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Review

Assessment of health-related quality of life after bone cancer in young people: Easier said than done

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ABSTRACT

Background: Improved survival rates coupled with awareness of physical and psychological late-effects have resulted in calls to consider the health-related quality of life (HRQOL) of survivors of childhood cancer. Survivors of bone tumours (osteosarcoma and Ewing's sarcoma) may be more vulnerable to compromised HRQOL than survivors of other cancers given their poor physical functioning.

Method: Current research is reviewed in relation to (i) HRQOL following a bone tumour compared with the healthy population and other child cancers and (ii) between those treated by amputation or limb salvage.

Results: Limitations of current research include (i) measurement of HRQOL; (ii) reliance on single informants, usually mothers and (iii) research design. In the process of adjustment to disease, patients reassess the meaning, value and importance of different domains, so that decisions about HRQOL are based on changing standards over time. These 'response shifts' challenge the validity of both cross-sectional and longitudinal research designs.

Conclusions: We conclude that methodological difficulties underlying previous work account for some of the discrepancies apparent in the current literature and challenge understanding of the complex processes of adjustment following a bone tumour.

1. Introduction

Survival rates following all childhood cancers have improved significantly in recent years.[1] Increases have also been observed for both osteosarcoma and Ewing's tumour, although overall survival rates remain lower than those for child cancer generally.[2] At the same time, recognition of late physical and psychological effects together with the decades of life remaining for survivors has raised questions about health-related quality of life (HRQOL). This refers to the broader impact of disease on everyday life[3] and includes physical, psychological and social implications[4] as well as disease- and treatment-related symptoms.[5]

Much research suggests that HRQOL in long-term survivors of child cancer is comparable with that of the general population. However there are differences depending on tumour group, and suggestions that HRQOL in survivors of some cancers including brain and bone tumours, is relatively poor compared with the general population or survivors of other cancers.[6]

There are several reasons why HRQOL following a bone tumour may be worse than that after other childhood cancers. First, while many cancers are diagnosed during early childhood, bone tumours are typically diagnosed during adolescence.[7] These patients are therefore more likely to be aware of the potentially life-threatening nature of the condition.

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Many experience mobility problems, and this can limit social life and employment prospects. Survivors need to monitor high-intensity physical activity (such as contact sports). Body image is especially important during adolescence, and is potentially compromised for those treated by amputation, as well as those undergoing limb salvage surgery (LSS).[8] For many reasons, then, patients with a bone tumour are likely to feel different from their peers. Second, adolescents and young people may be more aware of possible late-effects than younger children. These include those common to all survivors of child cancer (cardiac or fertility problems) and those unique to bone cancer (strength or mobility).

1.1. *Differences in QOL compared with a healthy population and other cancer survivors*

In order to determine the impact of a bone tumour on HRQOL, a common research design involves comparison of patients with the normal population, and less frequently, other cancer groups,[9] or sibling controls.[10] Recent reviews conclude that bone tumour survivors do not consistently report compromised HRQOL compared with the normal population.[8,11] However, problems with employment have been noted.[10] Patients are also less likely to marry, more likely to remain at home with parents and less likely to have children compared with the general population.[12] Compared with siblings, amputees have deficits in education and employment and difficulties in obtaining health insurance.[10]

Findings from two multi-centre studies (the CCSS: Childhood Cancer Survivor Study in the US and the BCCSS: British Childhood Cancer Survivor Study in the UK) overcome many of the statistical limitations of smaller studies, and crucially aim to be representative of the total cohort of survivors diagnosed within a specified time. Thus, findings from the CCSS showed that survivors of a bone tumour (odds ratio [OR], 2.1; 95% confidence interval [CI], 1.8–2.5; $p < .001$) or sarcoma (OR 1.2; 95% CI 1–1.5, $p < .01$) reported an increased risk of at least one adverse late-effect compared with survivors of childhood leukaemia.[13] Data from the BCCSS[14] suggest that bone tumour survivors reported their mental health to be comparable with the general population (and other cancer survivors). However they scored significantly below UK norms in terms of physical function. They were more limited in terms of daily activities (walking one mile (63%) compared with norms (16%)). Problems with other specific activities (walking 100 yards: 22%), bathing or dressing (21%) were almost four times higher than those for the general population (5%). These data suggest that bone tumour survivors experience significantly worse physical health compared with the rest of the population, with implications for work and leisure activities. Furthermore, for bone tumour and cancer survivors generally, physical health was rated worse with increasing chronological age, suggesting that perceived physical health declines more rapidly among cancer survivors than the general population.

