

# Surviving childhood cancer

It's the journey of a lifetime

→ Peter McIntyre

Childhood cancer is increasingly about being cured. But developing bodies can suffer life-long damage from toxic treatments, and developing personalities become moulded by the experience of battling cancer and living with uncertainty. In the third part of our series on *Living with the consequences*, survivors and doctors talk about managing a journey that never ends.

First, there is the journey through cancer. Then, with luck and good treatment, the journey beyond cancer. Aemilia Tsiros was diagnosed with acute lymphoblastic leukaemia (ALL) at the age of eight, and 20 years later is helping to organise survivors of childhood cancer throughout Greece. She references a modern classic fantasy to illustrate their quest.

"In *Lord of the Rings*, Frodo had to take a bad thing, the ring, and carry it on a dangerous journey in order to destroy it. To get there he has to pass through many dangerous places, a forest of darkness, oceans, mountains, but he got there and he managed to destroy it.

"The majority of us who have survived realised that we could not do anything except live, and that the way to live is to fight it. After some days in the hospital you know that not everybody survives, but you try to have a very positive idea about life. This makes us stronger definitely, that we are survivors and winners."

Aemilia is a role model for children currently undergoing treatment who need to know that there is life after cancer and their lives can return to 'normal'. There is and they can, but their lives are always likely to be a bit different, even after the cancer is pro-

nounced cured. For some there are long-term side-effects of surgery, radiotherapy or chemotherapy. For others there is the risk of the return of their cancer, or of a new cancer related to the treatment they received. Bad things happened before and could happen again.

As they grow into adulthood, some must overcome psychological barriers to becoming what a team of global experts set as a long-term aim: "a resilient, fully functioning, autonomous adult with an optimal health-related quality of life, accepted in the society at the same level of his/her age peers" (see the Erice statement, p 59).

The prospects for children with cancer have been revolutionised over the past 40 years. In the mid-1960s the five-year survival rate for children with ALL was under 5%. By the mid-1990s five-year survival was over 80% and still rising. For retinoblastoma and a few other childhood cancers five-year survival is around 96%. The rule of thumb is that more than two-thirds of childhood cancers (and in many places, more than 70%) can be cured with good-quality care at specialised cancer centres. Of course, this only applies in countries with well-developed health systems – which excludes 80% of the world's children.



PETER MCINTYRE

A role model. Twenty years after being treated for ALL, Aemilia Tsirou offers herself as living proof to young patients that there is life after cancer. She is pictured here at the Athens centre of the Floga parents' group, with a puzzle she made for young people undergoing treatment

About one in 500 children develop cancer. As more children survive, the number of survivors living as adults accumulates, and will exceed one in 700 adults. In the US alone, there are already more than 270,000 adult survivors of childhood cancer. The numbers in Europe also run into six figures.

According to the US Institute of Medicine, more than two-thirds of childhood cancer survivors experience some form of late effects, some of them serious or fatal. The largest study undertaken of five-year survivors showed a 10.8-fold increased risk of death in subsequent years covered by the study, which rose to 18-fold in females, although most of these deaths were from a recurrence of their original cancer rather than late effects related to treatment.

This US study (Mertens et al. *J Clin Oncol* 2001) looked retrospectively at what had happened to 20,000 people who had survived at least five years after diagnosis of childhood cancer. By the time of the

study, 18,000 were still alive and 2,000 had died. Of these seven in ten had died from a recurrence, and two in ten had died because of late effects.

Another study on the same American cohort found that 73% of survivors had at least one chronic health condition, while 42% had a grade 3–5 chronic condition (severe, life-threatening or fatal). Long-term survivors were eight times more likely to have a severe or life-threatening condition than their siblings (Oeffinger et al. *NEJM* 2006).

These figures are alarming, but neither study is an accurate guide to current risks. Hamish Wallace, consultant paediatric oncologist at the Royal Hospital for Sick Children Edinburgh, points out that the US cohort was hospital-based and may over-represent problems. Moreover, all the survivors were diagnosed between 1970 and 1986, when chemotherapy and radiotherapy was used most intensively.

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**LATE EFFECTS OF TREATMENT FOR CHILDHOOD CANCERS**

<b>Late effect</b>	<b>Probable treatment cause</b>
Breast cancer	Radiation to chest exceeding 40 Gy
Thyroid and other cancers Hypothyroidism and other thyroid dysfunction Decline in cognitive function	Cranial radiotherapy; radiotherapy to the neck; chemotherapy; cranial radiotherapy
Congestive cardiac failure Cardiac disease	High doses of anthracyclines; irradiation at higher doses
Pulmonary fibrosis, pulmonary toxicity, restrictive lung disease	Chemotherapy or radiotherapy
Growth problems and obesity	Cranial radiotherapy; bone marrow transplant (with radiotherapy); chemotherapy
Orofacial and dental development problems	Radiotherapy to the head or neck
Delayed puberty in girls	Cranial irradiation
Incomplete development of breasts	Irradiation to pre-pubertal breast tissue
Incomplete uterine growth damage to ovaries Premature menopause	Chemotherapy or radiotherapy
Fertility problems in boys	Chemotherapy or radiotherapy

Wallace says that things have changed. “We have been working really hard to decrease the number of patients who get radiotherapy and – for those patients who have to have radiotherapy – decrease the dose.”

