

**What are the long-term effects of treatment on survivors of childhood leukaemia? : a review of the literature**

WHITAKER, D. and GREEN, David

Available from Sheffield Hallam University Research Archive (SHURA) at:

<http://shura.shu.ac.uk/8371/>

---

This document is the author deposited version. You are advised to consult the publisher's version if you wish to cite from it.

**Published version**

WHITAKER, D. and GREEN, David (2014). What are the long-term effects of treatment on survivors of childhood leukaemia? : a review of the literature. *Journal of Radiotherapy in Practice*, 13 (03), 365-370.

---

**Copyright and re-use policy**

See <http://shura.shu.ac.uk/information.html>

**An investigation into the long-term effects on survivors of childhood leukaemia: a critical literature review**

D. Whitaker (BSc) & D. Green (MSc)\*

Radiotherapy Department, St James University Hospital, Leeds, \* Sheffield Hallam University, Sheffield

Correspondence to D. Whitaker C/O Radiotherapy Department, St James University Hospital, Leeds. LS9 7TF Danielle.Whitaker@Leedsth.nhs.uk

## **Abstract**

Key advances in cancer treatment have led to an increasing number of long-term cancer survivors. Knowledge of the long-term effects of cancer treatment of leukaemia survivors is to some degree limited. This article investigates the effects of the treatment of childhood leukaemia on the quality of life, physical and psychological wellbeing and general development of survivors. This article reviews current literature to examine existing gaps in knowledge and identify a potential focus of future research and clinical practice.

## **Keywords**

Quality of life, physical, psychosocial, survival, paediatric, late effects, follow up

## **Introduction**

Enhanced knowledge of causative factors and the development of effective paediatric cancer treatments has drastically improved survival rates.<sup>1-4</sup> An increase in five year survival rates from < 5% in the 1950s, to > 75% in 2004, indicates the vast improvements made<sup>5</sup>. A consequence of these increased survival rates has been subsequent research focus on the long-term effects of paediatric cancer<sup>6-7</sup>. Freyer and Kibrick-Lazear<sup>8</sup> stress the importance of prolonged monitoring and support of survivors to enable early detection and effective management of quality of life (QOL) issues.

Leukaemia is the most common malignancy in children, representing almost a third of all childhood cancers.<sup>9</sup> With the introduction of enhanced treatment regimes, cure rates of almost 80% have been achieved for childhood acute lymphoblastic leukaemia (ALL).<sup>10</sup> Treatment for leukaemia can involve; chemotherapy, radiotherapy, bone marrow/ stem cell transplants and steroids. Each modality has alternative implications for the future health and development of patients. Therefore, the impact of each must be known, to enable well informed treatment decisions.<sup>10</sup> As survival rates have greatly improved, the benefits of specific treatments need to take account of potential long-term problems.

The volume of current research regarding the chronic health and psychological problems faced by survivors of childhood leukaemia is steadily increasing. This is due to the improvement in aforementioned survival rates, which enables a greater number of participants to be recruited.<sup>4</sup>

The previous lack of research participants reduced the opportunity for longitudinal research needed to establish true long term issues.<sup>11</sup> As survival rates continue to improve, there will be increasing numbers of available participants for future work. Currently, the knowledge base is developing, and numerous primary research papers explore this topic.<sup>12-14</sup>

For the purpose of this review, it is necessary to synthesize the literature to determine the focus of future research. Subsequently, this article aims to assess information on the chronic effects of treatment on childhood survivors of leukaemia.

It will consider the physical, psychological and developmental effects of treatment and ways in which to manage them.

