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# The quality of survival after childhood cancer

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## 1. Introduction

There was a time when success in the treatment of childhood cancer was measured in terms of survival alone. However, as the survival rates have risen steadily, so attention has turned to the quality of that survival. The late effects of treatment for childhood cancer are now well recognised. However, our aim is not to give a comprehensive overview of the effects of therapy, which can be found elsewhere. Instead, we discuss the impact of the changes in therapy over the past three decades on the quality of survival and to explore important issues relevant to different cohorts of survivors as they progress through adolescence into adult life.

The question of balance must also be addressed. For a number of childhood cancers survival rates have improved to a level where the intensity and duration of therapy (particularly radiotherapy and mutilating surgery) can be reduced, sometimes with a profound improvement in quality of life for the survivor and usually with no reduction in survival rates. For others, increasing the intensity of therapy will improve the cure rate by only a small percentage, but at what cost to the majority? The issues differ depending on, for example, the tumour type, stage and site of disease, and the age of the child. Many questions are not yet resolved but may have a real impact in the long term for survivors. We are now in the privileged position of being able to consider the long-term consequences of therapy. The challenge is to minimise adverse sequelae, whilst maintaining and improving survival rates.

The evidence on which decisions are made regarding the impact of cancer and its therapy on survival is currently limited by the cross-sectional design of many follow-up studies. There are constant changes to treatment regimens, supportive care guidelines and, more recently, changes in the risk stratification of many groups of patients. Children undergoing treatment on current protocols do not receive the same therapy as those from whom the 'evidence' has been obtained and such details may alter the long-term impact of the therapy (for example, infusion regimens of doxorubicin, changes in fractionation and timing of radiotherapy or use of adjuvant chemotherapy). Although the need for the prospective evaluation of the late effects of therapy in children receiving cancer treatment today cannot be overemphasised, important lessons can nonetheless be learned from the experience of previous survivors.

The terms 'quality of survival' and 'quality of life' (QOL) are difficult to define. Both are fundamentally subjective phenomena and, when assessing quality of outcome it is important that, wherever possible, the perceptions of the survivors themselves are addressed, at least as part of the overall evaluation. Whilst this review extends beyond the question of QOL, it is appropriate to consider the meaning of the term and the limitations in attempting to measure it, particularly in children and young people.

### 1.1. How do we assess quality?

It is generally agreed that quality of life should be assessed from the perspective of the patients. The World Health Organisation (WHO) definition, as early as 1948, described health as "A state of complete physical, mental and social well-being, not merely the absence of disease or infirmity" [1], introducing the concept that health was more than just physical functioning. Others have addressed the issue of the subjective nature of the concept, defining QOL as "The individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Quality of life is multidimensional. It includes but is not limited to

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the social, physical and emotional functioning of the child and adolescent and, when indicated, his or her family'' [2]. When considering the assessment of QOL in children with cancer, the authors added that ''Measurement of QOL must be from the perspective of the child, adolescent and family and it must be sensitive to changes that occur throughout development''.

Many survivors of cancer adapt extraordinarily well to the physical late effects of therapy they face and some less well psychologically (this will be discussed below). One useful concept is that QOL identifies a discrepancy between individuals' actual selves (what they are able to do) and their ideal selves (what they would like to do) [3]. This idea also addresses the concept of resilience and the need to understand the way in which individuals come to terms with previous experiences. This includes the late effects of therapy and why, despite apparently significant physical problems following therapy, some patients adapt extremely well with minimal impact on their overall subjective QOL. It is therefore appropriate that, wherever possible, assessment of QOL or quality of survival should be from the perspective of both the patient *and* an observer to maximise information, although in the majority of settings the opinion of the patient should be rated more highly.

The importance of close scrutiny of any data relating to these issues and a clear understanding of the terms used cannot be overemphasised. A recent systematic review of measures of QOL in children closely evaluated 137 relevant publications. In 43, the development of a measure was the main focus of the report (19 generic and 24 disease-specific). The authors concluded that, based on their findings, only five measures (three generic and two disease-specific measures) fulfil very basic psychometric criteria [4]. Nonetheless, the real progress in defining and measuring QOL in the adult population will be increasingly relevant to cohorts of survivors as they move into and through adulthood.

