Models of care for LTFU: including therapy based risk stratification

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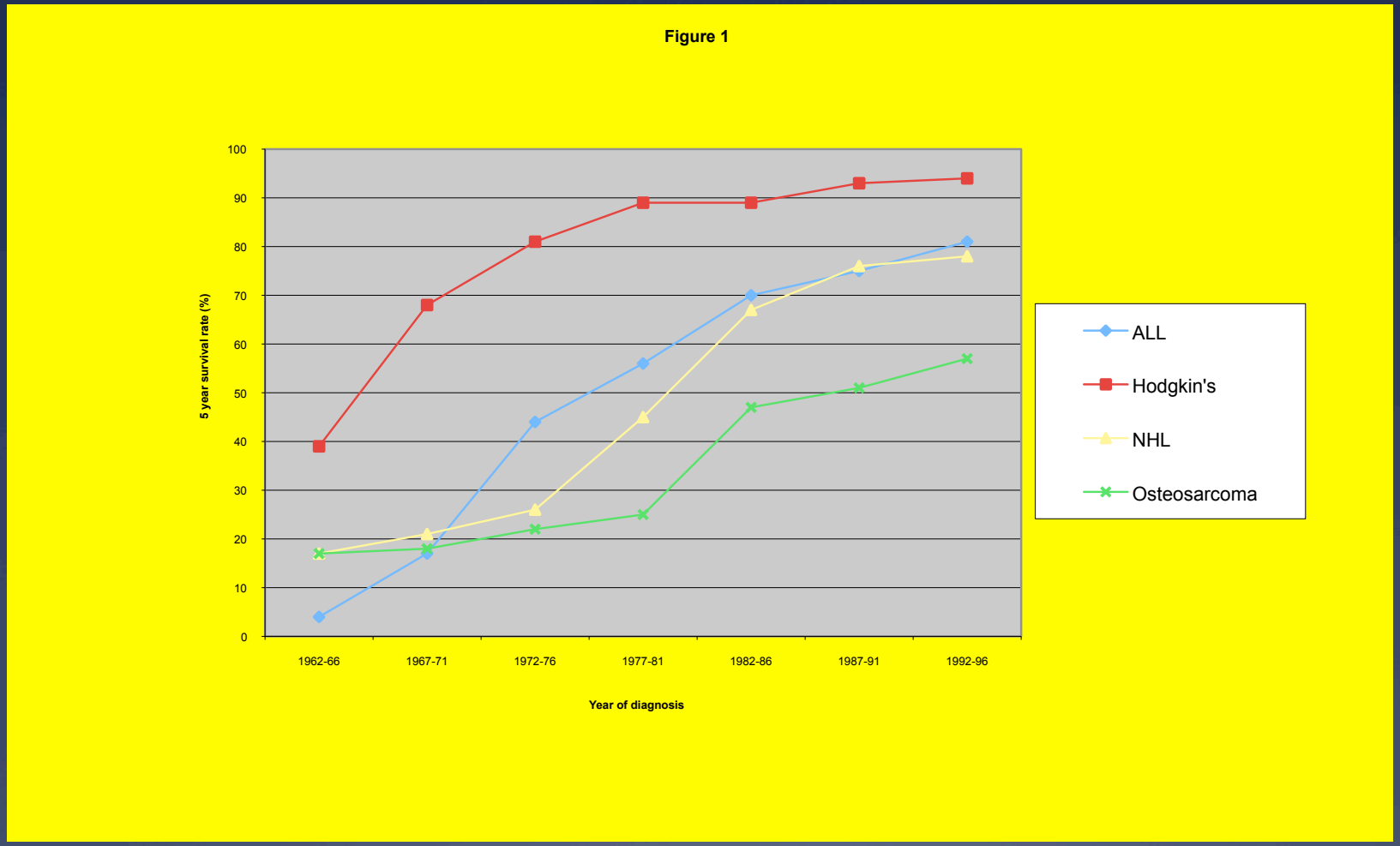
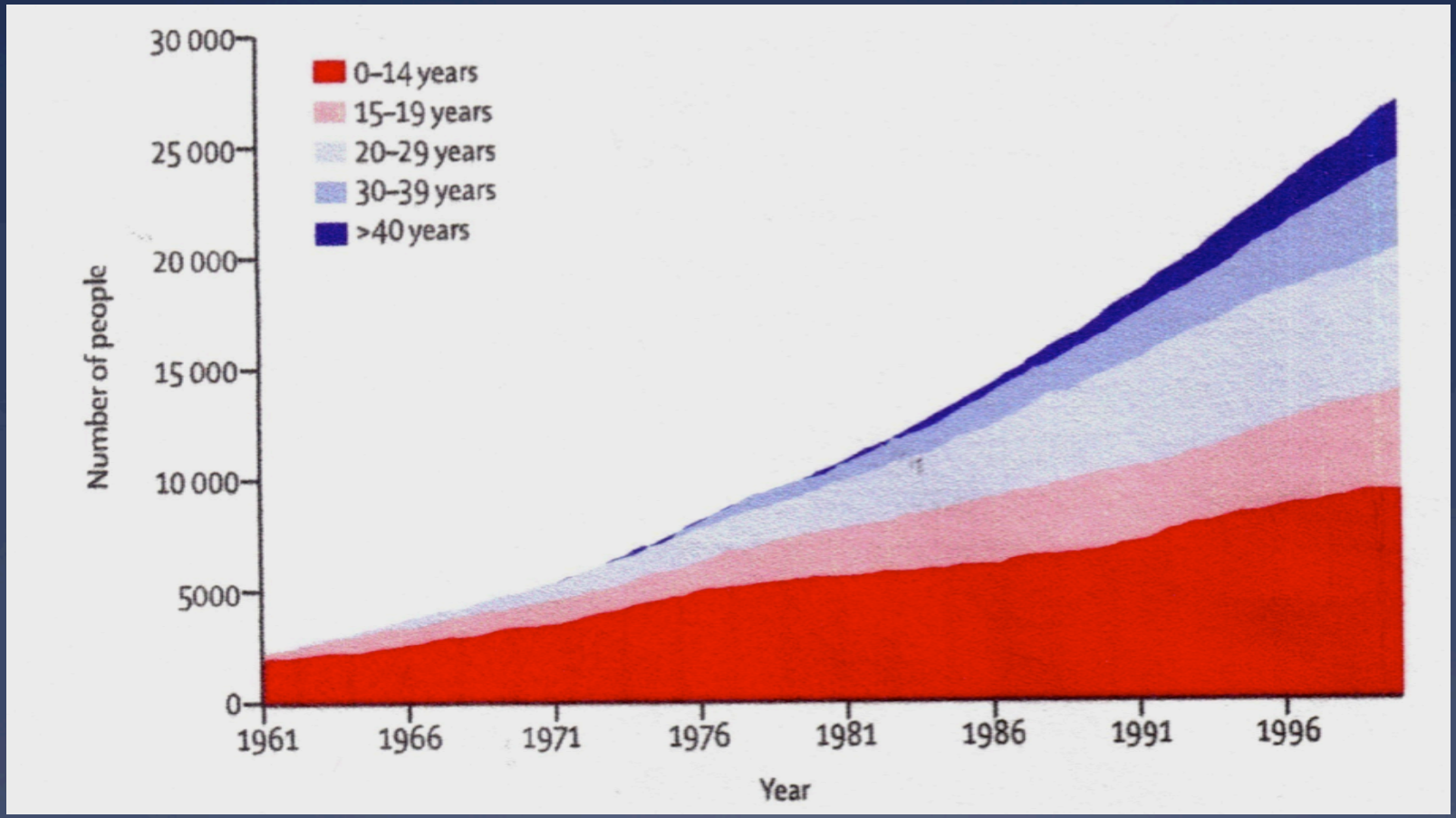
Epidemiology of Childhood Cancer