Survivors of childhood cancer are faced with multiple long-term effects which can greatly impact their QOL.<sup>15</sup> Around two thirds of survivors experience at least one long-term problem, whilst a quarter of survivors face a severe or life threatening late effect.<sup>16</sup> A number of studies highlight the relationship between treatment modality, age at diagnosis and the extent of long-term problems.<sup>12,14,17-18</sup> Chronic side effects in young patients treated with cranial irradiation appear to be exacerbated, with there being fewer chronic side effects noted between chemotherapy regimes.<sup>19</sup>

## **QOL**

QOL refers to a person's all around well being, considering both physical and psychosocial health.<sup>7</sup> With all cancer treatment there is the risk of acute and chronic side effects which may impact on a patient's QOL in both the short and long term. Therefore, considering treatment options in-depth to create the most effective treatment plan for each individual is essential. Understanding the risks associated with cancer therapies is the first step in improving care for the future.<sup>20-22</sup>

## **Physical effects**

The endocrine system is readily affected by cancer treatments, resulting in numerous long-term problems.<sup>23</sup> The extent of these problems appears to be directly related to the treatment modality, with problems rarely seen in those treated with chemotherapy only. In contrast, leukaemia patients treated with total body irradiation (TBI) and bone marrow transplants (BMT) often experience late endocrine

disorders.<sup>24</sup> Severe growth hormone deficiency (GHD) was seen in 50% of those treated with TBI/ BMT, with 56% experiencing thyroid dysfunction (mainly hypothyroidism). Steffens et al.<sup>24</sup> also found that 40% of males had biological signs of altered spermatogenesis, with all of the females treated with TBI/ BMT having ovarian failure. The majority of patients studied were on some form of hormone replacement therapy with the aim of improving the patient's QOL. Close long-term follow up regarding endocrine function is essential in ensuring survivors are well supported.<sup>23-26</sup>

There is not a clear consensus regarding percentage fat mass. Ness et al.<sup>27</sup> found the percentage fat mass of leukaemia survivors was significantly higher than the expected norms, with percentage skeletal and lean body mass significantly lower. In contrast, Tillmann et al.<sup>28</sup> did not find a significant difference in percentage fat mass between survivors and control subjects. Body mass index (BMI) has been found to be significantly higher in female survivors when compared to both the expected norms, and control subjects.<sup>29</sup> Females treated with high dose cranial irradiation (20 – 24Gy), at a young age were found to have a 55% chance of being overweight or obese in the future.<sup>30</sup>

Male survivors also demonstrated higher BMIs indicating weight problems. However, male control subjects also displayed signs of being overweight.<sup>29</sup> Therefore, the effect of cancer treatment on male survivors' body composition is not clear. In terms of bone mineral density (BMD), there were no differences between cases and controls, except regarding lumbar spine bone density, which was significantly lower in survivors.<sup>28</sup> No difference in BMD was found between groups who received cranial

irradiation, and those who did not.<sup>31</sup> This highlights the need for childhood survivors, especially female, to be given guidance on healthy lifestyles in the long-term to reduce the occurrence of obesity.

As a result of higher percentage fat masses, and lower BMD in some cases, problems with mobility and strength have been detected. Knee extension strength in particular is significantly lower in leukaemia survivors than the expected norms and control groups tested.<sup>32</sup> As a result, survivors walked significantly shorter distances in two minutes, demonstrating their impaired mobility.<sup>27</sup> Cranial irradiation was found to be related to reduced strength and mobility, particularly in female survivors. One explanation for reduced mobility could be the effect cancer (radiation) treatment has on motor nerve conduction.<sup>33</sup> This study identified a significant difference regarding motor nerve conduction and lower extremities, resulting in a lack of knee extension strength. Survivors' balance was also affected by treatment somewhat, with one third of patients unable to complete the most challenging task.<sup>34</sup> Balance problems became clear when vision was removed, and survivors were tested with uneven surfaces. These problems pose a potential threat to survivors in terms of physical activity.