### *1.2. How are 'late effects' defined and reported?*

The frequency and severity of late effects following treatment for childhood cancer vary widely. Several recent reports of cohorts of survivors of childhood cancer have determined the incidence and severity of late effects [5–7]. All the studies have included survivors of brain tumours, yet the frequency of late effects ranges from 33% with 'one or more serious therapy-related health problems' to 75% 'with at least one chronic medical problem', of whom 50% needed permanent medical support [6]. Clearly, the demographic details of the cohorts must be closely examined, as there will be many factors influencing such data and generalities may lead to misunderstandings. Whilst the reporting of the incidence and severity of late effects is important, it is essential that the data are closely evaluated and conclusions limited to well-defined patient groups. One issue of particular importance is whether or not the cohort is population-based. Where access to follow-up is limited (for example by distance, financial constraints or inclination) there is likely to be a greater proportion of patients with significant problems attending for follow-up, compared with cultural systems where follow-up is currently almost universal (e.g. in the UK) [8]. In the latter setting, a lower incidence of problems may be reported overall. A high incidence of second cancers (standardised incidence ratio 18.1 (95% confidence interval (CI) 14.3–22.3)) has been reported following therapy for Hodgkin's disease [9]. The majority of these second malignancies were breast cancer with an estimated actuarial incidence in women approaching 35% (95% CI 17.4–52.6). Others have found a lower incidence [10,11] of breast cancer following Hodgkin's disease and it is interesting to speculate whether the variation seen in the breast cancer rates is related to the demographic selection of the cohort or to other differences such as the use of mediastinal radiotherapy.

A large epidemiological study in the US has recently been completed [12] and a similar study exploring the prevalence and manifestations of late effects following childhood cancer is currently underway in the UK. A detailed interview of 13 674 subjects in the US study has been completed and it hoped that a similar number will participate in the UK. Children, adolescents and adults treated for cancer during childhood over the past four decades are eligible and these studies will provide a powerful database for future reference. However, although valuable information will be obtained through comprehensive questionnaires and accurate reporting of therapy received, many late effects of therapy are subclinical and prospective studies exploring particular issues (e.g. fertility, cardiac function) are needed.

## 2. Quality of survival at different ages

As a child matures, change is normal. It follows that the impact of any late sequelae on the QOL of the child may also change. For example, impairment of growth or delays in pubertal development may have a significant impact on the QOL of a young child or teenager. The impact of infertility or failure to obtain life insurance is likely to be more important to the adult survivor. For these reasons, we will address the influence of different factors on survivors at different stages of their development.

There are, of course, some issues that have a significant impact from the moment they occur, e.g. amputation of a limb or enucleation of the eye. However, for many, maturity may bring with it an acceptance or adjustment to the situation, thus altering the impact of the late effect on the quality of survival. Although

psychological adjustment appears to be good for the majority, for some, advancing age may bring no such comfort and, where there is evidence of stress or increased anxiety, it is important that it is identified, as psychological intervention may bring real benefit.

### 2.1. From childhood

On completion of therapy, most of the children return swiftly to normal life and are able to return to school, although some will have lost a significant period of schooling. There are a small number who have clear, immediate significant late effects, usually surgical (e.g. amputation) or neurological, but the majority will be physically recovering from their period of immunosuppression and adapting to their 'normal' environment. A number of issues are of particular importance to the prepubertal child; these include intellectual and psychological well-being (including school 're-entry'), growth, spontaneous progression through puberty and normal physical development. Adjusting to normal family life, rather than being the centre of attention, may also be a challenge.