- Cumulative Risk of childhood cancer: 1 in 444 boys; 1 in 594 girls (1500 cases/yr in UK)
- >75% of children with cancer will survive five years, 70% are ten year survivors
- 1 in 570 young adults (20-34 years) is a childhood cancer survivor in UK
- In 2010, one in 715 of the adult population is a long term survivor of childhood cancer in UK

Trends in five year survival rates



Increasing numbers of five year UK survivors by current age



Skinner et al 2006 Lancet Oncology 7:489

What do we know about childhood cancer

survivors as a group?

Oeffinger K et al.

N Engl J Med 2006:355,1572-82

Chronic health conditions in Adult survivors of Childhood Cancer

* 10,397 survivors, diagnosed 1970-1986
* 3,034 siblings

Grading of conditions:

Common Terminology Criteria for Adverse Events

* Grade 1	Mild
* Grade 2	Moderate
* Grade 3	Severe
* Grade 4	Life-threatening or disabling
* Grade 5	Death

Oeffinger et al. N Engl J Med 2006

Demographics

Characteristics	Survivors (N=10,397)	Siblings (N=3,034)
Gender: female	46%	53%
Race		
Non-Hispanic white	84%	92%
Minorities	16%	8%
Age at interview	27	29
Mean (range), years	(18 - 48)	(18 - 56)
Interval from cancer dx	18	
Mean (range), years	(6 - 31)	NA