Physical activity during childhood and adolescent years is very important due to its effect on percentage fat mass, and peak bone mass.<sup>28</sup> Maximal oxygen uptake ( $VO_{2max}$ ) was significantly lower in survivors indicating a reduced level of physical fitness.<sup>32</sup> Tillmann et al.<sup>28</sup> found survivors to have significantly lower weekly activity scores than the control group (geometric mean 50 vs geometric mean 74;  $p < 0.05$ ). Thus demonstrating a possible lower exercise capacity similar to that seen by Jarfelt

et al<sup>31</sup>. In this study, male survivors previously treated with cranial irradiation, especially with existing GHD, experienced much lower exercise capacities, with no differences seen between female groups. Both aerobic and anaerobic exercise capacity have been seen to be reduced in leukaemia survivors, along with self reported cardio-pulmonary fitness levels.<sup>27</sup> In contrast, the subjects in the study by Heath, Ramzy and Donath,<sup>3</sup> either met or exceeded the national standards for physical activity, with the exception of three children out of nineteen. This may suggest that with clear education on the importance of physical activity, the effects of cancer treatment on physical fitness and function can be minimised.

### **Psychological and developmental effects**

Glover et al.<sup>35</sup> investigated the relationship between cranial irradiation and a survivor's psychological mood. Those diagnosed at a younger age (<12.5 years) displayed significantly greater levels of mood disturbance. When investigating ethnic differences, the racial and ethnic minority group appear to be greater affected by mood disturbance with 34.4% being mood disturbed, compared with 22.5% of Caucasian survivors. Almost a quarter of the participants displayed signs of mood disturbance. Cranial irradiation does increase the occurrence of mood disturbance, however not significantly. Thus suggesting treatment modality is not a direct risk factor of mood disturbance.



Cranial irradiation has been shown to increase the extent of neuropsychological impairment, especially within male survivors.<sup>36</sup> When compared to a chemotherapy only group, those previously treated with radiotherapy scored lower in tests for verbal Intelligence Quotient (IQ), attention and concentration ability, and memory. Spiegler et al.<sup>19</sup> also found survivors treated with radiation scored significantly lower in arithmetic and reading/ comprehension tests, whereas differences in attention and intellect were not detected.<sup>37</sup> Thus suggesting that prophylactic cranial irradiation increases the risk of survivors experiencing neuropsychological impairment, resulting in certain cognitive and intellectual deficits.<sup>36</sup> Reduced volumes of white matter correspond to greater deficit in intelligence and academic achievement, as a result of both cranial irradiation, and chemotherapy to a lesser extent.<sup>37</sup>

With regards to patients treated with chemotherapy only; selective aspects of cognitive functioning are impaired, especially visual processing.<sup>38</sup> Intensified courses of chemotherapy have been seen to cause extensive deficits regarding attentional flexibility, and visuo-motor control.<sup>39</sup> Those diagnosed at a younger age appear more likely to be affected by certain deficits; however it is unclear as to whether this is as a result of a greater susceptibility to chemotherapy drugs.<sup>40</sup> Although chemotherapy appeared to have little consequences concerning intellectual functioning, two young patients out of twenty one did show a decline of greater than 10 IQ points. However, greater educational support has been shown to reduce these effects on a survivor's intellectual functioning, thus early interventions can be successful.<sup>38</sup>

Health related quality of life (HRQOL) is important for survivors of childhood leukaemia as a result of their predicted long survival rates. Following the completion

of the Strength and Difficulties questionnaire (SDQ) for children, no statistically significant differences in psychosocial health were seen. However, the SDQ for mothers of childhood leukaemia survivors displayed significantly poorer scores in terms of emotional symptoms<sup>41</sup>. Link et al.<sup>42</sup> found there to be no differences in self reported QOL, yet a significantly lower level of education was reached. Only 23% of survivors reached university level, in comparison to 55% of healthy controls. In contrast, Reinfjell et al.<sup>43</sup> concluded that there was a significantly lower HRQOL amongst survivors of leukaemia when compared to healthy controls. Intellectual functioning was determined to be within the normal range, but lower than that of the control group. Fathers of childhood leukaemia survivors were found to be significantly more anxious and depressed than control subjects<sup>41</sup>, indicating the importance of providing support for the entire family. Chiou et al.<sup>44</sup> found the problems experienced by cancer survivors, impacted upon a family's normal routine, as a result of significant impairments across both physical and psychosocial domains.