There is a clear relationship between cranial radiotherapy and the subsequent development of learning difficulties. Whilst these are well-defined following radiation doses of 40 Gy or above to the whole brain, there is more controversy around the impact of the lower doses of 18 or 24 Gy previously used as prophylaxis (and now infrequently as therapy) in the treatment of acute lymphoblastic leukaemia (ALL). The severity of any impairment appears to be related to the dose administered, the age of the child at the time of therapy (the younger the child, the greater the impairment [13,14]) and gender (girls are more vulnerable than boys [15]). It is important to accurately define any problem the child has and provide support as necessary. This can be difficult, particularly if there are subtle learning difficulties, such as an isolated impairment, e.g. in non-verbal IQ, or information processing skills which may be both difficult to recognise and address. However, accurate assessment and appropriate intervention may make a significant difference to the quality of outcome for the child. This has been recently demonstrated in a small cohort of children treated at a young age ($<5$ years), in which impairment of information processing skills and non verbal IQ were seen following cranial XRT. Notably, improvement in reading and spelling were achieved in this group as a result of the interventions introduced following the initial assessments [16].

A recent review of up to 176 survivors of childhood ALL has suggested that overall behavioural adjustment and social functioning following intrathecal methotrexate with or without 1800 cGy cranial radiation is good [17]. The report was based on parental and teacher reports. Other reports, however, suggest that there may be problems of adjustment (see below) and there are inconsistencies. It does appear, however, that children with standard-risk ALL who do not relapse have a relatively good outcome, at least in the short term. Nevertheless, the impact on the child and family cannot be overemphasised and further prospective work in this area is needed.

### 2.2. Through puberty

There is an acceleration of growth and development through puberty, which can result in an increase in the physical impairment caused by therapy received. This may be, for example, a relative loss of bone or soft tissue in the thoraco-abdominal wall following flank radiotherapy for Wilms' tumour [18], a failure to develop normal secondary sexual characteristics [19], or an acute deterioration in cardiac function [20]. There is currently no evidence of significant pulmonary, hepatic or renal impairment occurring particularly during puberty. However, as treatment regimens intensify, clinicians must be thorough in their observation of this group of survivors at a potentially vulnerable time.

#### 2.2.1. Cardiotoxicity

Treatment-induced cardiotoxicity has become a much debated subject in the late effects literature; however, the true clinical effect on survivors remains unknown. Anthracycline-induced cardiotoxicity is the most frequently encountered, as at least 50% of survivors receive these drugs. Cardiac damage rarely causes problems at the end of treatment with all protocols now recognising the importance of maintaining the anthracycline dose below 450 mg/m$^2$. Above this dose, there is an exponential increase in early onset clinical cardiac failure [21]. However, late cardiac dysfunction occurs at lower cumulative doses and may become an issue during puberty. Studies suggest that cumulative dose linked with increasing length of follow-up appears to be the most significant risk factor for the development and progression of deterioration in cardiac performance [22]. It may be, therefore, that cardiac damage becomes clinically detectable during adolescence. Alternatively the survivor may be asymptomatic, with abnormalities only identifiable on echocardiography [22–24]. The incidence of subclinical damage varies between 16 and 65%, related in part to total dose and but also to the method of surveillance. These individuals require more frequent surveillance and advice on life style (exercise limitations, no weight lifting, no smoking). This can be a difficult concept for the increasingly independent teenager. A smaller number will develop symptomatic cardiac failure with the prospect of irreversible failure requiring referral for cardiac transplantation [20]. However, a review of patients treated on US National Wilms' Tumor Study (NWTS) 1–4 trials identified a cumulative incidence of congestive heart failure at 20

years of 4.4% in event-free survivors, rising to 17.4% in those who had suffered a relapse [25]. Markers predictive of late cardiotoxicity are desperately required in order to identify those patients at risk of significant late damage so that early intervention may prevent further deterioration in cardiac function. This may also provide the ability to test cardioprotective options (length of administration, packaging (e.g. liposomal formulations), or cardioprotective agents). Early, reliable results could hasten the development of effective treatments and reduce this legacy of cancer treatment.