Changes in treatment are not yet reflected in a reduction in late effects, because they take so long to show up. For example, in Hodgkin’s lymphoma, second malignancies occurring within the radiation field are seen about 20 years after the original treatment. However, the incidence of second malignancies is related to dosage, so it is reasonable to assume that current treatments will produce fewer second malignancies.

**A CHRONIC DISEASE?**

Wallace chaired the development group that drew up Scottish national guidelines for long-term follow-up of survivors of childhood cancer. He says that rapid changes in treatment need to be matched by changes in attitude.

“Now what I am asking as an oncologist looking towards the future is, ‘Is childhood cancer a chronic illness?’ You have a cancer which is by and large cured, but it is not easy to say quite when you are

cured. If you have Wilm’s tumour at the age of five and you take it out and give some chemotherapy, it does not tend to relapse. But if you are female and you have radiation to the abdomen, then you are probably going to be infertile. So if you ask, ‘Is this the treatment or the disease?’ Well, she would not have got the treatment if she did not have the disease, so you are dealing with a long-term effect of the original disease.”

Helen Kosmidis who pioneered paediatric oncology services in Athens, Greece, posed a similar question when she spoke at ECCO 14 in September 2007: “Is cancer in children an endless story for the survivor and the physician?”

She has been consultant paediatric oncologist at the A&K Kyriakou Children’s Hospital in Athens since the oncology department took its first patient in 1979, and her unit treats almost one-third of the 250–270 new cases of childhood cancer each year in Greece. She goes to the weddings of many former patients and to the christenings of their children. But it is the occasional funerals that make her realise that there is still a long way to go.

“We have had 30 or 31 second cancers in the 28

## “Survivors of childhood cancer need lifelong vigilance and some form of regular check-up”

years I have been here, and they hurt me more than the 1,800 newly diagnosed cancers.”

She has opened a weekly ‘late-effects clinic’ to offer check-ups for former patients. But it is hard to organise a service of this sort. Paediatric oncologists are not trained for example to palpate an adult woman’s breast and are not specialists in heart disease. “If children just needed to be followed up by the oncologist that would be fine, but you also need a whole bunch of people, the cardiologist, the endocrinologist, the radiologist, the social worker and the psychologist.”

Kosmidis believes that current treatment regimens in protocols outlined by the International Society of Paediatric Oncology (SIOP) and others have reduced risks.

“Paediatric oncology has decided for many years that we will try to get a balance between cure and least possible late effects. This is not easy, but I believe in the protocols and I dare to call them wise. They use as much therapy needed to provide a cure with the least toxicity.

“In the past we used to give each and every child with acute leukaemia a set amount of anthracyclines, which is a potential hazard to the heart muscle. Now we decrease the total dose, especially in children who have good-risk disease.

“When I was in training in the United States, every patient with leukaemia received prophylactic radiation to the CNS [central nervous system]. We know that this cut down the number of relapses in the CNS, but there were too many late effects, especially in patients given radiation to the brain.

“We have cognitive problems, verbal IQ, memory, attention span, learning disabilities, especially in girls. The common age for ALL is three, four or five years. The female brain matures faster during those years than the male brain, so toxicity is greater.

“Nowadays we give high-dosage methotrexate which crosses the blood brain barrier, so we have better results and do not need to give every patient prophylactic radiation to the CNS, except to high-risk patients”

However, she learns to expect the unexpected. “You can give a drug to 200 patients and then get an adverse effect for the first time. Everyone handles a drug in a different way.”

There is general agreement that survivors of childhood cancer need lifelong vigilance and some form of regular check-up.

The Erice statement (see box) says that children can be considered cured “when they have reached a time point at which the chance that they will die from their original disease is no greater than that of age peers in the general population of dying from any cause”. This is usually reached 2–10 relapse-free years after diagnosis.

However, the Erice statement reflects the ambiguity of the term ‘cure’, and underlines the difficulties of explaining risks and uncertainties to young and vulnerable survivors. It says, “The term ‘cured’ should be used when discussing the survivors’ status with them and in the larger society; vice versa, the term ‘long-term survivor’ should continue to be used in scientific research and related literature to alert professionals to sequelae which require care and attention.”