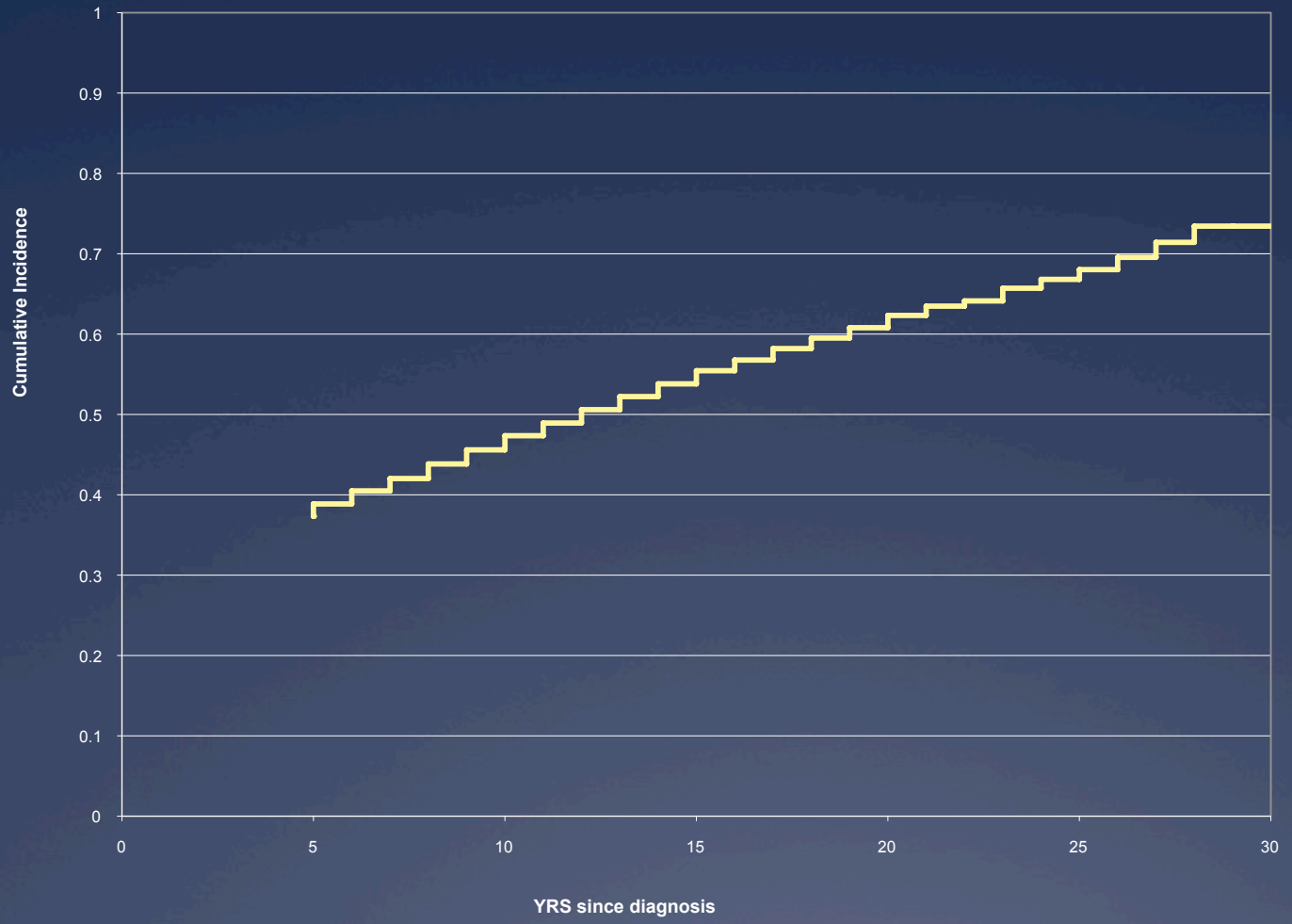
Relative risk of chronic health conditions in survivors compared with siblings

Adjusted for age, sex, and race

Primary Cancer	Any Grade	Grade 3 or 4	≥ 2 Conditions
Bone tumor	10.3	38.9	10.7
CNS tumor	7.1	12.6	12.4
Hodgkin's	4.6	10.2	8.7
Sarcoma	3.5	8.9	5.2
NHL	3.2	6.8	4.3
Neuroblastoma	2.0	4.7	2.5
Leukemia	2.2	4.1	2.8
Wilms' tumor	1.9	4.1	2.5

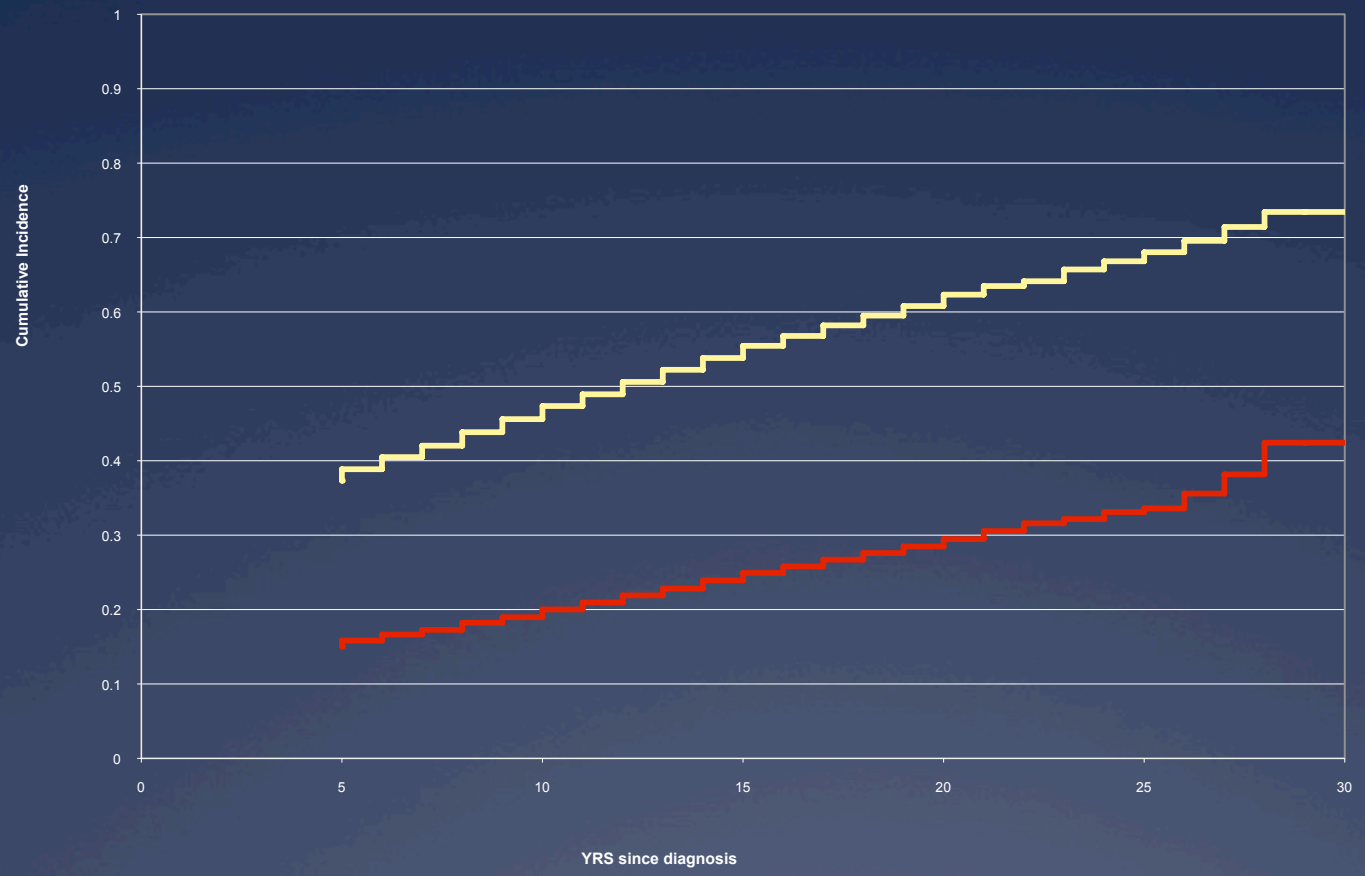
All estimates are significant at $p < 0.001$