#### 2.2.2. Endocrine function

The majority of survivors of childhood malignancy advance normally through puberty. However, radiotherapy to the gonads, if bilateral, will result in delay or failure of progression though puberty in both boys and girls. Problems may be encountered if very high cumulative doses of gonadotoxic chemotherapeutic agents have been received or moderate to high-dose cranial radiotherapy. A group of patients of particular interest are survivors of ALL who may have alteration in the timing of menarche secondary to radiotherapy. In one study, almost 10% of children who had undergone therapy for ALL had evidence of early puberty. The majority were girls and there appeared to be a relationship between young age at onset of treatment and early menarche. Most had received 24 Gy cranial radiation, although some had relapsed and undergone further cranial irradiation [26]. Interestingly, in a more recent study of 188 female survivors of leukaemia who were premenarchal at diagnosis, there was no significant difference overall in the timing of, and progression through, puberty [27]. However those survivors who had received 18 Gy cranial irradiation before the age of 8 years had significantly earlier menarche compared with the girls in the control sample. Conversely, those who had received 24 Gy of craniospinal radiotherapy with or without abdominal radiotherapy had significantly later menarche than the control subjects. This study illustrates the differences in outcome for survivors dependent on therapy (particularly radiotherapy) received and its timing. However, it should be emphasised that these treatment strategies are now rarely used. The majority of children can now be cured without radiotherapy (with the exception of 24 Gy cranial radiotherapy for those with ALL and evidence of disease within the central nervous system (CNS)).

#### 2.2.3. Osteoporosis

It has been increasingly recognised that abnormalities of bone mineral density occur during treatment for childhood cancer [28] and in survivors, particularly those who have received therapy for ALL [29,30]. The cause of the osteopenia appears to be multifactorial and related to a number of factors including prior cranial radiation [29,31], time since completion of therapy [31], and chemotherapy [32,33] including steroids [34], although not growth hormone deficiency [35]. Inactivity may also be an important factor as it is also recognised that many of these survivors engage in less physical activity than their peers [36,37].

The majority of studies are based on cross-sectional data from patients treated in the 1970s and 1980s. A more recent cross-sectional study of 75 subjects who underwent therapy between 1991 and 1997 has suggested that the bone mineral density (BMD) z score overall was within normal limits, and improving with time following completion of therapy [38]. The authors suggest that the different outcome is related to shorter hospital stays and the lower number of children now receiving cranial radiotherapy compared with the earlier studies. In contrast, in another recent study of 176 children treated between 1987 and 1995 in the US, the bone morbidity was high with a cumulative incidence of any bony morbidity of 30% (5-year CI of fractures 28% and osteonecrosis 7%). Older children (age 9–18 years at diagnosis), male gender and use of dexamethasone were independent predictors of morbidity on multivariate analysis. However, it should be noted that the morbidity occurred early and for the majority of patients, within the first 2 years from diagnosis (i.e. whilst on therapy) [35].

The outcome for an individual patient clearly depends on a number of factors and a greater understanding of the pathophysiology of bony morbidity, both in the short and long term, is also required. There may be a role for interventions such as exercise or hormonal therapy to optimise outcome as these survivors pass through puberty and into adulthood. However, further evaluation is required in order to improve understanding and to identify those at greatest risk.

### 2.3. Into adulthood

Expectations of adults differ from children. Their horizons widen, relationships develop and the future becomes important. Questions are raised about life expectancy and their ability to have economic independence. Is this the same as their peers? If they have children will they see them become adults? For many, the answers to these questions (again) remain unknown and this may cause uncertainty and have an adverse impact on their QOL.

