The treatment is over: What next?

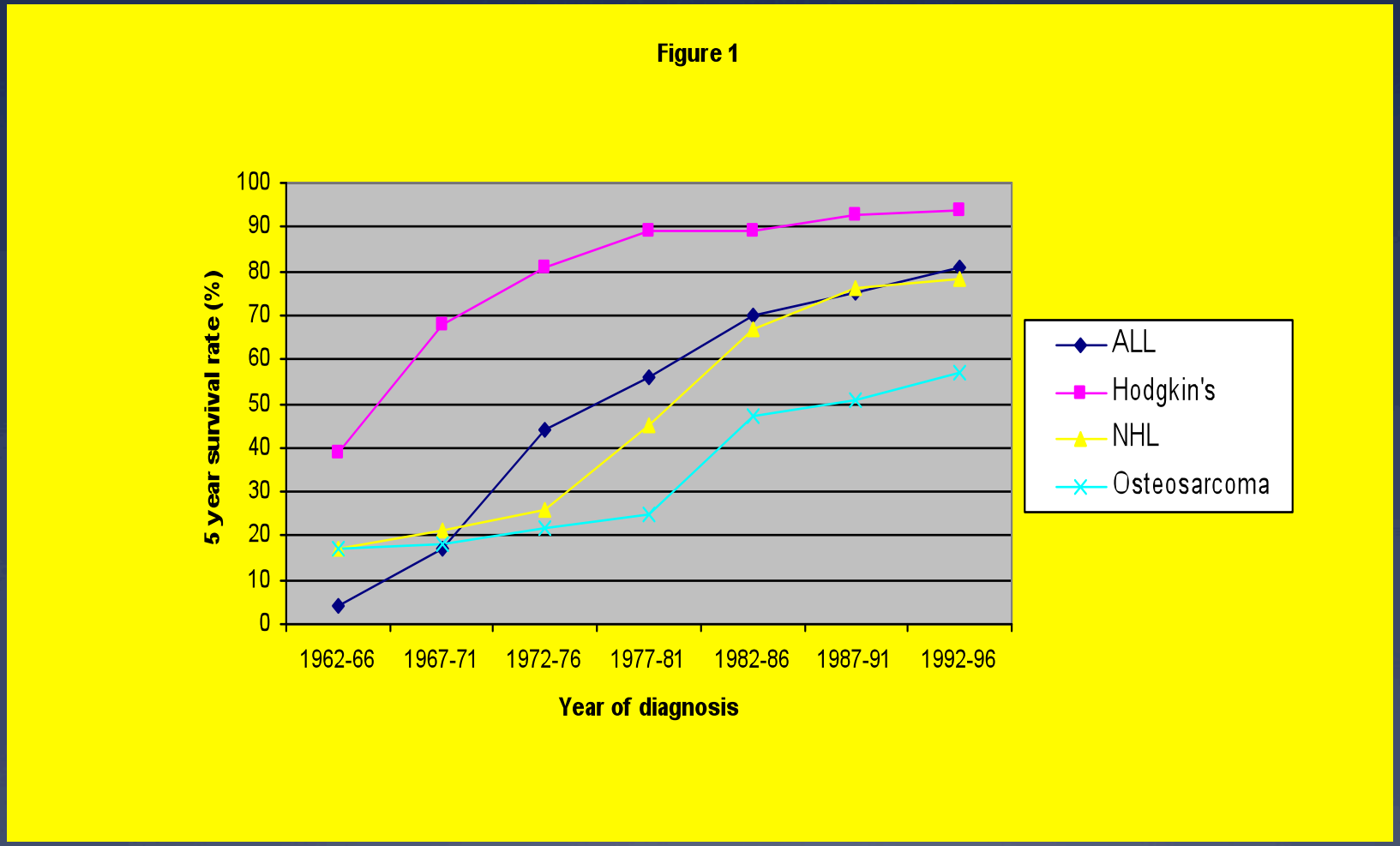
W. Hamish Wallace
Paediatric Oncologist,
Edinburgh, Scotland, UK