Cumulative incidence curves of chronic health conditions in survivors, by GRADE 1-5 and GRADE 3-5



Grade 1-5

Cumulative incidence curves of chronic health conditions in survivors, by GRADE 1-5 and GRADE 3-5



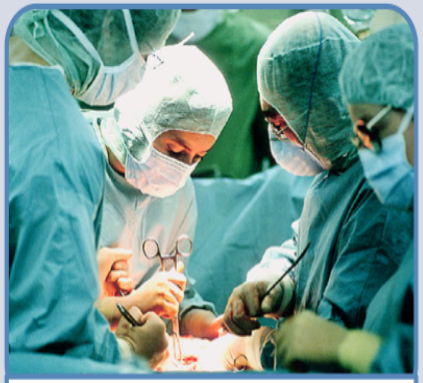
Grade 1-5

Grade 3-5

Morbidity of Survivors

* By 30 years post cancer:
  - 73% survivors with at least one condition
  - 42% with a grade 3-5 condition
  - 32% with multiple conditions
* Survivors – 8.2 times more likely to have a severe or life-threatening health condition than siblings

What do we know about the relationship between the treatment received and the potential for a late effect?



Surgery

- Cosmetic
- Functional
- Scars / Adhesions
- Hernias
- Systemic
  - Splenectomy
  - Thyroidectomy
  - Nephrectomy
  - Ooophretomy
  - Hysterectomy

Chemotherapy

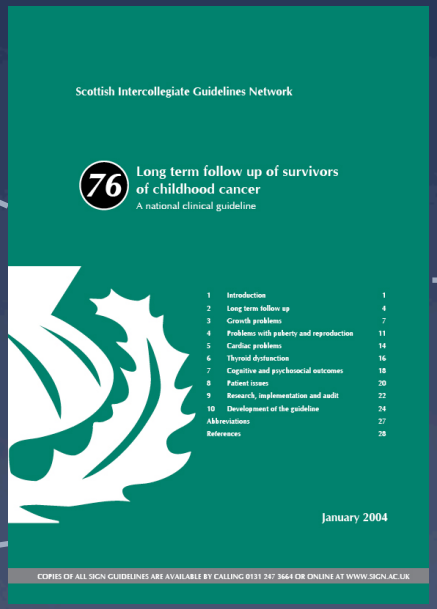
- Neurocognitive
- 2nd malignancy
- Pulmonary
- Endocrinological
- Cardiovascular
- Musculoskeletal
- Renal/urological
- Reproductive

Radiotherapy

- Cosmetic
- Neurocognitive
- 2nd malignancy
- Pulmonary
- Endocrinological
- Cardiovascular
- Musculoskeletal
- Renal/urological
- Reproductive

SIGN 76: long term follow up of survivors of childhood cancer

All survivors of childhood cancer should be actively followed up for life

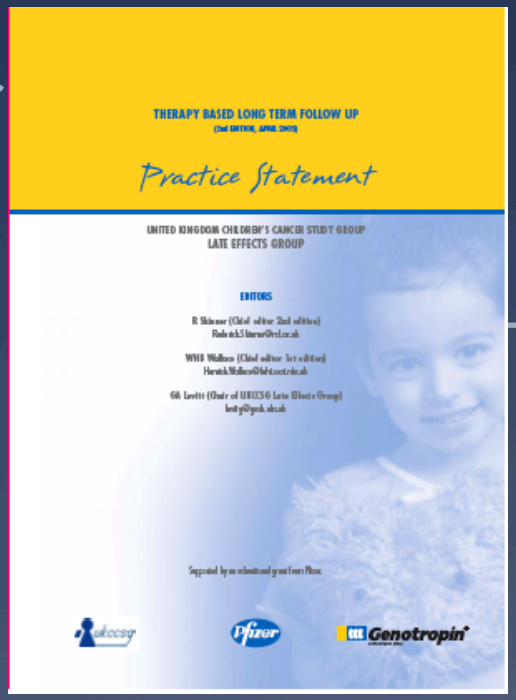


At the end of a course of cancer treatment, patients, their parents/carers and GPs should be given a summary of the treatment and a list of signs of late effects to look out for

Each survivor of childhood cancer should have access to an appropriate designated key worker to co-ordinate care