With greater than two thirds of children diagnosed with cancer achieving disease free survival, it is essential to be aware of the long-term effects which may arise.<sup>45</sup> Early detection and interventions can improve the QOL of both cancer survivors and their family by relieving pressures and reducing the extent of problems.<sup>15</sup> Where cure is the aim, it is also necessary that the potential chronic issues do not outweigh the advantages. Treatment modality does play a part in the chronic effects experienced, therefore treatment plans need to be discussed in depth to provide the best care for each patient.<sup>46</sup>

Further analysis of the research papers is required, along with the inclusion of further samples of literature. With this, clearer conclusions regarding the long-term QOL of survivors of childhood leukaemia will be detected. Furthermore, the majority of the research papers focused on survivors of ALL and did not include other types such as Acute Myeloid Leukaemia and Chronic Myeloid Leukaemia. Other forms of leukaemia are rarer thus the research available is limited. Nevertheless, it is important to investigate whether there are differences between the long-term effects for the different types of leukaemia.

## **Conclusion**

As a result of this literature review, it is clear that childhood survivors of leukaemia face many chronic side effects that can greatly impact upon their QOL. This is currently an inevitable consequence of curative treatment received. This highlights the importance of long-term follow up, especially for those diagnosed at a young age.<sup>44</sup> There are clear relationships between the extent of chronic effects, and the treatment modality, with cranial irradiation and TBI causing greater impairments.<sup>24</sup> Further research into this area is required to enable health professionals to shape the treatment of paediatrics, with the aim of providing them with the best QOL possible. The dearth of research surrounding rarer forms of leukaemia also implies the need for future research to determine the chronic effects of treatment on patients suffering from rare forms of leukaemia.

Future practice must be concerned with long-term QOL as well as curing the short term problem. Research suggests that the family is equally affected by a child's treatment and subsequent long-term problems. As a result, guidance and support is

fundamental to creating a positive atmosphere for each family. Consequently, further research regarding the effects of childhood cancer on the family unit is essential.

**3703**

## References

1. Ribeiro RC, Pui C. Saving the children - improving childhood cancer treatment in developing countries. *New England Journal of Medicine* 2005; 352 (21): 2158-2160.
2. Cantrell MA, Ruble K. Multidisciplinary care in paediatric oncology. *Journal of Multidisciplinary Healthcare* 2011; 4 (1): 171-181.
3. Heath JA, Ramzy JM, Donath SM. Physical activity in survivors of childhood acute lymphoblastic leukaemia. *Journal of Paediatrics & Child Health* 2010; 46 (4): 149-153.
4. Hunger SP. Improved survival for children and adolescents with acute lymphoblastic leukaemia between 1990 and 2005: A report from the children's oncology group. *Journal of Clinical Oncology* 2012; 30 (14): 1663-9.
5. Bradwell M. Survivors of childhood cancer. *Paediatric Nursing* 2009; 21 (4): 21-24.
6. Berg C, Nuefeld P, Harvey J, Downes A, Hayashi RJ. Late effects of childhood cancer, participation, and quality of life of adolescents. *OTJR: Occupation, Participation & Health* 2009; 29 (3): 116-124.
7. Ness KK, Gurney JG, Zeltzer LK et al. The impact of limitations in physical, executive and emotional function on health related quality of life among adult

survivors of childhood cancer: a report from the childhood cancer survivor study. *Archives of Physical Medicine and Rehabilitation* 2008 ; 89 (1): 128-36.

8. Freyer DR, Kibrick-Lazear R. In sickness and in health. *Cancer* 2006; 107 (Suppl. 7): 1702- 1709.
9. Shah A, Coleman MP. Increasing incidence of childhood leukaemia: A controversy re-examined. *British Journal of Cancer* 2007; 97 (7): 1009-1012.
10. Rubnitz JE, Pui CH. Recent advances in the treatment and understanding of childhood acute lymphoblastic leukaemia. *Cancer Treatment Reviews* 2003; 29 (1): 31-44.
11. Van Der Lee JH, Wesseling J, Tanck MWT, Offringa M. Efficient ways exist to obtain the optimal sample size in clinical trials in rare diseases. *Journal of Clinical Epidemiology* 2008; 61 (4): 324-330.
12. Daams M, Schuitema I, Van Dijk BW et al. Long-term effects of cranial irradiation and intrathecal chemotherapy in treatment of childhood leukaemia: a MEG study of power spectrum and correlated cognitive dysfunction. *BMC Neurology* 2012; 12 (1): 84.
13. Mud MS, Kremer LC, Sieswerda E, Van Der Pal HJ. Care for survivors of childhood cancer in the Netherlands. *Ned Tijdschr Geneeskd*, 2012; 156 (9): A4199.