Survivors day,
Sydney, Australia, 2010

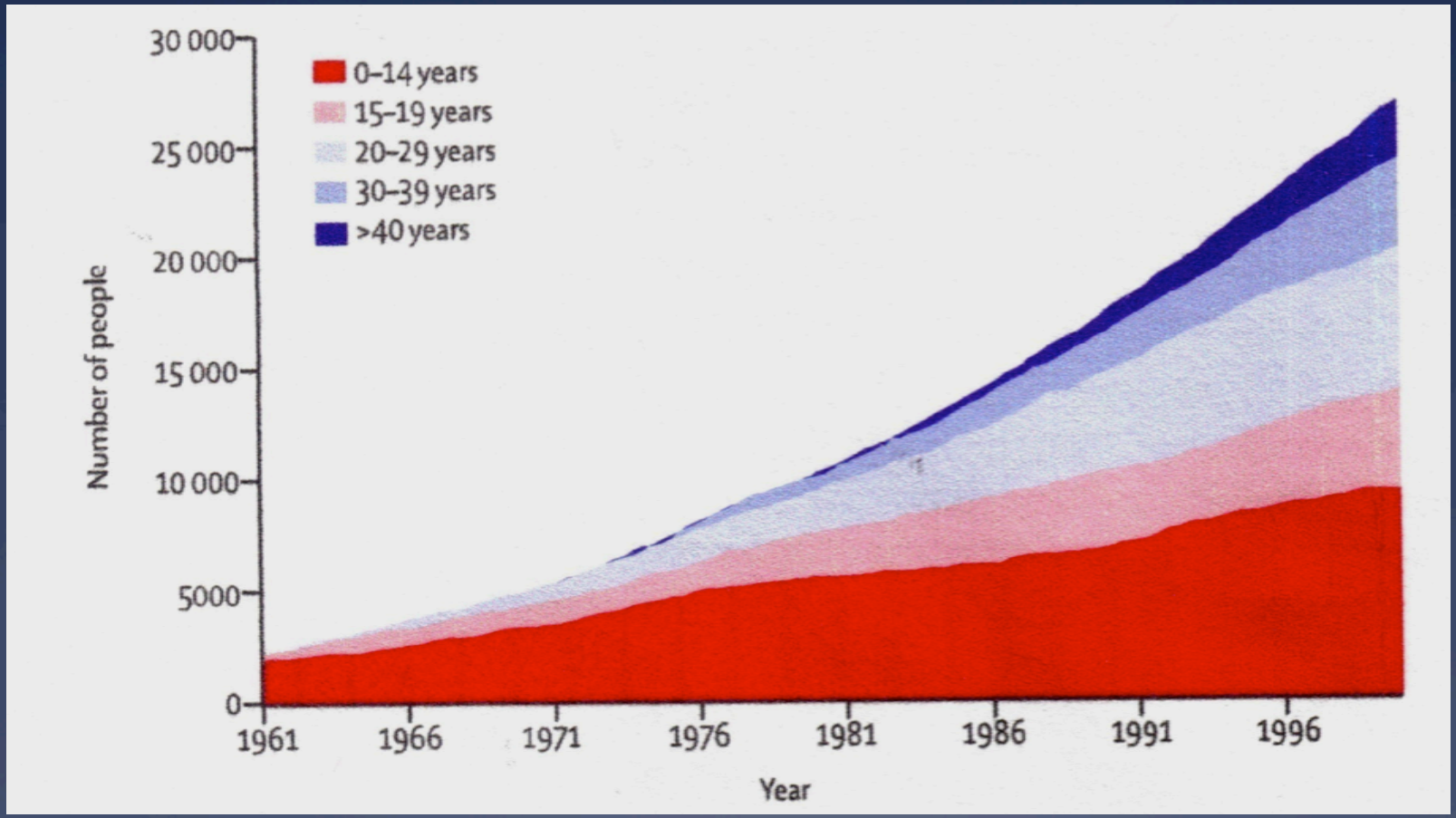
Epidemiology of Childhood Cancer

- 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

Lucca, Italy

San Michele in Foro, Lucca

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* Learn
* Understand
* Contact
* Communication
* Achieve

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Learn your diagnosis and treatment

* It is not the cancer diagnosis that determines what late effects you are at risk of…
* It is the treatment delivered:
  * Chemotherapy
  * Radiotherapy
  * Surgery

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Understand

* How your treatment may put you at risk of a late effect
  * Anthracycline exposure - Cardiomyopathy
  * Radiotherapy – Second Malignancy
  * Alkylating agents/ Radiotherapy to the pelvis - Infertility

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Contact

* Key worker (May change as you grow older)
  * Nurse
  * Doctor
    * Oncologist
    * Surgeon
    * Primary care

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Communication

* Learn and Understand your risks
* Discuss them with your contact (Key worker)
* Plan your Long-term follow up

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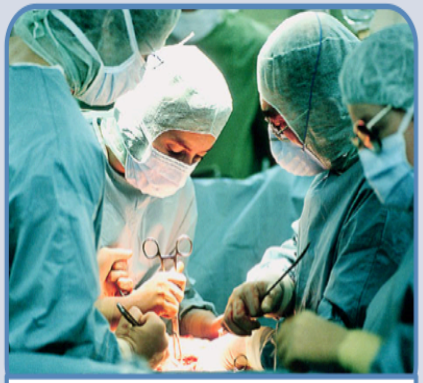
Achieve your potential

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

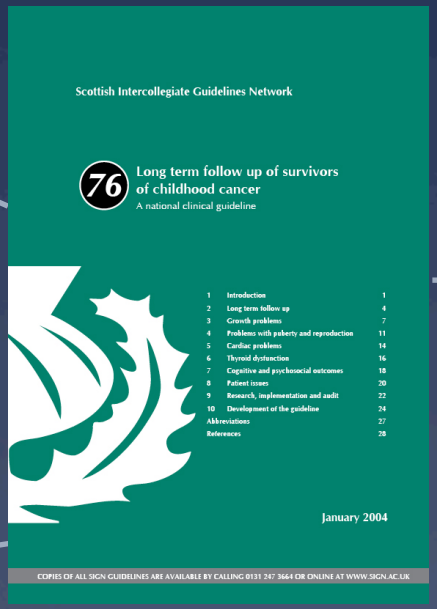
- Neurocognitive
- 2nd malignancy
- Pulmonary
- Endocrinological
- Cardiovascular
- Musculoskeletal
- Renal/urological
- Reproductive