#### 2.3.1. Life expectancy

Population- and hospital-based studies of late mortality suggest there is an increased risk of early death although 90% of patients initially cured of their malignancy survive long term (5–35 years) [39,40–43]. There is agreement across the studies that the majority of deaths are due to recurrent disease (61–70%); even at 20

years from diagnosis, a third die from the initial tumour. Those at most risk are survivors of leukaemia, tumours of the CNS and bone tumours. About 20% of deaths are due to treatment-related causes, including second malignant neoplasms (SMN). Survivors of Hodgkin's disease are at most risk of SMN. The causes of the SMN are radiation therapy, alkylating agents and epipodophyllotoxins [41]. Other treatment-related complications contributing to the higher standardised mortality ratios were cardiovascular, pulmonary, renal and neurological [39,42]. Survivors of Wilms' tumour were at significant risk of treatment-related deaths, although their overall survival was excellent. Encouragingly, Moller found deaths in the 1980s, the era of more intensive treatment, were fewer than in earlier decades. This reduction was due to a fall in tumour recurrence and no increase in treatment-related deaths. These findings are important and reassuring, although the follow-up currently is relatively short and more cases of SMN may appear [39–43].

### 2.3.2. Fertility

The continuation of the germ line is an inherent need and thus any constraint may cause psychological hardship to infertile couples [44]. Survivors of childhood cancer are no exception, even if they have lived with this possibility for many years and are aware of the cause. The most important factors leading to infertility are gonadal radiation (TBI, whole abdominal radiation for inoperable Wilms' tumour or testicular radiation for testicular relapse of acute lymphoblastic leukaemia) and alkylating agents. The testes are particularly sensitive with studies showing abnormalities of spermatogenesis in 90% patients following cumulative cyclophosphamide doses of $>7.5$ gm/m$^2$ [45,46]. It is important to appreciate that, in males, there is a divergence of susceptibility to damage between Sertoli (responsible for sperm production) and Leydig cells. There can therefore be a significant impairment in fertility with little or no adverse effect on progression through puberty or sexual function. Rarely, sexual function is affected; impotence can be caused by pelvic surgery (in particular for pelvic/prostatic rhabdomyosarcomas, and pelvic neuroblastomas [47,48]), or due to the tumour itself. Early appreciation of problems is important for effective counselling. Although the ovaries are less sensitive to gonadotoxic chemotherapy, there are studies suggesting that females may have a shortened reproductive life with a premature menopause [49]. This important information needs to be given to the patients so they can, if they choose, start a family earlier rather than later.

To date, the outcome for the offspring of survivors has been reassuring, with low rates of congenital defects and malignancies during childhood [50], except in families where there is a well recognised increased risk of malignancy (e.g. Li–Fraumeni syndrome).

### 2.3.3. Employment prospects

Independent living with the prospect of financial independence contributes to an individual's QOL. In the UK, there are now in excess of 14 000 survivors of childhood cancer over 18. As survivors enter the employment market, some may find this a difficult time when unexpected barriers appear, or unrealistic expectations have to be faced. Early sharing of information and assessments of capability are important to optimise opportunities, particularly for those with physical or intellectual impairments. For patients who were treated with cranial radiation, short-term memory can be impaired, thus excluding certain occupations and educational opportunities [51]. There are reports that some childhood cancer survivors may not meet the requirements set for military service in the US and Europe, and some may be rejected simply on the basis of a former cancer diagnosis ([52,53] and personal observation), but, in general, other job opportunities have been available. The percentage of childhood cancer survivors unemployed in the USA is nearly equivalent to the national average and has been improving over the last decade, but survivors of brain tumours are still disadvantaged [54]. In the UK recently, patients have been refused pilot licences if they have been treated with anthracyclines, and those with licences are required to be regularly reviewed above that expected for other pilots (Civil Aviation Authority, data not shown). The knowledge that therapy-related problems may cause later disabilities appears to be increasingly influencing the survivor's ability to obtain health/life insurance and pensions without penalty [40,52,55].