14. Fulbright JM, Raman S, McClellan WS, August KJ. Late effects of childhood leukaemia therapy. *Current Hematologic Malignancy Reports* 2011; 6 (3): 195-205.
15. Langeveld NE, Stam H, Grootenhuis M, Last B. Quality of life in young adult survivors of childhood cancer. *Supportive Care in Cancer: Official Journal of the Multinational Association of Supportive Care in Cancer* 2002; 10 (8): 579-600.
16. Bhatia S, Landier W. Evaluating survivors of paediatric cancer. *Cancer Journal* 2005; 11 (4): 340-354.
17. Oeffinger KC, Nathan PC, Kremer LCM. Challenges after curative treatment for childhood cancer and long-term follow up of survivors. *Hematology/Oncology Clinics of North America*, 2010; 24 (1): 129-149.
18. Dietz AC, Mulrooney DA. Life beyond the disease: relationships, parenting and quality of life among survivors of childhood cancer. *Haematologica* 2011; 96 (5): 643-645.
19. Spiegler BJ, Kennedy K, Maze R et al. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukaemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. *Journal of Clinical Oncology* 2006; 24 (24):3858-3864.

20. Bradley Eilertsen ME, Jozefiak T, Rannestad T, Indredavik MS, Vik T. Quality of life in children and adolescents surviving cancer. *European Journal of Oncology Nursing* 2012; 16 (2): 185-193.
21. Levin TT, Li Y, Riskind J, Rai K. Depression, anxiety and quality of life in chronic lymphocytic leukaemia cohort. *General Hospital Psychiatry* 2007; 29 (1): 251-256.
22. Redaelli A, Stephens JM, Brandt S, Botteman MF, Pashos CL. Short and long-term effects of acute myeloid leukaemia on patient health-related quality of life. *Cancer Treatment Reviews* 2004; 30 (1): 103-117.
23. Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumours. *The Neurologist* 2004; 10 (6): 293-310.
24. Steffens M, Beauloye V, Brichard B et al. Endocrine and metabolic disorders in young adult survivors of childhood acute lymphoblastic leukaemia (ALL) or non-Hodgkin lymphoma (NHL). *Clinical Endocrinology* 2008; 69 (5): 819-827.
25. Thomas IH Bone mineral density in young adult survivors of acute lymphoblastic leukaemia. *Cancer* 2008; 113 (11): 3248-56.
26. Baronio F, Battist L, Radetti G. Central hypothyroidism following chemotherapy for acute lymphoblastic leukaemia. *Journal of Paediatric Endocrinology and Metabolism* 2011; 24 (11-12): 903-6.



27. Ness K K, Baker KS, Dengal DR et al. Body composition, muscle strength deficits and mobility limitations in adult survivors of childhood acute lymphoblastic leukaemia. *Paediatric Blood & Cancer* 2006; 49 (7): 975-981.
28. Tillman V, Darlington, ASE, Eiser C, Bishop NJ, Davies HA. Male sex and low physical activity are associated with reduced spine bone mineral density in survivors of childhood acute lymphoblastic leukaemia. *Journal of bone and mineral research: The Official Journal of the American Society for Bone and Mineral Research* 2002; 17 (6): 1073-1080.
29. Warner JT, Evans WD, Webb, DK, Gregory JW. Body composition of long-term survivors of acute lymphoblastic leukaemia. *Medical and Paediatric Oncology* 2002; 38 (3): 165-172.
30. Oeffinger KC, Mertens AC, Sklar CA et al. Obesity in adult survivors of childhood acute lymphoblastic leukaemia: A report from the children's cancer group. *Journal of Clinical Oncology* 2003; 21 (7): 1359 – 1365.
31. Jarfelt M, Fors H, Lannering B, Bjarnason R. Bone mineral density and bone turnover in young adult survivors of childhood acute lymphoblastic leukaemia. *European Journal of Endocrinology / European Federation of Endocrine Societies*, 2006; 154 (2): 303-309.
32. Van Brussel M, Takken T, Net JVD et al. Physical function and fitness in long-term survivors of childhood leukaemia. *Paediatric Rehabilitation*, 2006; 9 (3): 267-274.