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

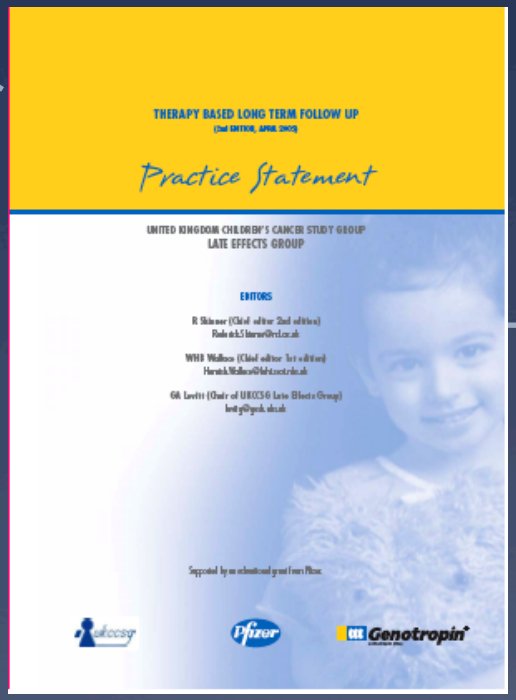


At the end of a course of cancer treatment, patients, their parents/carers and GPs should be given a summary of the treatment and a list of signs of late effects to look out for

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.

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

Long-Term Follow-Up Guidelines

for Survivors of Childhood, Adolescent, and Young Adult Cancers

Version 2.0 – March 2006

CureSearch

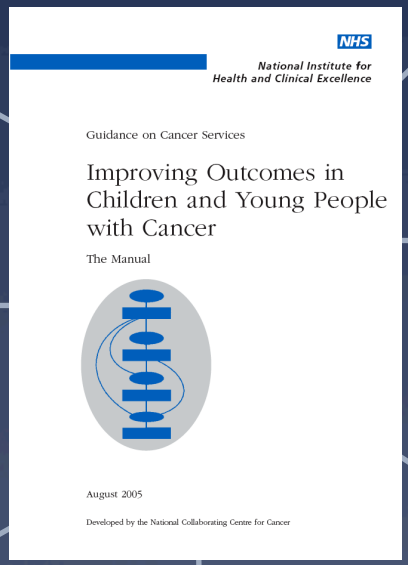
Children's Oncology Group

www.survivorshipguidelines.org

NICE: Improving outcomes in children and young people with cancer[1]

Late effects clinician

Multidisciplinary team (MDT)



Risk of late effects discussed with the patient and parents/ carers

Surveillance of survivors

Clear lines of communication

Care plans

Key worker

Reference: 1. NICE guidance on cancer services: Improving outcomes in children and young people with cancer, August 2005.

Cardiovascular problems

Cardiac dysfunction

- Anthracycline related cardiac damage[1]
  - Focal myocyte death and fibrosis - cardiomyopathy
  - Higher cumulative dose
  - Younger age at treatment
  - Female gender
- Radiotherapy[2]
  - Mediastinal irradiation >30 Gy
  - Young age at irradiation

1. Nysom. JCO, 1998; 16: 545. 2. Hancock. JCO, 1993; 11:1208.

Monitoring cardiovascular problems

- Echocardiography [C]
  - Fractional shortening
  - At regular intervals during treatment
  - End of Rx, 2yrs and 5yrs?
- ECG
  - Assessment of the QTc interval
- Cardiovascular risk factors
  - Lipid profile, blood pressure, insulin resistance

Management of cardiovascular problems

- Reducing cardiovascular risk factors
  - Life-style changes
    - Exercise, diet, weight reduction, stop smoking
  - Therapeutic intervention
    - ACE inhibitors
    - Lipid lowering drugs

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.

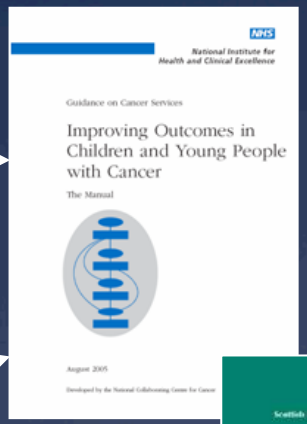
National guidelines for long term follow up

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

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

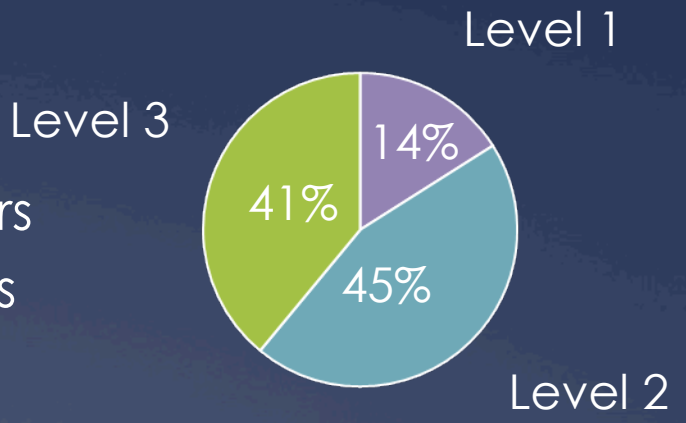
* To determine the safety of therapy-based, risk stratified follow-up by evaluating adverse health outcomes in cancer survivors retrospectively assigned a risk category.

