |
|--|---|---|
| Year off-treatment | Modality | Frequency |
| 0 – 6 months | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 1-monthly At 6 month time-point |
| 6 – 12 months | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 2-monthly At 12 month time-point |
| 2 nd | H/PE | 4-monthly |
| 3 rd | H/PE | 6-monthly |

| Non-Hodgkin Lymphoma – Diffuse Large B Cell | | |
|--|---|---|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 1-monthly At 6 and 12 month time-points |
| 2 nd | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 3-monthly At 18 and 24 month time-points |
| 3 rd | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 6-monthly At 30 and 36 month time-points |

Non-Hodgkin Lymphoma – mature B (Burkitt's)

| Year off-treatment | Modality | Frequency |
|--------------------|---|---|
| 0 – 6 months | H/PE When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 1-monthly At 6 month time-point |
| 6 – 12 months | When possible recurrence not clinically assessable, CXR(PA & lat); US abdo (image only previously involved sites) | 2-monthly At 12 month time-point |
| 2 nd | H/PE | 4-monthly |
| 3 rd | H/PE | 6-monthly |

Non-Hodgkin Lymphoma - T precursor

| Year off-treatment | Modality | Frequency |
|--------------------|-----------|------------|
| 1 st | H/PE; FBC | 6-8 weekly |
| 2 nd | H/PE; FBC | 2-monthly |
| 3 rd | H/PE; FBC | 3-monthly |
| 4 th | H/PE; FBC | 6-monthly |

Osteosarcoma

| Year off-treatment | Modality | Frequency |
|------------------------------------|--|-----------|
| 1 st | H/PE CT chest Plain X-ray (or other imaging) primary site | 3-monthly |
| 2 nd | H/PE CT chest Plain X-ray (or other imaging) primary site | 3-monthly |
| 3 rd | H/PE CXR(PA & lat) Plain X-ray (or other imaging) primary site | 6-monthly |
| 4 th | H/PE CXR(PA & lat) | 6-monthly |
| 5 th | H/PE CXR(PA & lat) | 6-monthly |
| 6 th – 10 th | CXR(PA & lat) | 6-monthly |

| Retinoblastoma | | |
|---|-------------|-------------|
| Year off-treatment | Modality | Frequency |
| 1 st and 2 nd | H/PE MRI | 3-4 monthly |
| 3 rd , 4 th , 5 th | H/PE MRI | 6-monthly |
| 6 th and subsequent | H/PE | Annual |

Notes:

1. This applies to all retinoblastoma; unilateral/bilateral/enucleated eye/salvaged eye, chemo/no chemo, GLM negative/positive/mosaic
2. After year 3, MRI may be omitted for GLM negative patients at the discretion of the paediatric oncologist
3. MRI includes orbits, optic nerves, brain including pineal, pre-auricular and high cervical nodes but not spinal cord
4. Metastatic patients will have individualized investigations
5. Ophthalmology follow-up will be individualized and at a site and frequency decided by the ophthalmologist.
6. Most recurrences will occur by 3 years

| Rhabdomyosarcoma | | |
|--------------------|---|-----------|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE CXR(PA & lat) Image primary site | 3-monthly |
| 2 nd | H/PE CXR(PA & lat) Image primary site | 4-monthly |
| 3 rd | H/PE CXR(PA & lat) Image primary site | 4-monthly |
| 4 th | H/PE | 6-monthly |
| 5 th | H/PE | 6-monthly |

| Wilms' Tumour | | |
|--------------------|---|---|
| Year off-treatment | Modality | Frequency |
| 1 st | H/PE Ultrasound abdomen CXR(PA & lat) CT chest | 3-monthly 3-monthly At 3 and 9 months At 6 and 12 months |
| 2 nd | H/PE Ultrasound abdomen CXR(PA & lat) CT chest | 3-monthly 3-monthly At 15, 18 and 21 months At 24 months |
| 3 rd | H/PE Ultrasound abdomen CXR(PA & lat) | 6-monthly |
| 4 th | H/PE Ultrasound abdomen CXR(PA & lat) | 6-monthly |

Guidelines adapted from:

1. Acute Lymphoblastic Leukaemia B-precursor COG AALL0932
2. Acute Lymphoblastic Leukaemia T-precursor COG AALL0434
3. Acute Lymphoblastic Leukaemia B-precursor COG AALL1731
4. Acute Lymphoblastic Leukaemia B-precursor COG AALL1732
5. Acute Myeloid Leukaemia COG AAML1031
6. Brain Tumour
 - a. ATRT COG ACNS0333
 - b. Choroid Plexus Tumours CPT SIOP 2009
 - c. Ependymoma COG ACNS0831
 - d. Germ cell tumour COG ACNS1123
UK Guidelines 2006
 - e. Infant Brain Tumours ANZCCSG BB99
SJYC07
 - f. Low Grade Glioma SIOP LGG 2004 v2
COG ACNS0221
 - g. High Grade Glioma COG ACNS0126
 - h. Medulloblastoma COG ACNS0331
 - i. Primitive Neuroectodermal Tumour COG ACNS0331
7. Ewing Sarcoma COG AEWS1031
8. Germ Cell Tumours (extracranial) COG AGCT0132
CRCTU (UK) GC2005-04
9. Hepatoblastoma SIOPEL 6
10. Hodgkin Lymphoma Journal of Clinical Oncology 2012: 30 (21): 2635-2640
11. Langerhans Cell Histiocytosis LCH III
12. Neuroblastoma –Low and Intermediate Risk COG ANBL0531
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13. Neuroblastoma – High Risk COG ANBL0532
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16. Rhabdomyosarcoma EpSSG RMS 2005
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17. NHL – Anaplastic Large Cell Lymphoma ALCL 99
ANHL0131
18. NHL – Diffuse Large B Cell ANHL1131
19. NHL – Mature B COG ANHL1131
UKCCSG B NHL Guidelines 2003
20. NHL – T precursor COG AALL0434
21. Wilms' Tumour COG AREN0533
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5. Robbins E. Radiation risk from imaging studies in children with cancer. *Pediatr Blood Cancer* 2008;51:453-457