### THE ERICE STATEMENT

In October 2006, the International Berlin-Frankfurt-Munster (I-BMF) early and late toxicity educational committee invited 45 paediatric cancer experts to Erice in Sicily to discuss what constituted a ‘cure’ of childhood cancer and when follow-up care was required. The group comprised oncologists, psychologists, nurses, epidemiologists, parents and survivors from 13 European countries and from north America.

The Erice statement was published in May 2007, emphasising the need for information, communication, systematic follow-up, and research. It addressed the need to empower survivors and families, to better inform the general public and to address inequalities of treatment. The statement is online at [http://www.icccpo.org/articles/general/erice\\_statement\\_2007.html](http://www.icccpo.org/articles/general/erice_statement_2007.html)

It adds, "Information about risk should be delivered to survivors and families in language that is easily understood and in a positive light. ... Survivors and families have the right to be fully informed in person and in writing about being cured, as well as about the remaining risks of late effects, recurrence of the primary disease or second malignancies where applicable." This is a tall order, as the Erice statement acknowledges. "Communication of risk is difficult and challenging."



A dangerous journey ahead. Five-year-old Nikos at the K&A Kyriakou Children's Hospital in Athens is still being treated for his leukaemia. He is sitting with his doctor, Helen Kosmidis

#### PSYCHOSOCIAL EFFECTS

Some studies suggest that survivors of childhood cancer become vulnerable adults, but others indicate a resilience developed in childhood that continues into later life. A study of Greek survivors is the latest to demonstrate resilience, based on questionnaires and interviews with 103 childhood cancer survivors over the age of 15, whose mean age at diagnosis had been 8.8 years (Servitzoglou et al. *Support Care Cancer* 2007). One in three had mild to moderate late effects or side-effects, while 15 had severe effects.

The results show a reduced level of social functioning compared with other young people of a similar age. Female adults had higher levels of anxiety, especially those diagnosed at a younger age. There was also a tendency towards 'distancing', denial and wishful thinking. One-third regarded the future as uncertain and were more likely to expect to die young and for their own children to become seriously ill. However, in general they maintained a positive outlook on life, and were closer to their families and friends. They were less likely than the control group to blame themselves for bad events in their lives.

Lead researcher, Marina Servitzoglou, has since been working at Great Ormond Street Hospital in London, and is now on a one-year clinical fellowship at the Institut Gustave Roussy. She says that because stigma levels about cancer are still quite high in Greece, some young survivors only found out years later exactly what disease they had had.

"There are still parents who try to protect them from information, even now that they are adults. But that does not mean that they do not understand. If you talk to the children, they try to protect the parents in the same way as the parents try to protect them. Sometimes they do not want to discuss their feelings, or their fears because they don't want to affect their parents."

The psychological impact of cancer at a young age was very strong, partly perhaps because this is the period in a child's life where she or he develops identity, personality and character.

However, Servitzoglou says that many survivors develop an inner toughness. "I think they are much more mature and they have learned to fight. They are much stronger emotionally. They have learned a lesson that nobody knows what will happen tomorrow.

"They deal with their problems and have a positive attitude. In the back of their minds they still have fears about their health, but they say, 'I am grateful I am alive.' Their whole mentality, and priorities and outlook on life changes completely."

Aemilia Tsirou fits this positive pattern. "I was eight when I was diagnosed. I understood it was a really difficult situation. I did not know that I had leukaemia, but a very scary anaemia. My parents were

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really scared and we had to come three or four times a week for chemotherapy and radiation.”

The real nature of her disease gradually became apparent to her later, when her parents became involved with the parents’ group Floga (Flame), but she says that, deep down, she already knew. “At the hospital I saw many young children without hair. I knew children who the doctor said went back to the village, but I understood that they did not go back. There was no other reference to these children. You don’t discuss this while you are under treatment, not with your parents and not with your doctors. If you don’t say it, you don’t admit its existence. Even now, survivors do not discuss this with our parents. Many parents are scared and say to their children, ‘Just forget it’. This is problematic. We should know what we have gone through so we can take care of ourselves.”

Far from forgetting about it, Tsiro, who works as an IT manager and teaches Greek literature and philosophy, has helped to create Kyttaro (the Greek for ‘cell’), an organisation for survivors of childhood cancer. Their primary aim is mutual support, socially and practically, but the 30 members also visit children undergoing treatment to talk about films, music and life. “They have a different relationship with us because we are survivors. They are really open to us, because they feel comfortable. They take off their hats. They enjoy being with us.”

Group members support the late-effects clinic and talk to family members. They have a commitment both to normal life and to each other. “Some members of Kyttaro have serious late effects but are still coming to the group. These people have had a relapse or second cancers. They have lived with more pain and suffering than me, but they come back to tell us that, ‘OK it was bad, but you can live with this and you can win.’”