### 2.3.4. Psychosocial issues

A recent large study of psychosocial outcomes in long-term survivors of ALL and Wilms' tumour suggested no increase in rates of psychiatric disorders when compared with a control peer group [56]. However, there was evidence of poorer functioning in the area of relationships and friendships in the survivors when compared with the control subjects. Poorer coping was associated with lower intellectual ability scores. Other studies suggest very low levels of psychological distress and significantly better health than expected [57]. The complexity of this area, however, should be emphasised and exploring issues such as adaptation though appropriate or repressive mechanisms is beyond the scope of this review. Clearly, a positive psychological outcome is achieved by many, but it is dependent on many issues beyond the diagnosis alone including factors such as therapy received [58], family functioning and length of time following therapy [59,60]. For those caring for these survivors, important issues include the identification of those at greatest risk of long-term psychological problems and provision of early intervention wherever possible.

*2.3.5. Long-term relationships*

Marriage or stable cohabitation can be used as a surrogate marker of successful long-term relationships. A review of a cohort treated between 1945 and 1975 demonstrated that, compared with sibling controls, survivors were less likely to marry and that marriages were of shorter length. Survivors of brain tumours were the least likely to marry [61]. This is supported in the preliminary report of participants in the US Childhood Cancer Survivor Study [62]. A further review of survivors treated more recently (1960–1984) again demonstrated that marriage rates were significantly lower than the general population (58% were married), but the divorce rates were similar [63]. Females were less likely to marry and, of those not married, 15% said it was due to their childhood cancer. There was no disease-specific effect but only 3% of the respondents had received treatment for brain tumours.

## 3. A question of balance

As survival rates improve, so the issues and relative importance of the late effects of therapy increase. Where a small further improvement in survival rates is achieved through intensification of therapy for the majority, is this justified? Conversely, is a reduction in treatment burden, in order to reduce late adverse sequelae, safe in terms of survival rates? There have been changes in the emphasis and relative use of the different modalities of therapy—surgery, chemotherapy and radiotherapy—over the past three decades. Examples of such changes are given below. Of particular interest is the concept of giving treatment choices to the patients and families (e.g. those with low-stage Hodgkin's disease) based on the anticipated late sequelae.

### *3.1. Surgery*

Surgery is the oldest tool used for childhood cancer and remains vital in the multidisciplinary approach to treatment of certain tumours (e.g. hepatoblastoma, Wilms', brain tumours and bone sarcomas). With the development of effective chemotherapeutic regimes and advances in surgical and imaging techniques, the morbidity has been considerably reduced. Preoperative reduction of the size of the tumour with chemotherapy reduced the risks of surgery.

The International Society of Paediatric Oncology (SIOP) Wilms' tumour trial used preoperative chemotherapy with good effect, reducing the size of the tumour and the rupture rate [64]. This approach is also used successfully in the treatment of bilateral Wilms' tumour, in many cases resulting in bilateral partial nephrectomies, in contrast to more radical nephron surgery, which may endanger renal function [65].

Advances in the development of limb prosthesis and effective chemotherapy, and the centralisation of care for patients with extremity bone sarcomas, has enabled many to preserve their limbs whilst maintaining survival rates. Although the surgeons and physicians involved feel that this advancement will improve the QOL of these patients, it is important to monitor patients' views on new developments such as this. To date, no comprehensive study comparing limb preservation with amputation has been published [66], which is an important issue because there are suggestions that patients rate their mobility and satisfaction lower than their surgeons do [66,67]. In Europe, a study is currently underway to try to establish the role of limb salvage, rotationplasty and amputation in these patients and assess their QOL (the European Bone Tumour Outcome Study).

A reduction in the need for radical surgery for some patients with soft-tissue sarcomas has also been possible (e.g. genitourinary tract). The role of major surgery (e.g. bladder removal) is controversial. An increased risk of relapse may be associated with a conservative surgical approach, but such surgery appears possible in carefully selected cases [68].

### *3.2. Radiotherapy*

Radiotherapy in growing children causes impairment of growth with loss of function. It is also implicated in the development of second tumours. Illustrated below are examples of diagnostic tumour groups where radiation therapy has been modified in an attempt to reduce late sequelae.