33. Lehtinen SS, Huuskonen UE, Harila-Saari AH, Tolonen U, Vainionpaa LK, Lanning BM. Motor nervous system impairment persists in long-term survivors of childhood acute lymphoblastic leukaemia. *Cancer* 2002; 94 (9): 2466-2473.
34. Galea V, Wright MJ, Barr RD. Measurement of balance in survivors of acute lymphoblastic leukaemia in childhood. *Gait and posture* 2004; 19 (1): 1–10.
35. Glover DA, Byrne J, Mills JL et al. Impact of CNS treatment on mood in adult survivors of childhood leukaemia: A report from the children's cancer group. *Journal of Clinical Oncology* 2003; 21 (23): 4395 – 4401.
36. Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL therapy in childhood. part III: Neuropsychological performance in long-term survivors of childhood ALL: Impairments of concentration, attention, and memory. *Medical and Paediatric Oncology* 2002; 38 (5): 320-328.
37. Reddick WE, Shan ZY, Glass JO et al. Smaller white-matter volumes are associated with larger deficits in attention and learning among long-term survivors of acute lymphoblastic leukaemia. *Cancer* 2006; 106 (4): 941-949.
38. Mennes M, Stiers P, Vandebussche E et al. Attention and information processing in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only. *Paediatric Blood & Cancer* 2005; 44 (5): 479-486.

39. Buizer AI, De Sonnevile LM, Van Der Heuvel-Eibrink MM, Veerman AJ. Chemotherapy and attentional dysfunction in survivors of childhood acute lymphoblastic leukaemia: Effect of treatment intensity. *Paediatric Blood & Cancer* 2005; 45 (3): 281-290.
40. Jansen NC, Kingma A, Schuitema A et al. Post-treatment intellectual functioning in children treated for acute lymphoblastic leukaemia (ALL) with chemotherapy-only: A prospective, sibling-controlled study. *European Journal of Cancer* 2006; 42 (16): 2765-2772.
41. Reinfjell T, Lofstad GE, Nordahl HM, Vikan A, Diseth TH. Children in remission from acute lymphoblastic leukaemia: Mental health, psychosocial adjustment and parental functioning. *European Journal of Cancer Care* 2009; 18 (4): 364-370.
42. Link K, Moëll C, Osterberg K et al. Adult survivors of childhood acute lymphoblastic leukaemia with GH deficiency have normal self-rated quality of life but impaired neuropsychological performance 20 years after cranial irradiation. *Clinical Endocrinology* 2006; 65 (5): 617-625.
43. Reinfjell T, Lofstad GE, Veenstra M, Vikan A, Diseth TH. Health-related quality of life and intellectual functioning in children in remission from acute lymphoblastic leukaemia. *Acta Paediatrica* 2007; 96 (9): 1280-1285.
44. Chiou SS, Jang RC, Laio YM, Yang P. Health-related quality of life and cognitive outcomes among child and adolescent survivors of leukaemia.

Supportive care in cancer: Official Journal of the Multinational Association of Supportive Care in Cancer 2010; 18 (12): 1581-1587.

45. Quin S. The long-term psychosocial effects of cancer diagnosis and treatment on children and their families. *Social Work in Health Care*, 2004; 39 (1): 129-149.

46. Temming P, Jenney MEM. The neurodevelopmental sequelae of childhood leukaemia and its treatment. *Archives of Disease in Childhood* 2010; 95 (11): 936-940