1.2. *Relation between QOL and amputation or limb salvage*

A second line of study has involved comparison between those treated by amputation or limb salvage procedures. Several studies suggest better functioning following limb salvage compared with amputation[15] but others find no differences.[16] A recent review concludes that there 'did not appear to be a large QOL benefit for the survivors who had limb-sparing surgery over amputees'[11] (p. 10).

2. Methodological issues

In interpreting these discrepant findings, it is necessary to consider the methodological difficulties in conducting research of this kind. These include (1) measurement of HRQOL, (2) reliance on single informants of HRQOL (usually mothers) and (3) research design (cross-sectional or longitudinal studies).

2.1. *Measurement of HRQOL*

A critical distinction has been made between *objective measures* such as clinical indices that patients would not use themselves or be aware of; *functional performance* (daily activities such as climbing stairs); and *subjective evaluation* of the experience or patient's own awareness of being able to complete an activity.[17] This subjective component is integral to the concept of HRQOL, but pose a huge challenge to measurement.

Further distinctions between generic and disease-specific measures can be made. *Generic* measures focus on broad, global issues. These are considered most useful when the purpose of assessment is to compare differences between disease groups, or between disease groups and the healthy population. Thus, it is possible to determine whether the group of interest has comparable or worse HRQOL compared with the healthy population or in relation to other cancers or indeed other chronic conditions. Generic measures do not provide detailed information regarding how specific aspects of treatment compromise HRQOL.

In contrast, *disease-specific* measures include symptom checklists and disease and treatment-related issues. They are thought to be more sensitive to clinical change and are preferred when the purpose is to determine changes associated with different arms of a clinical trial, or when evaluating alternative interventions. For cancer, *cancer-site* or *problem-specific* measures can also be identified. The European Organisation for Research and Treatment of Cancer (EORTC) has developed both a general cancer measure and site-specific modules[18] but to date there is no bone tumour specific module. Generic measures with complementary site-specific modules are available for children and adolescents,[19,20] but again no site-specific module for bone tumour currently exists.

In a clinical trial, the purpose may also be to compare the cost-effectiveness of different treatments. The Health Utilities Index (HUI) is a standardised system to measure health status and HRQOL and was developed to assess: (i) the experience of patients undergoing therapy; (ii) long-term outcomes; (iii) efficacy, efficiency and effectiveness of health care interventions and (iv) health status of the general population.[21] HUI enables calculation of a utility score on a generic scale where dead = .00 and perfect health = 1.00. Utility scores

are used to calculate HRQOL and quality-adjusted life years (QALYs). In practice, the HUI reflects a different perspective on HRQOL compared with more psychological approaches, drawing on definitions that emphasise 'the value assigned to duration of life as modified by impairments, functional states, perceptions and social opportunities that are influenced by disease, injury, treatment or policy.'[22]

HRQOL measures are typically targeted either at children or adults. Neither is likely to be sensitive to issues that affect young people. Body image, autonomy, friends, family relationships and intimate/sexual relationships are likely to form key components of HRQOL during adolescence and young adult life.

A second limitation associated with age is that measures tend to target specific age-groups. The most commonly used generic measure is the PedsQL.[23] However this is only valid for children between 5 and 18 years and an alternative measure is necessary for survivors above this age. The most commonly used generic measure for adults (SF36:24) allows calculation of a physical health component score (PCS) and a mental health component score (MCS) as well as a total QOL score. However, there is no information regarding the relationship between child and adult measures, making it impossible to determine changes in HRQOL over time. This is especially a limitation when working with survivors of bone tumours, who are often diagnosed during adolescence. On diagnosis, measurement of HRQOL is most appropriate using a child-orientated measure, but even a relatively short follow-up requires an adult-orientated measure.