There has been a steady reduction over the past three decades in both the number of children with Wilms' tumour receiving radiotherapy and the dose and volume of radiotherapy administered. This has not been at the expense of survival rates and the resulting toxicity has been minimised for children who are usually $<5$ years old at the time of therapy and, therefore, particularly vulnerable to significant long-term toxicity. Whole abdominal radiotherapy causes several late sequelae, with poor soft-tissue and bone growth, impairment of lung function [18] and an increased risk of mid term abortion or premature labour in those girls that remain fertile [69,70].

When flank irradiation is required, treatment is delivered using a field crossing the spinal column to avoid the later development of scoliosis. Damage to bone, soft tissue and lung can still occur but the changes are limited to a smaller volume. There are a number of reports of late cardiac toxicity in survivors of Wilms' tumour [24,25]. Although this is largely due to the administration of relatively high doses of anthracyclines, it must be remembered that the upper border of the abdominal or

flank radiotherapy field can impinge on the cardiac ventricle and exacerbate any underlying damage.

The use of radiotherapy in children with soft-tissue sarcomas has been more controversial and different treatment strategies have been used in different national and international collaborative groups. The SIOP trials have adopted a strategy of avoiding systematic radiotherapy for some subgroups of patients (e.g. orbital, bladder/prostate) in front-line therapy, using it only where there is residual disease following chemotherapy. The balance of cure versus sequelae has recently been explored through an international workshop comprising four collaborative groups (IRSG, SIOP, German CWS and Italian ICG [71]). Although there was no difference in overall survival for the whole cohort whether or not radiotherapy was used, there were significant differences between these groups with respect to the use of radiotherapy and event-free survival. Only 39% of patients in the SIOP group received radiotherapy as part of their primary therapy compared with between 70 and 93% in the other co-operative groups. However, where initial radiotherapy rates were lower, the relapse rates were higher and therefore the burden of therapy for this subgroup of children was greater overall. This workshop emphasises the importance of accurate disease stratification. Some children can clearly be cured without radiotherapy to the orbit and the late sequelae that result. However, for those who relapse, the overall burden of therapy will be greater. As imaging improves and the biology of these diseases is better understood, it is hoped that accurate disease stratification will lead to optimal therapy for the majority of patients. The incidence of second cancers will also be important but length of follow-up is currently too short. A similar international workshop is planned to consider the outcome for children with bladder and prostate rhabdomyosarcoma in the near future where similar issues will be explored.

The use of radiotherapy has been steadily reduced in the management of children with ALL. The introduction of craniospinal radiotherapy in the late 1960s transformed the survival rates for children. It was then realised that spinal radiotherapy (with its adverse effects on growth and marrow suppression) could be omitted for the majority of children who did not have disease within the CNS with the administration of a prolonged, more intensive course of chemotherapy. It has subsequently been recognised that survival rates could be both maintained and improved as chemotherapy schedules have intensified, with a steady reduction in the systematic use of cranial radiotherapy. Only those children who present with disease within the CNS now receive cranial radiotherapy routinely in the majority of treatment schedules. Thus, the late toxicities following radiotherapy (fall in IQ, impairment of growth hormone production, obesity) are reduced. However, it should not be assumed that current strategies cause no long-term sequelae. Children receiving more intensive chemotherapy in some schedules must also be carefully observed for other late effects in the long term.

In an attempt to reduce the profound effects of radiation to the whole brain in the very young child, radiotherapy is withheld if at all possible in these children and chemotherapy used in an attempt to delay (and even occasionally avoid) radiotherapy [72]. Such strategies have had variable success, depending on the tumour type. For some young children, e.g. those with primitive neuroectodermal tumours, the outlook remains poor in terms of survival [73,74]. In contrast, a recent report from the French group suggests that, for those patients with ependymomas, the use of chemotherapy, delaying radiation until relapse, did not compromise overall survival and some patients were successfully treated without radiation [75].