CCLG: Therapy-based long-term follow-up practice statement

Guidance for surveillance of survivors at least 3 years off therapy



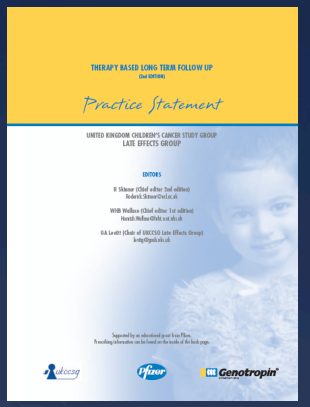
Protocols should be used in out-patient clinic

Summarise treatment received under the headings:

- Chemotherapy
- Radiotherapy
- Surgery

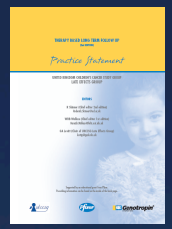
Reference: 1. UKCCSG Late Effects Group. Therapy-based long-term follow-up, 2nd edition, April 2005.

WHY IS THIS PRACTICE STATEMENT NEEDED?



- Directly applicable to LTFU Clinic
  - Ease of use
  - Rapid access to clinically important information
- Templates to facilitate development of follow up protocols

TREATMENT SUMMARY



Current Name	Date of Birth
Name at Diagnosis	Hospital Number
Diagnosis	Site(s)
Date of Diagnosis	Protocol
Date of Recurrence	Site(s)
Relapse Protocol	Date of Treatment Completion

Chemotherapy (include dates completed, and dose of anthracyclines and alkylating agents)

Radiotherapy

Date	Site	Dose	Fractions
Date	Site	Dose	Fractions

Bone Marrow Transplant

Date	Allo / Auto	Allo Donor / HLA matching	
Chemotherapy Conditioning (include doses)			
TBI / Other Radiotherapy Conditioning	Site	Dose	Fractions

Acute GvHD (Grade, site)	Chronic GvHD (Grade, site)	Treatment

Surgery Details
Complications during treatment
Complications after treatment completion
Parental height: Father Mother
Familial factors / Syndromes

14. Cardiac

ALL PATIENTS

Regularly at Long Term Follow Up clinic:

1) Enquire re:
   - Exercise tolerance
   - Chest pain
   - Palpitations
   - Shortness of breath
2) Measure blood pressure

ALL PATIENTS WHO HAVE RECEIVED ANTHRACYCLINES REQUIRE:

1) Echocardiogram 1-3 months after last dose of anthracycline
2) If normal at this time, repeat echocardiogram 5 yearly from last dose of anthracycline +/- at end of pubertal growth spurt
3) If abnormal at any stage, discuss with Cardiologist

NB Patients who have not had an echocardiogram within the first 6 months after last anthracycline dose should undergo echocardiography 3 yearly if repeatedly normal.

Abnormal echocardiogram defined as shortening fraction ≤28% (Cube method)

RISK FACTORS

- Anthracyclines and related
  - Daunorubicin
  - Doxorubicin
  - Epirubicin
  - Mitozantrone
  - Idarubicin
  - Amsacrine
- ?High dose cyclophosphamide
- Radiotherapy to field including thorax, thoracic spine or mediastinum (including left flank, TBI).

RECIPIENTS OF THORACIC / MEDIASTINAL RADIOTHERAPY ONLY (IE NO CARDIOTOXIC CHEMOTHERAPY)

1) In view of risk of ischaemic heart disease, consider review of other risk factors eg fasting lipid measurement
2) Prompt investigation of cardiac symptoms as clinically indicated

HIGHER RISK PATIENTS WHO MAY WARRANT MORE FREQUENT SURVEILLANCE INCLUDE:

- Patients previously treated for early anthracycline cardiotoxicity
- Total anthracycline dose >250 mg/m²
- Combination of radiotherapy and anthracycline
- Strenuous exercise eg weightlifting
- Pregnancy - close monitoring **essential**
- Patients on growth hormone therapy
- Patients on sex steroid replacement therapy
- Patients with congenital heart disease

SPECIALIST REFERRAL

1) All patients with an abnormal clinical examination should be referred to a Cardiologist for assessment and advice about further management
2) Patients with abnormal echocardiogram (see above) should be referred to a Cardiologist for assessment and advice about further management
3) All female patients with a risk factor for cardiotoxicity who become pregnant require close liaison with an Obstetrician

All patients:
Enquire about cardiac symptoms
Measure blood pressure

Anthracyclines:
Echo 1 – 3 months after last dose
If normal, repeat 5 yearly
If abnormal, discuss with cardiologist

Thoracic / Mediastinal RT:
Review ischaemic HD risk factors
Prompt investigation of cardiac symptoms

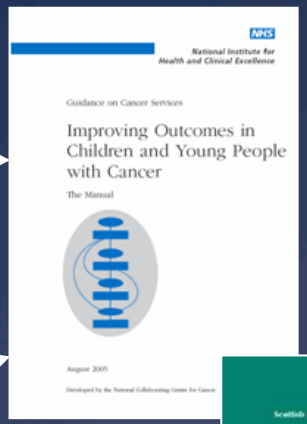
National guidelines for long term follow up

Care plans

Multidisciplinary team (MDT)

Nurse-led services

Transition



Clinical guidance

Communication

Protocol driven health surveillance

Key worker

End of treatment summaries

Life-long follow up

Evidence-based recommendations

Risk-stratified levels of follow-up

What do we know about long-term follow-up in the UK?