Methods

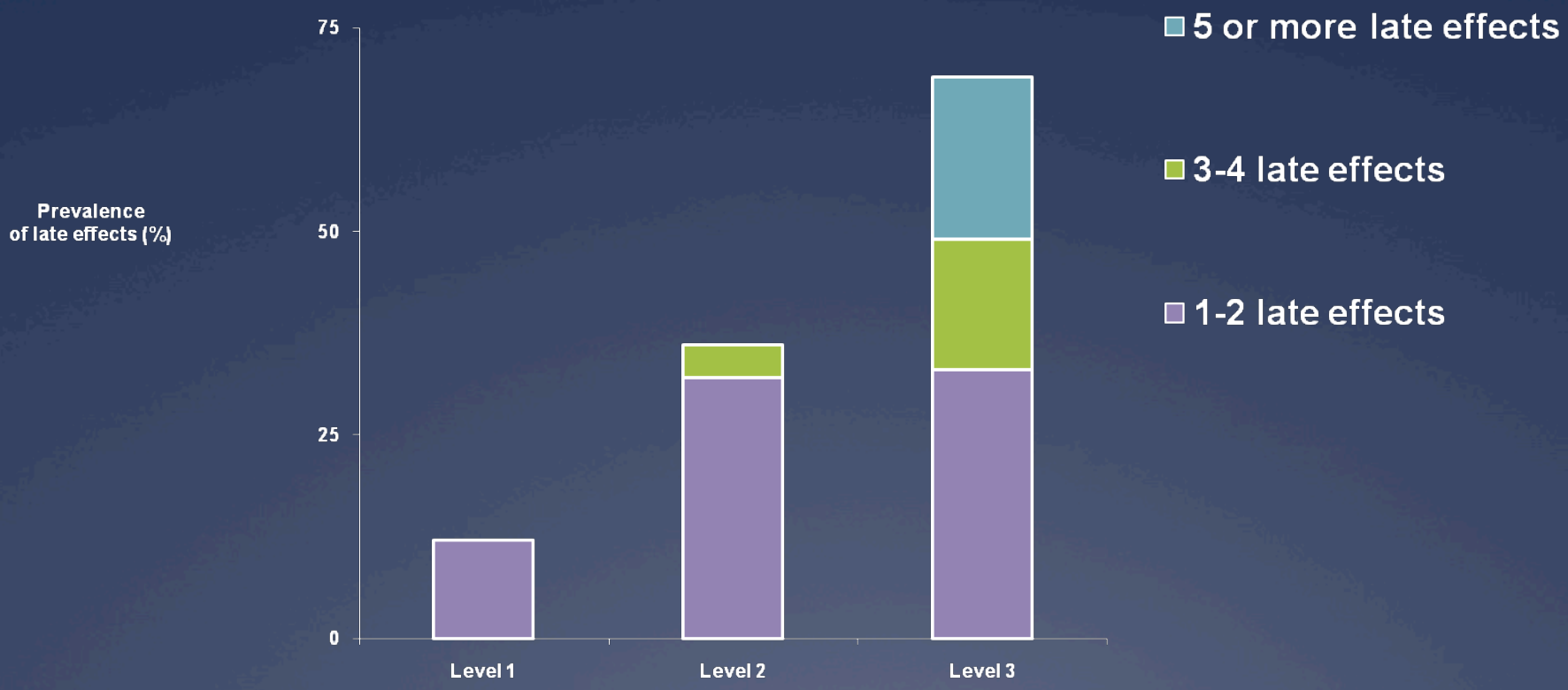
- All long-term survivors of childhood cancer (<19yrs)
  - Diagnosed between1971 and 1st July 2004
  - More than five years from diagnosis
  - Oxford Children's Cancer Registry from 1992 onwards
  - Scottish Cancer Registry and hospital records pre-1992
- Retrospectively assigned a therapy-based intensity 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 and risk stratification