The use of radiotherapy for Hodgkin's disease has varied widely and in some centres radiotherapy has been extensively used. It was noted that, whilst cure rates were satisfactory, a proportion later died from cardiovascular causes mainly coronary artery disease (CAD). The risk for fatal or non-fatal CAD was 8.1% at 22 years after therapy [76] and these patients had all received mediastinal radiation. Reviewing the incidence of CAD in the light of changing radiation techniques, it became clear that the use of subcarinal blocks at 30–35 Gy and limiting daily fraction doses reduced the incidence of CAD to nearly zero, although the follow-up interval to date is relatively short [76].

### 3.3. Chemotherapy

Chemotherapy carries a significant burden for some patients and we have already given some illustrations of this (e.g. effect of alkylating agents on male fertility, anthracycline-induced cardiotoxicity). As the use of radiotherapy is reduced and chemotherapy increased for many children, particularly with the use of high-dose therapy and stem cell rescue, the true burden of toxicity (particularly sub-fertility and second malignancy) will not be known for many years.

Hodgkin's disease provides an illustration of the changes in chemotherapy strategies used in an attempt to minimise late effects. It is a good example as both radiation and chemotherapy, including alkylating agents, are very effective used either alone or in combination in achieving survival rates above 80% overall and for patients with low stage disease greater than 95% [11,77]. Late effects include a high incidence of infertility in males due to the cumulative dose of alkylating agents [78] and a significant risk of the development of second malignant tumours (SMN), particularly following radiotherapy [9,79]. A number of strategies have been employed to address these sequelae. The German colla-

borative group have achieved a reduction in the cumulative dose of alkylating agents by stratifying patients according to a number of prognostic factors (stage, histological type). Follow-up studies of patients have demonstrated a group of fertile males [80]. In the UK, low-stage disease has been treated with radiation alone, thus maintaining fertility. However, 30% subsequently relapsed and were salvaged using gonadotoxic regimes, resulting in a higher burden of therapy overall. Furthermore, although there is good chance of cure after relapse, there is a correlation between the development of a second tumour and the number of relapses experienced [81] because more treatment is needed.

## 4. Quality of survival—a question of choice for patients and their physicians?

As yet, we have little information from patients and parents about their perception of the relative importance of different late sequelae and whether an increased risk of relapse, albeit with a favourable outcome after treatment, is acceptable. Is the risk of infertility a worse scenario than the risk of a second tumour? A controversial strategy in the UK has been to offer a choice of radiotherapy or combination chemotherapy to the parents, and those patients over the age of 10 years, of children with stage 1 Hodgkin's disease. Quantifying the relative impact of potential infertility following alkylating agents, and cardiotoxicity following anthracyclines (albeit at lower cumulative doses), compared with a no-needle, shorter treatment course, an increased risk of hypothyroidism and second malignancy following radiotherapy is extremely difficult. However, the outcome of this study will be informative, not only to help establish what is important to patients and their parents but also in the exploration of information delivery and the effect of conscious choice on subsequent QOL.

## 5. Conclusion

The treatment of childhood cancer has been increasingly successful over the past four decades. Attention is now rightly turning to the quality of survival whilst trying to ensure that cure rates are not compromised. Assessing the burden of survival is complex and dependent on both objective evaluation, preferably within the context of a clinical trial, and obtaining the subjective views of the survivors and sometimes of their family or other proxies. We have attempted to illustrate the issues that we believe are of particular relevance to the survivors as they pass through different stages of life, and also the ways in which attempts are now being made prospectively to minimise late effects of therapy. The careful stratification of patients into different levels of risk of relapse will help to lower the burden of therapy for those with a good chance of cure but will perhaps increase toxicity for those with a less favourable prognosis. However, with an improved understanding of the biology of disease, further advances are sure to be made.

It should be possible, even where the burden of therapy is high, to improve outcome by using psychological, surgical, therapeutic or educational interventions. However, there is relatively little research in this area and there is still much to learn from close evaluation of different patient groups whose quality of survival may be greatly enhanced by such interventions. Although the numbers of children with cancer are small, they will generally survive for many more years than adults with cancer. Investment in developing strategies to improve the quality of that survival will not be wasted.

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