* Cross-sectional survey of CCLG clinicians (22 centres) and the GP's of 10,979 five years survivors (BCSS) [1]

Clinicians:

* 52% CCLG clinicians follow-up all survivors for life
* 97% discharge to the GP
* 14% reported nurses undertook a specialist role

GP's:

* 65% of GPs reported patients not on regular hospital follow-up

Highlights need for:

* Regularly updated national guidelines giving clear, structured levels of follow-up for specific groups of survivors defined principally by treatment received

Reference: 1. Taylor A et al. Pediatr Blood Cancer 2004; 42(2): 161-168.

Long-term follow up?

- Do all survivors need the same level of follow up?
- Increasing pressure to provide cost effective health care
  - Limited resources - hard choices
- Increasing shared/local care
  - Need for effective dissemination of effective practice methods

Therapy-based recommended levels of follow-up

Level	Treatment	Follow up	Frequency	Examples
1	Surgery alone Low risk chemotherapy	Postal or telephone	1-2 years	Low risk Wilms' LCH (single-system) GCT (surgery only)
2	Chemotherapy Low-dose cranial irradiation (<24 Gy)	Nurse-led or primary care	1-2 years	Majority of patients (eg ALL)
3	Radiotherapy (>24Gy) Megatherapy	Medically supervised LTFU clinic	Annually	Brain tumours Post BMT Any Stage 4 patients

Wallace WH et al. BMJ, (2001) 323:271-4

Objective

* To determine the safety of therapy-based, risk stratified follow-up by evaluating adverse health outcomes in cancer survivors retrospectively assigned a risk category.

Methods

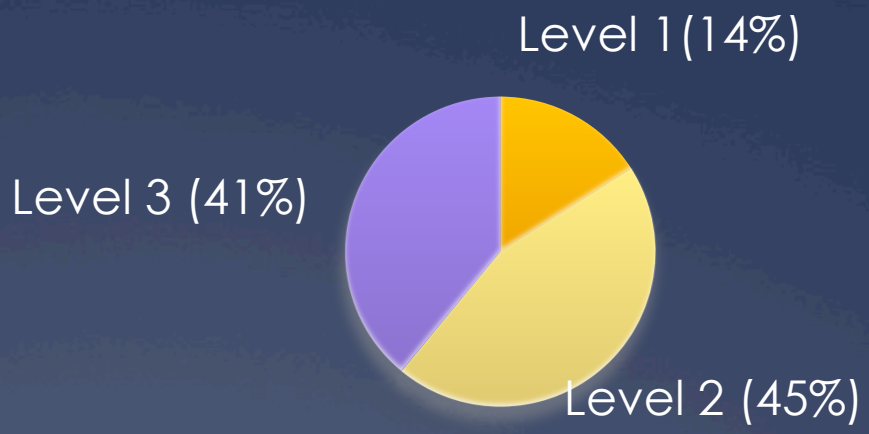
- All long-term survivors of childhood cancer (<19yrs)
  - Diagnosed between1971 and 1st July 2004
  - More than five years from diagnosis
  - Oxford Children's Cancer Registry from 1992 onwards
  - Scottish Cancer Registry and hospital records pre-1992
- Retrospectively assigned a therapy-based intensity of FU
  - Level 1, 2, 3: low, moderate or high risk of developing late effects
- Review of medical records
  - Prevalence and severity of late effects
    - Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3)
- Follow-up status

Study population

- 879 children with cancer 1971-2004
- 598 long–term survivors (OS 68%)
- Information available on 573
  - Males 303 (53%)
  - Median age (range): 19.4 (5.1-45.1) yrs
  - Disease free survival: 11.3 (0.5-38.3) yrs

Risk stratification

- Risk-stratification
  - Level 1: 83 (14%)
  - Level 2: 258 (45%)
  - Level 3: 232 (41%)