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



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

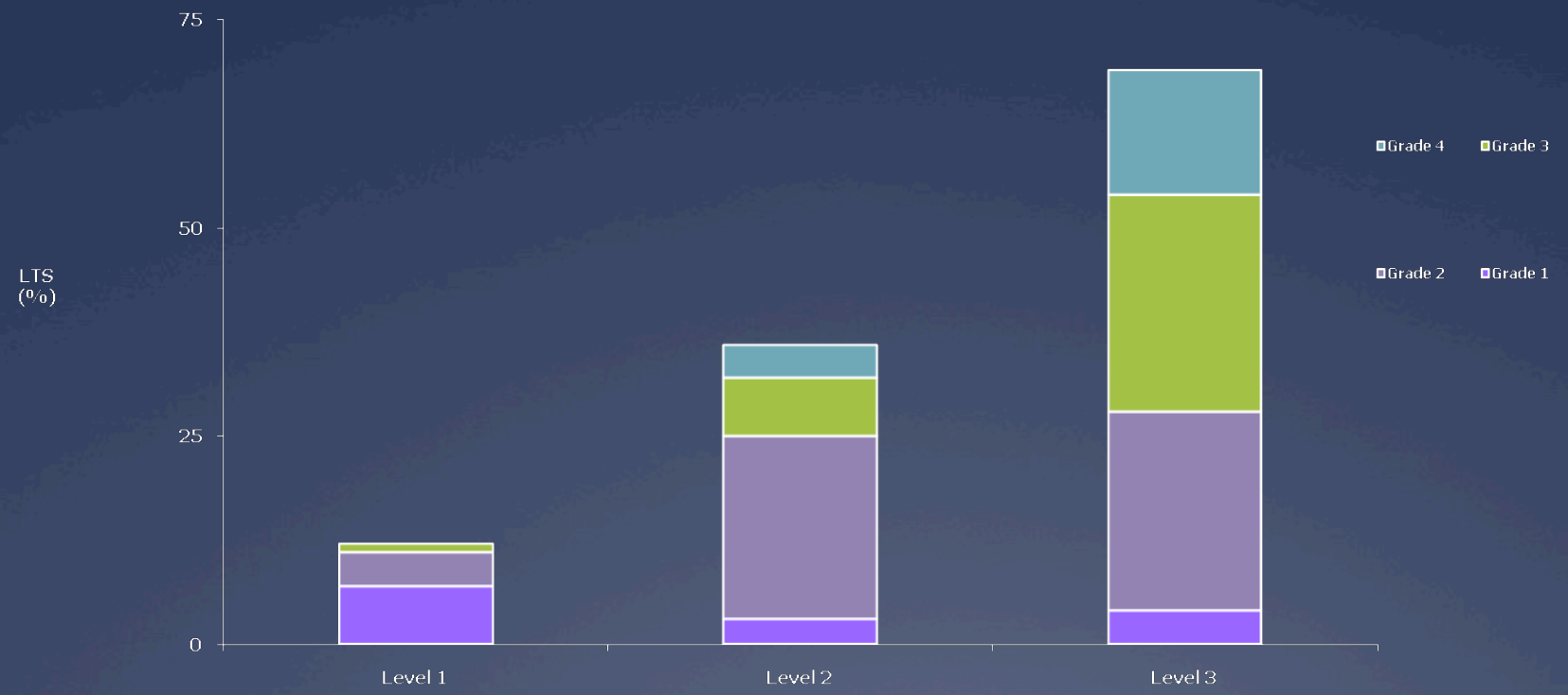


Severity of late effects by level

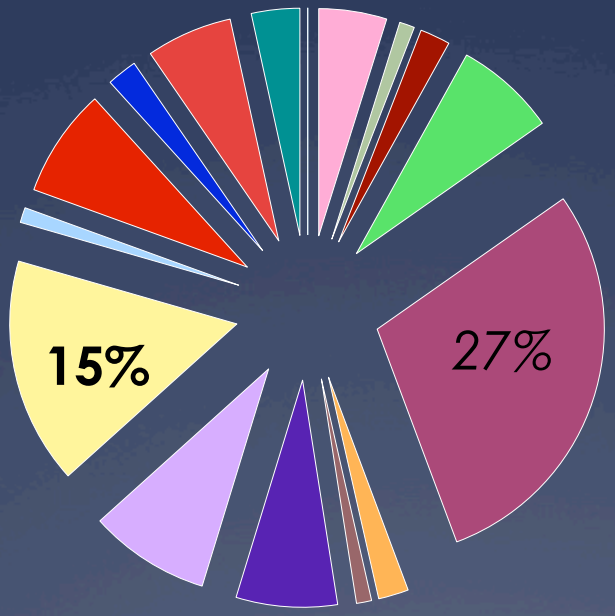
Common Terminology Criteria for Adverse Events