Survivor groups are being formed in an increasing number of countries. But if survivors and doctors are to better understand risks and monitor health, they need better data. Helen Kosmidis is president of the Hellenic Society of Paediatric Haematology Oncology,

and expects the first Greek national registry of childhood cancer to be up and running by January 2008. Starting as a database of children undergoing treatment, it will in time also become a database of survivors.

The UK launched the British Childhood Cancer Survivors’ Study in 1999, led by Mike Hawkins, professor of Epidemiology at Birmingham University. Although this study started years after the Childhood Cancer Survivors’ Study in the US, it has the advantage of being population based, and therefore more representative, and includes children who have received more up-to-date treatments.

As a sign of the growing interest in this issue, in April 2007, Christian Moëll from Lund, Sweden, and Wallace from Edinburgh organised the first European Symposium on Late Complications after Childhood Cancer. A European late-effects group is being discussed.

Scottish guidelines (Scottish Intercollegiate Guidelines Network, 2004) recommend a range of follow-up regimens from an annual or two-yearly contact by phone or questionnaire, to an annual visit to a nurse or primary care physician. Where treatment has included high-dose radiotherapy, megatherapy (high-dose anti-blastic drugs, possibly with radiotherapy) or bone marrow transplant, a medically led long-term follow-up clinic three or four times a year is recommended until final height is achieved, and annually thereafter.

### A LASTING RELATIONSHIP

Paediatric oncologists will be central to this work, because most want an ongoing relationship with their patients, and because survivors often prefer being seen by paediatric staff. Survivor Clare Dawson told the 2006 International Conference on Teenage and Young Adult Cancer Medicine, “When you have notes a foot high, going to someone who does not know you and knows nothing does not help. There is a real confidence from going back to see someone who does know you. You don’t have to explain. He just knows.”

## “You can’t talk to a 5-year-old about fertility, but you can talk about whether they’ll be able to go to school”

Helen Kosmidis says that you have to learn to become a talking doctor to talk to children undergoing treatment and to survivors. She recently counselled a boy who had completed two years of treatment and three years of observation, but who was still pre-adolescent. “I tell him he will have to take care of himself. ‘You are never going to smoke, promise me that.’ I tell him that in future he will be checked by a heart doctor and a thyroid doctor. He says, ‘Why? I have already had chest X-rays and heart examinations.’ I said that the treatment he had could have caused some damage to those organs.”

The ugly fact is that the risk of heart problems increases rather than decreases as the years since treatment pass. But Kosmidis does not think that the cold numbers are always helpful for parents or children. “The chances of them having childhood cancer in the first place were very low, but they had it. If we tell a parent your child has a 30% chance of being cured, and the child is cured, it is for them 100%. If we say your child has a 90% chance of being cured and the child dies, that is for them a 100% death rate. It is individual, and so you don’t give them a number.”

The same applies to survivors – the facts are given, but both doctor and patient recognise that this is an individual journey of absolutes.

Wallace agrees that you cannot talk to survivors unless you build trust with them as patients. “You cannot counsel the children once they have grown up and come to see you on their own, unless you made them the centre of their care as a child. It is the child that has the cancer. Often you see a tendency for doctors to ignore the child, and speak to the parents. Of course, the parents are very, very anxious, and often try to protect their children from the reality. But if you come to our ward and see these children running around, they could tell you exactly what they have got.

“My concept of leukaemia, the parent’s concept and the child’s concept are all different. Paediatricians have to understand the child’s concept – what it means to them.

“You could not talk to a five-year-old about ferti-



Prepared for an uncertain future. This picture, by Aemelia Tsirou, was prompted by the discovery of a new tumour, 12 years after she had successfully beaten leukaemia

ity, and they would not be interested. But you could talk to them about whether they will be able to go to school. You could talk about what they could do if their hair falls out. You have to try to get inside their world and find out what it is they are worried about.

“Discussions can be very therapeutic with somebody at the right age. A 16-year-old girl I am treating has a sarcoma in her pelvis. Her major concern is fertility. I don’t see how we can avoid giving her radiation to her pelvis, which will cause her ovaries to fail very early and will irradiate her womb. The fact that we say we could take a bit of your ovary and put it in the fridge for later on, gives her an inkling that someone believes that she is going to be alive later on.”

After surviving cancer as a child, Aemelia Tsirou felt she was invulnerable. But in the year 2000, she found a new growth in her left ear. After months of tests, it was established that this was a benign tumour, and although it has left her deaf in one ear, she is still clear of cancer. It also made her realise she was not superwoman. She wrote in her diary, “After the malignancy came a new sense: I can win everything. After the benign tumour came a completely new truth: life can make anything happen. It is not the point to believe you can win everything. The point is to be prepared to meet anything that life serves you.”