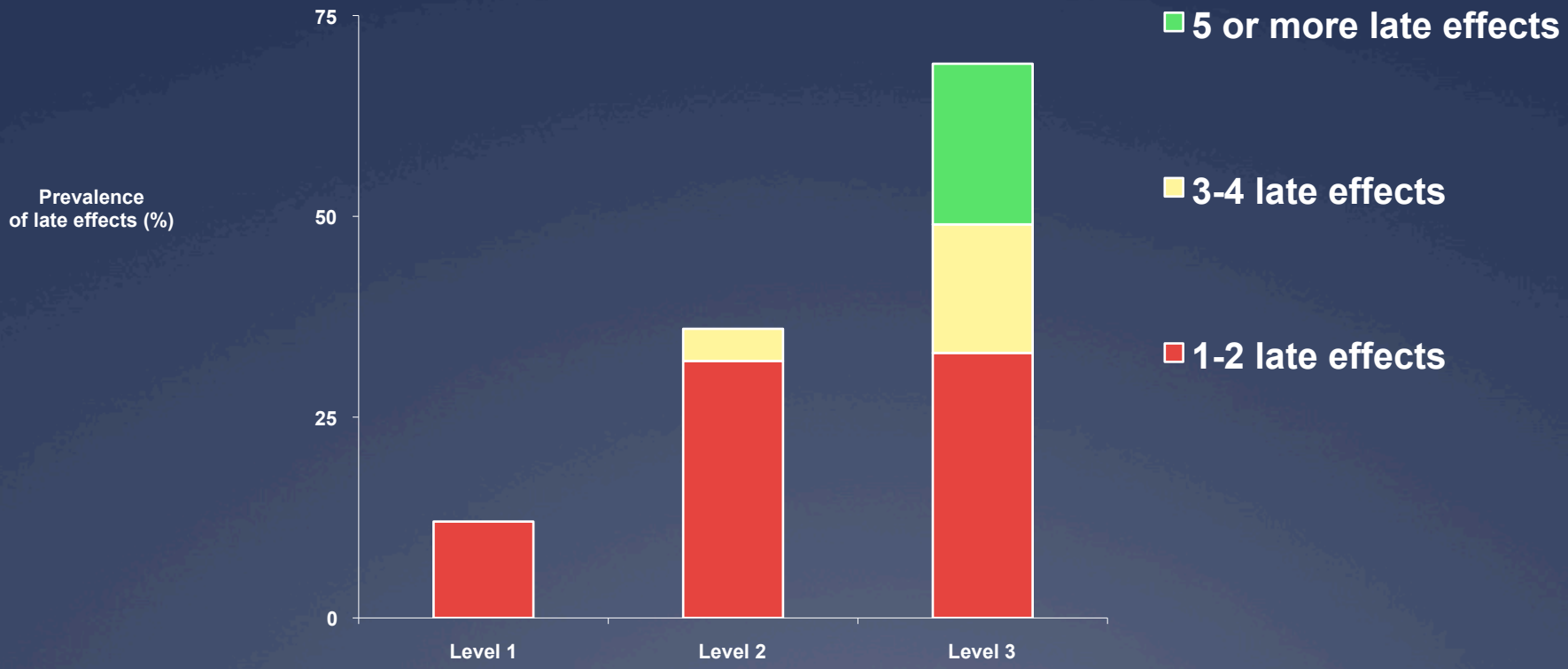


Therapy-based recommended levels of follow-up

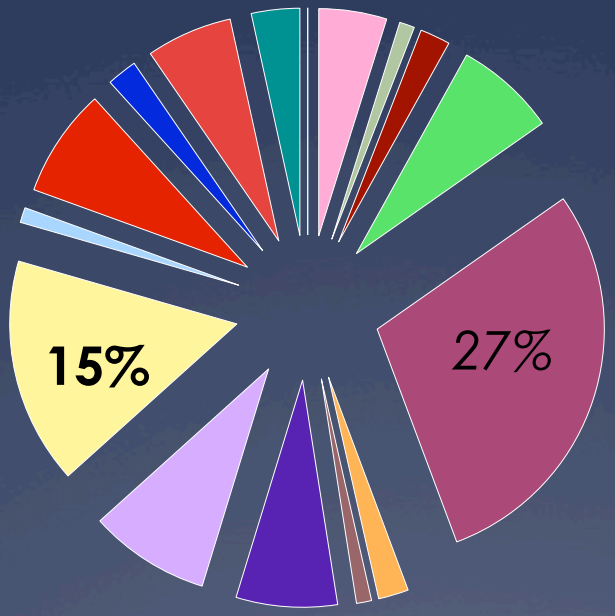
Level	Treatment	Follow up	Frequency	Examples
1 **(14%)**	Surgery alone Low risk chemotherapy	Postal or telephone	1-2 years	Low risk Wilms' LCH (single-system) GCT (surgery only)
2 **(45%)**	Chemotherapy Low-dose cranial irradiation (<24 Gy)	Nurse-led or primary care	1-2 years	Majority of patients (eg ALL)
3 **(41%)**	Radiotherapy (>24Gy) Megatherapy	Medically supervised LTFU clinic	Annually	Brain tumours Post BMT Any Stage 4 patients