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

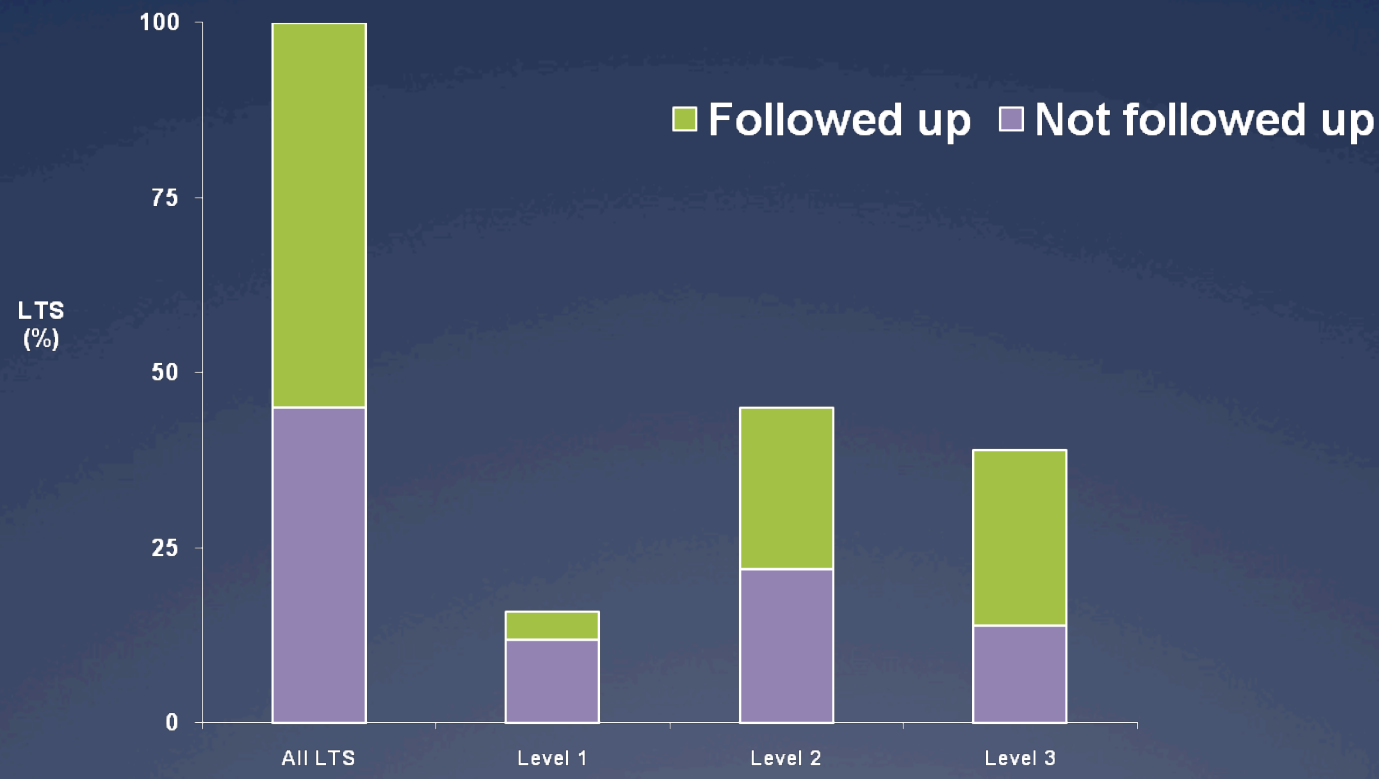
Severity of late effects by level



Late effects profile



Follow-up of survivors by level



Conclusions

- >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
- 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

Late mortality experience in Five-Year survivors

- The childhood cancer survivor study
  - Hospital based, United States
  - Diagnosis of cancer < 21 years
    - Brain tumours
  - 1970-1986
  - Cohort 20,227

Mertens et al. JCO 19:3163-3172,2001

Late mortality experience in Five-Year survivors

208,947 person-years of follow up

- Standardised Mortality Ratio (SMR) = 10.8
  - Females: SMR = 18.2
  - < 5 years at diagnosis: SMR = 14.0
  - Leukaemia: SMR = 15.5
  - CNS tumour: SMR = 15.7

Mertens et al. JCO 19:3163-3172,2001

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Late mortality experience in Five-Year survivors

Summary

- Overall risk of death from the original cancer ~7%
  - Highest: Leukaemia, CNS tumours & bone tumours
- Treatment-related death ~2%,
  - Highest : Hodgkin's lymphoma, Wilms' tumour
  - up to 25 years after diagnosis.

Mertens et al. JCO 19:3163-3172,2001

Late mortality experience in Five-Year survivors

- Cohort: 20,227
- Alive: 18,197 (90%).
- Dead: 2,030 (10.0%)
  - Death due to recurrent cancer: 1,246 (67.4%)
    - Highest 5 to 9 years after diagnosis
    - CNS tumours; Leukaemia; Bone tumours
      - Treatment-related causes: 394 (21.3%)
        - Death due to a second cancer: 235 (12.7%)
        - Cardiac toxicity: 83 (4.5%)
        - Pulmonary complications: 33 (1.8%)

- No excess mortality from external causes (SMR = 0.8)

