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 imaging[1]
- 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 illness[4]
- 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 below[5]:

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 others[2]:

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 individuals[5]. "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 and T precursor)		
Year off-treatment	**Modality**	**Frequency**
1st	H/PE; FBC	6-8 weekly
2nd	H/PE; FBC	2-monthly
3rd	H/PE; FBC	3-monthly
4th	H/PE; FBC	6-monthly
5th	H/PE; FBC	12-monthly

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

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

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

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

Brain Tumour – Germ Cell Tumour		
Year off-treatment	**Modality**	**Frequency**
1st	Serum markers H/PE; MRI brain and spine	3-monthly 3-monthly
2nd	H/PE; MRI brain and spine; serum markers	4-monthly
3rd - 5th	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**
1st	H/PE; ophthalmology exam (if affecting optic pathway); MRI	3-monthly 6-monthly
2nd - 4th	H/PE; MRI; ophthalmology exam (if affecting optic pathway)	6-monthly
5th 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**
1st	H/PE; MRI	4-monthly
2nd	H/PE; MRI	6-monthly
3rd	H/PE; MRI	6-monthly
4th	H/PE; MRI	At 48 months
5th	H/PE; MRI	At 60 months

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

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

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

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

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

Hodgkin Lymphoma		
Year off-treatment	**Modality**	**Frequency**
1st	H/PE/labs – FBC;ESR;LDH When possible recurrence not clinically assessable, CT initial involved sites *only*[π]	3-monthly 6-monthly
2nd	H/PE/labs – FBC;ESR;LDH CXR (PA & lat)	6-monthly At 24 months
3rd	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**
1st	<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
2nd – 5th 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**
1st	H/PE Urine catecholamines Image primary Only in case of MIBG positive *skeletal* disease at end of therapy - MIBG scan	3-monthly Repeat 3-monthly until negative. Then perform annually.
2nd	H/PE Urine catecholamines Image primary Only in case of MIBG positive *skeletal* disease at end of therapy - MIBG scan	3-monthly At 24 months
3rd	H/PE Urine catecholamines Image primary Only in case of MIBG positive *skeletal* disease at end of therapy - MIBG scan	6-monthly At 36 months

Neuroblastoma – High Risk		
Year off-treatment	**Modality**	**Frequency**
1st	H/PE Urine catecholamines Image primary site Only in case of MIBG positive *skeletal* disease at end of therapy - MIBG scan	3-monthly Repeat 3-monthly until negative (or progression)
2nd - 5th	H/PE Urine catecholamines Image primary site Only in case of MIBG positive *skeletal* 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
2nd	H/PE	4-monthly
3rd	H/PE	6-monthly

Non-Hodgkin Lymphoma – Diffuse Large B Cell		
Year off-treatment	**Modality**	**Frequency**
1st	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
2nd	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
3rd	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
2nd	H/PE	4-monthly
3rd	H/PE	6-monthly

Non-Hodgkin Lymphoma - T precursor		
Year off-treatment	**Modality**	**Frequency**
1st	H/PE; FBC	6-8 weekly
2nd	H/PE; FBC	2-monthly
3rd	H/PE; FBC	3-monthly
4th	H/PE; FBC	6-monthly

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

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

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

Guidelines adapted from:

1. Acute Lymphoblastic Leukaemia B-precursor COG AALL0932
2. Acute Lymphoblastic Leukaemia B-precursor COG AALL0434
3. Acute Myeloid Leukaemia COG AAML1031
4. 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

5. Ewing Sarcoma	COG AEWS1031
6. Germ Cell Tumours (extracranial)	COG AGCT0132 CRCTU (UK) GC2005-04
7. Hepatoblastoma	SIOPEL 6
8. Hodgkin Lymphoma	Journal of Clinical Oncology 2012: 30 (21): 2635-2640
9. Langerhans Cell Histiocytosis	LCH III
10. Neuroblastoma –Low and Intermediate Risk	COG ANBL0531 SIOPEN LINES
11. Neuroblastoma – High Risk	COG ANBL0532 SIOPEN HR-NBL-1.5
12. Osteosarcoma	CCG7921 Pediatr Blood Cancer 2012: 59 (6); 976
13. Rhabdomyosarcoma	EpSSG RMS 2005 COG ARST 0531
14. NHL – Anaplastic Large Cell Lymphoma	ALCL 99 ANHL0131
15. NHL – Diffuse Large B Cell	ANHL1131
16. NHL – Mature B	COG ANHL1131 UKCCSG B NHL Guidelines 2003
17. NHL – T precursor	COG AALL0434
18. Wilms' Tumour	COG AREN0533 SIOP WT 2001

References

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4. Voss SD, Chen L, Constine LS et al. Surveillance computed tomography imaging and detection of relapse in intermediate- and advanced -stage pediatric Hodgkin's lymphoma: a report from the Children's Oncology Group. 2012;30:2635-2640
5. Robbins E. Radiation risk from imaging studies in children with cancer. Pediatr Blood Cancer 2008;51:453-457