Wallace WH et al. BMJ, (2001) 323:271-4

Prevalence of late effects by risk stratified level of follow-up



Late effects profile

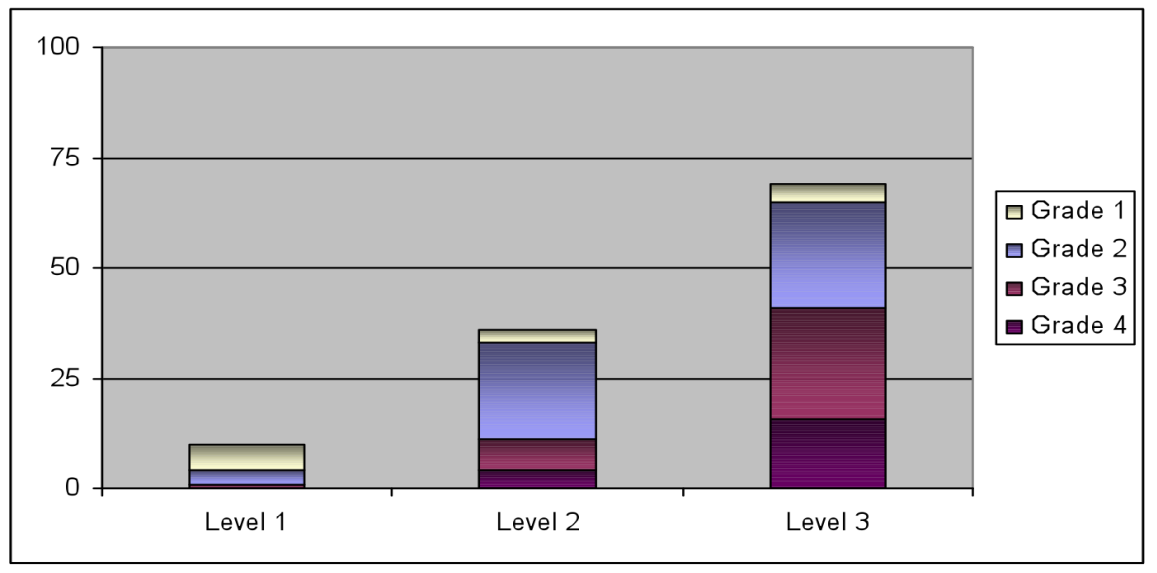


Severity of late effects by level

Common Terminology Criteria for Adverse Events

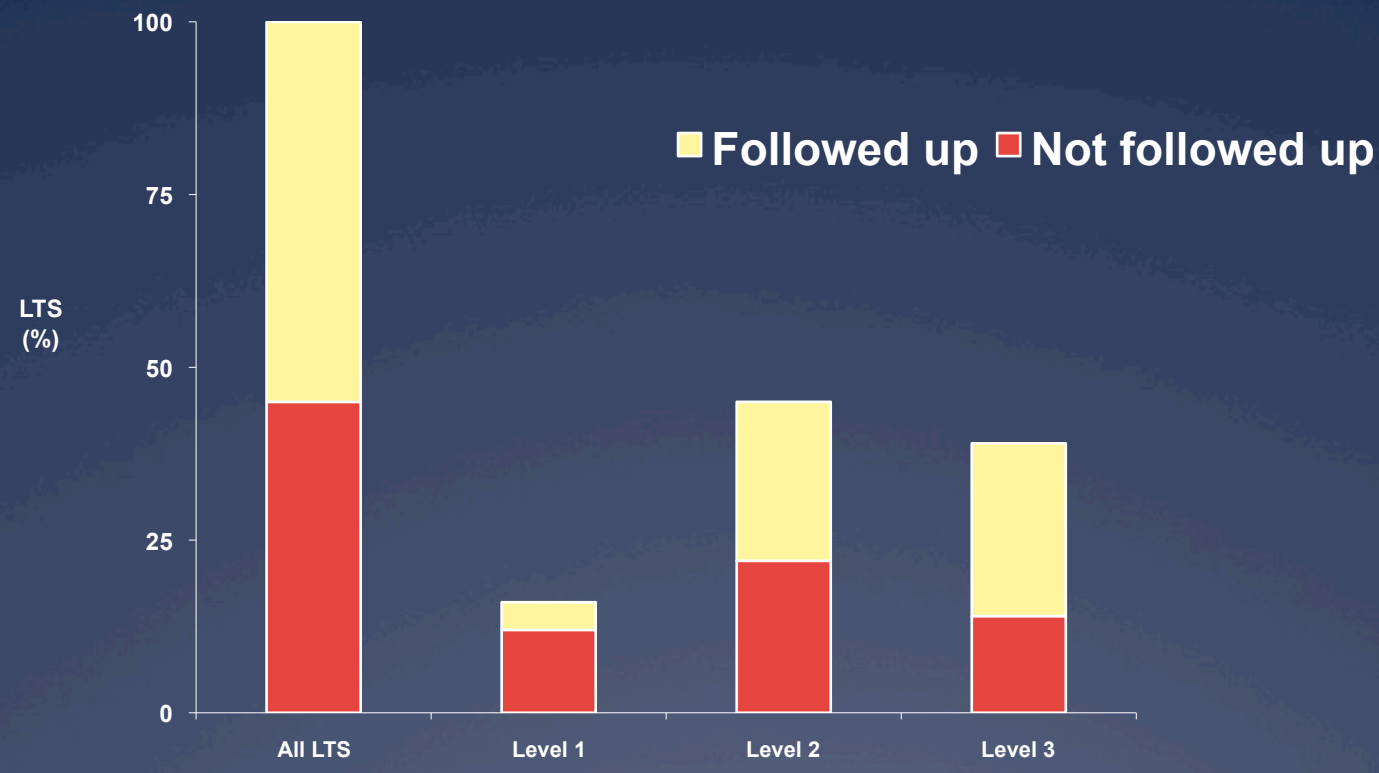
* Grade 1 Mild
* Grade 2 Moderate
* Grade 3 Severe
* Grade 4 Life-threatening or disabling
* Grade 5 Death

Severity of Late effects



	Level 1	Level 2	Level 3
Grade 1	7	3	4
Grade 2	4	22	24
Grade 3	1	7	26
Grade 4	0	4	15

Follow-up of survivors by level



Conclusions 1

- >1/3 of survivors of childhood cancer are considered to be at high risk of developing late effects
- Almost all level 3 survivors develop late effects
  - >50% have 3 or more late effects
  - >50% have at least one late effect of grade 3-4 severity
- Level 1 survivors rarely develop late effects
- Almost half of level 2 survivors develop late effects, the majority of which are grade 1-2 severity

Conclusions 2

* Therapy-based risk stratification of survivors can safely predict which patients are at significant risk of side-effects
* Our data support the development of a nurse-led service, with protocol driven, health surveillance for level 1 and 2 survivors of childhood cancer

Long-term follow up

- Multidisciplinary
  - Paediatric oncologist
  - Paediatric endocrinologist and reproductive specialist
  - Paediatric neurologist
  - Radiation oncologist
  - Paediatric neurosurgeon
  - Clinical psychologist
  - Specialist nurse
  - Social worker

Benefits of long-term follow-up

- Decrease morbidity and mortality by identifying and treating treatment-related late effects
- Educate survivors
- Encouragement of health promoting behaviour for improved outcomes
  - Increased patient satisfaction/quality of life
- Research
  - Follow new treatments/treatment regimens over the long-term

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