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

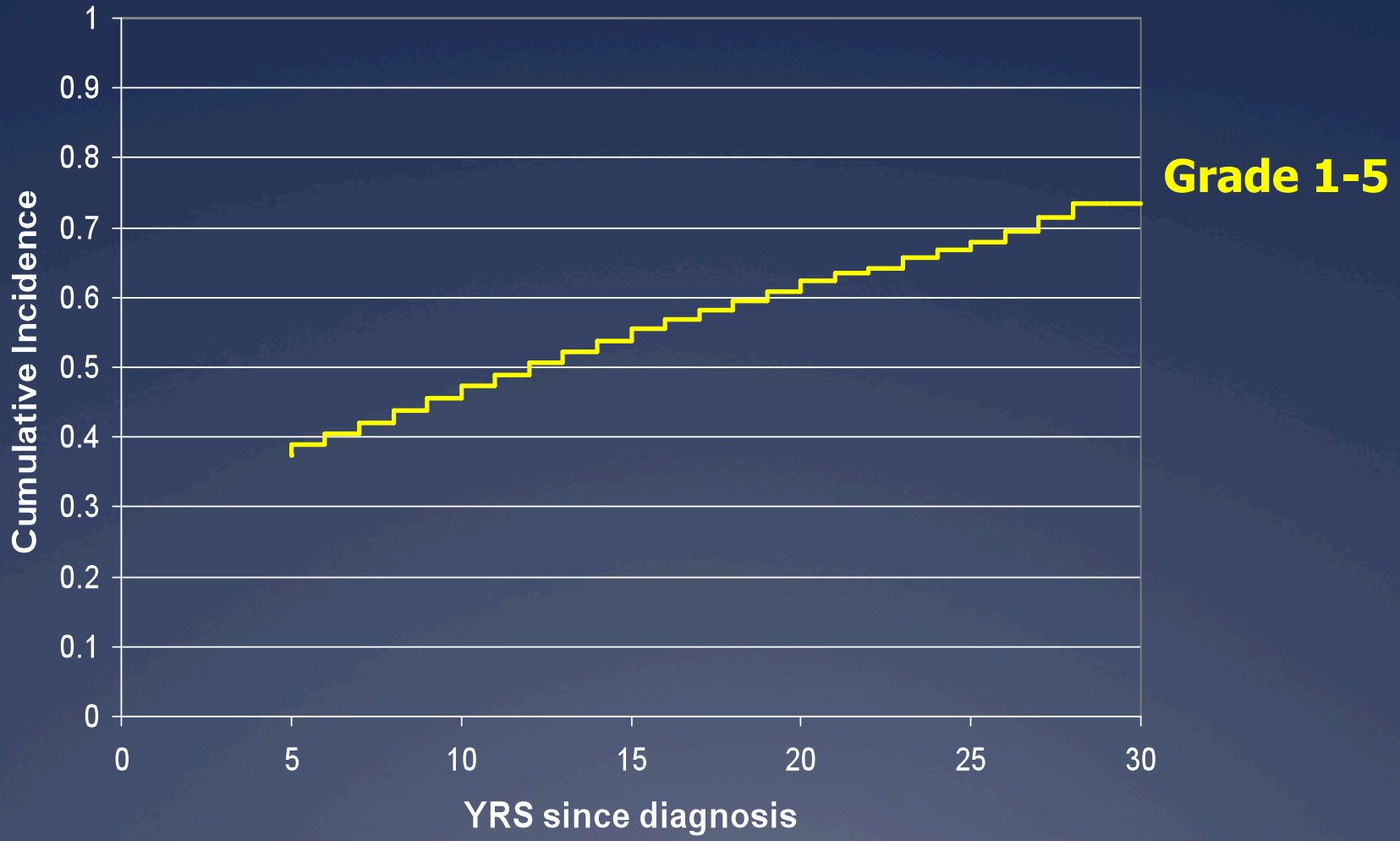
Relative risk of chronic health conditions in survivors compared with siblings

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



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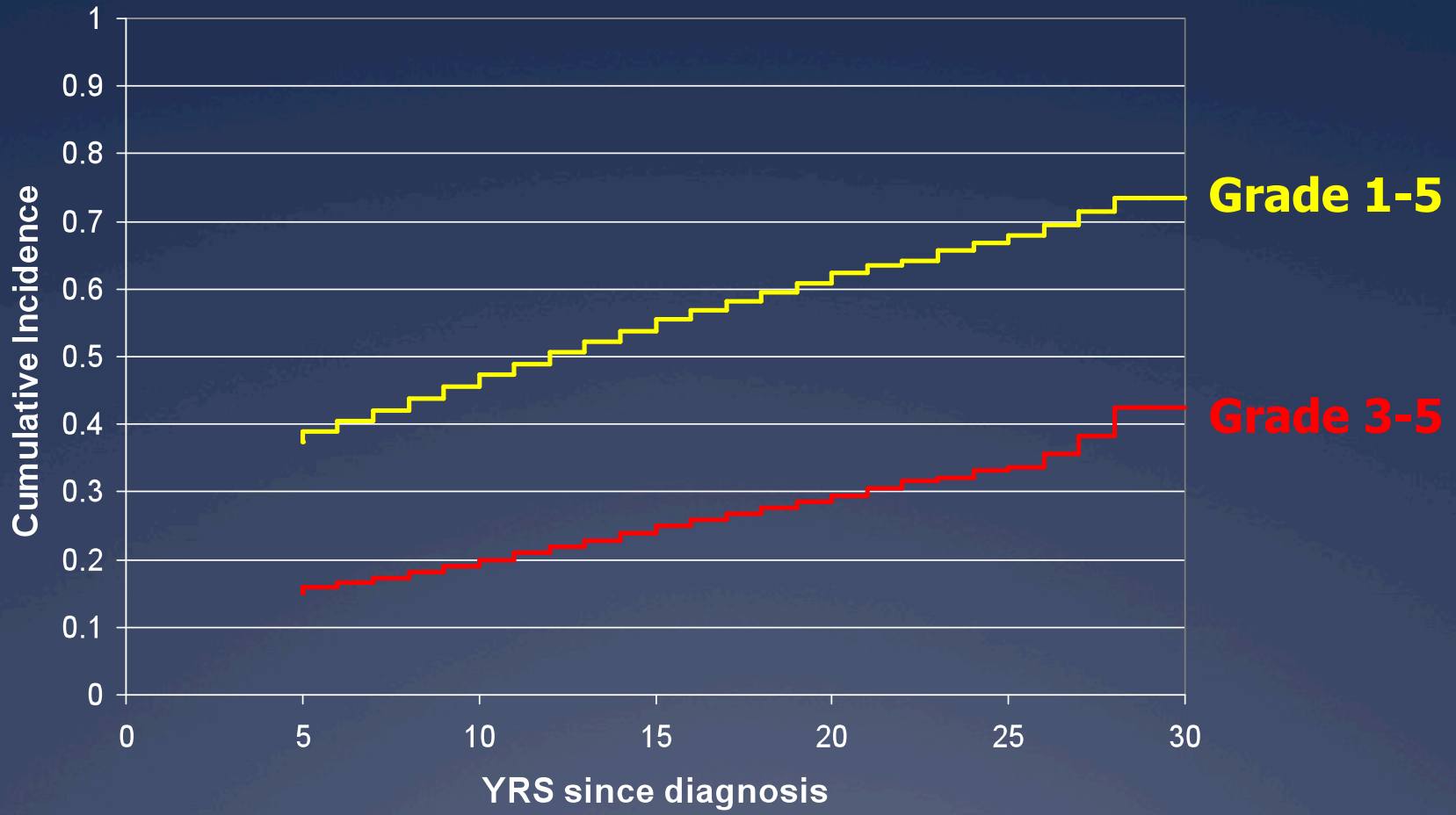