A further problem associated with measurement follows from the low incidence of bone tumours. Most treatment centres have insufficient numbers to enable reliable work to be conducted, so that national or international studies are called for. International studies require measures that have been validated for different languages.

In both the CCSS and the BCCSS, as well as work by the national Scandinavian Sarcoma group,[9,16] a 'generic' HRQOL measure for adults[24] was used. Single generic measures of HRQOL, developed for adults rather than young people, may be appropriate for epidemiological work, but cannot provide insight to issues involving younger children, changes in HRQOL from childhood to later life or the specific aspects of treatment that are most likely to compromise HRQOL.

2.2. *Informants*

Most research concerned with bone tumour survivors, including both the CCSS and the BCCSS, relies on information from the survivor only. Current opinion is that it is essential to derive information from both patient and parent/carer in order to gain a more comprehensive picture.[25] This can contribute towards understanding how far patients under-report or 'deny' their problems.

2.3. *Research design*

The issue of under-reporting or denying problems following serious or life-threatening illness and treatment is not unique to survivors of childhood bone tumours. At least three theoretical explanations have been proposed. The first involves denial. By denying or suppressing the threatening nature of the illness, the patient is able to maintain continuity with the past, denial can extend to issues other than the illness. O'Leary et al.[26] reported that survivors of childhood cancer show a biased response style or systematic tendency to deny difficulties. Second, Crisis theory assumes that experience of a crisis upsets the balance between problem perception and problem-solving capacity.[27] With time, problem-solving capacity increases and a new balance is achieved, but there is some evidence that cancer patients differ from healthy controls in problem-solving capacity.

By far the most influential theory is 'response shift bias'.[28] It is argued that an extreme experience such as cancer creates a shift in internal norms, so that initial and final measurements are not on the same scale. For example, an individual may, before diagnosis, value sport highly, but subsequently dismiss it as unimportant. This means that the values on which ratings of HRQOL are based, change over time. Furthermore, a score on any scale may have a different meaning for cancer patients compared with others.

This points to a potential bias in much research so that reports of higher than expected HRQOL post-treatment are at least partly due to shifts in internal standards. There are implications for longitudinal work, in that suggestions that HRQOL improves from diagnosis despite intensive treatment and experience of side-effects, may reflect (i) very depressed HRQOL on diagnosis and (ii) changing expectations and values over time.

3. Conclusions

The question of HRQOL following a bone tumour in childhood is an important one, with implications for communication and decision-making.[29] The methodological challenges are, however, considerable. In addition to the specific issues considered, there are also major practical barriers to national and international studies, including requirements for multiple ethics approvals. Patients themselves also contribute a significant barrier. Young people move around the country and are difficult to trace, and perhaps their age also means they are not interested in taking part.

Epidemiological studies that rely on generic measures of HRQOL provide limited data regarding the real burden involved in surviving bone cancer. Current measures were developed either for children or adults, and neither capture HRQOL during adolescence and young adult life. Indeed conclusions based on current measures must be interpreted with caution, since there is limited evidence regarding comparability across different HRQOL measures when used with similar populations,[30] and certainly none addressing issues of change from childhood to adult life.

Furthermore, the phenomenon of 'response bias' may result in changes in the importance of different aspects of HRQOL following a bone tumour. This can affect the validity of cross-sectional studies where comparisons are made between bone tumour survivors and another group, whether this is normal controls, siblings or other patient groups. It is also a major challenge to longitudinal work since linear improvements in HRQOL from diagnosis may simply reflect

changes in values that occur in the process of adjustment to illness. Statistical analysis therefore needs to be supplemented by qualitative research that captures how and when changes in values occur. This qualitative work may also yield insight as to why some patients fail to make adjustments to internal values needed to adjust to the restrictions experienced following a bone tumour and its treatment. Understanding how response bias develops may give key insights into adjustment and HRQOL in survivors of childhood cancer, and provide an evidence-base on which to base intervention techniques.

Conflict of interest statement

None declared.

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