Morbidity of Survivors

* 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

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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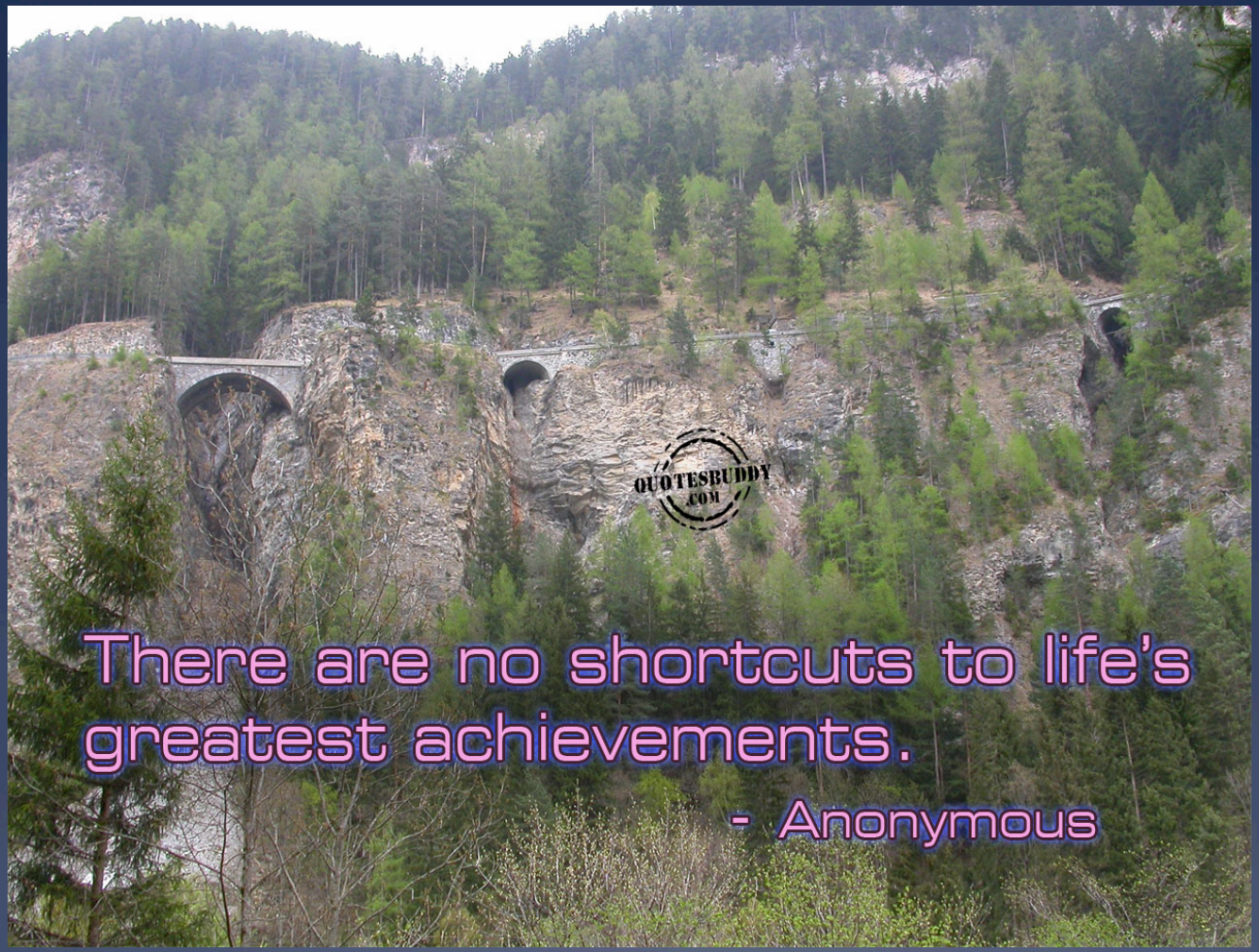
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There are no shortcuts to life's greatest achievements.
- Anonymous

Thank You

Acknowledgements

* Dr Angela Edgar
* Sarah Harrison
* Sarah-Louise Kelly
* Matthew Haywood
* Kathleen Duffin
* Stephen Borthwick
* Dr Paula Shaw