SURVIVING RADIOTHERAPY - WHAT THE FUTURE HOLDS

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Abstract

The dramatic increase in the cure rates of malignancies over the last generation, especially in the paediatric population, has led to an increasing number of survivors. There is an increasing recognition of the late effects of the tumour, and its treatment whether it is surgery, radiotherapy or chemotherapy. Radiotherapy, being the oldest conventional cancer treatment, is the most studied and many long-term effects are known. There are significant impacts on patients' lives after treatment, including academic performance, ability to hold a job and even to obtain insurance. As the professions responsible for the cure of both children and adults, there is a medico legal and moral obligation to screen for, prevent and treat or mitigate the consequences of our treatment.

Most cancer patients' goal is to arrive at the point where their doctor tells them: "You're cured!". They can then get back to their normal life and forget that it ever happened. Of course this almost never occurs. The psychological trauma of facing a life threatening condition may have long-term implications for their mental health, and there is increasing recognition of the consequences of aggressive treatment. The concept of survivorship is relatively recent and has been championed through long-term follow-up clinics and adolescent and young adult cancer services. Curing significant numbers of cancers has been a recent phenomenon, in the last 35 to 40 years. When Faber first used methotrexate to treat children with leukaemia in 1948, short remissions resulted, but ultimately all patients succumbed. His initial report in the *New England Journal of Medicine* in 1948 was met with derision,[1] as the prevailing view was that leukaemias were incurable and that the children should be allowed to "die in peace". The use of multi-agent chemotherapy in the late 1960s led to the first reported durable remissions for children with acute lymphoblastic leukaemia. The 1970s saw a dramatic rise in cure rates for many malignancies. It is humbling to realise that many of these children are now in their forties and fifties, still relatively young. There have been significant, though not as impressive improvements in adult cancers too, and the number of long-term survivors continues to grow.

Before this, the only long-term survivors of cancers resulted from surgery or radiation. The numbers were small, but even then there was a cost seen with growth effects, neuro-cognitive and neuro-endocrine complications and the suggestion of increased second malignancies. In Blooms seminal paper on the role of radiotherapy in medulloblastoma,[2] children under two years old often required ongoing institutional care after receiving craniospinal radiotherapy. Prior to this, Lampe expressed concern regarding brain damage that could result from radiation to brains of younger patients.[3]

It was hoped that chemotherapy would eliminate the need for radiation and be free of long-term consequences, but unfortunately this was not to be. Until the 1990s, once a patient was deemed cured they were usually discharged and told to live normally with a reasonable expectation that they would. There has been an increasing recognition over the last 20 years of the many complications that may result from cancer treatments.

As a result of this improvement in treatment, it is now expected that 80% of childhood cancer patients will become long-term survivors.[4] In the general population, one in 640 young adults 20-39 are cancer survivors, with the average general practice expected to have at least two patients per physician. The overall survivor numbers are greater if adult patients are included. In the adult setting, many patients now survive decades after their treatment and their surveillance and follow up is equally necessary. About one third of the patients in our clinic are referred after having had therapy as an adult.

Physical effects from the cancer itself

Long-lasting problems can occur prior to any therapeutic intervention. In brain tumours, having a tumour itself can cause disturbance of the hypothalamic pituitary axis before any treatment.[5] Hydrocephalus is recognised as an independent cause of significant neurocognitive decline in patients, previously attributed solely to radiotherapy.[6] Damage to neurones may not be repairable, and so timely intervention is crucial in the setting of cord compression or the optic chiasm compromise.

Late effects from radiotherapy and chemotherapy

The most famous victim of radiation late effects was probably Marie Curie, who discovered radium along with her husband Pierre. Marie died of aplastic anaemia from her long-term radiation exposure. Her daughter Irene, also a Nobel Prize winning physicist, also died from acute leukaemia. Pierre Curie however, was spared a similar fate – he was run over by a horse drawn cart on the streets of Paris in 1906.

The first patients were treated with radiotherapy in the late 1890s and until the advent of chemotherapy, it was the only effective non-surgical treatment for cancer. However, from early on the effects of radiotherapy were appreciated.

> *"The dangers from the use of x-rays may be grouped as immediate and remote. During the actual exposure, the possibility of making contact with a high-tension lead carrying a very high voltage has to be guarded against. An accident of this kind may easily be fatal… Constitutional disorders, anaemia and sterility not infrequently arise in operators who are constantly exposed to x-rays."*[7]

In 1935, the concept of immediate and long-term or late-effects was very simple. Late-effects now refer to complications that arise many months to years after the completion of therapy.

Much of the early data regarding adverse effects from radiation isn't from treatment – rather from the Hiroshima and Nagasaki atomic bomb data, industrial accidents and use in benign conditions. For example, superficial irradiation was a commonly used treatment for tinea capitis with doses of 0.04-0.45 Gy used.[8] Reports from the 1960s suggested an increase in leukaemias, thyroid, brain and other head and neck cancers and interestingly 'mental disorders,' and in the large cohort of Israeli immigrants treated for tinea in the 1940s and 50s.[9]

Much of the current data regarding late effects of cancer treatments has been developed for the retrospective cohort of 10,000 patients with matched sibling controls in the Childhood Cancer Survivors Study group.[4,10-13] Much of this data and other published literature has been brought together in the long-term follow-up guidelines of the Children's Oncology Group.[14] These guidelines are used as the basis for many long-term follow-up programs. It is beyond the scope of this paper to exhaustively detail the physical effects of chemotherapy and radiotherapy, however a brief overview follows.

Head and neck region

Alopecia is physically the most insignificant side-effect of cancer treatment, but psychosocially one of the more distressing, particularly for teenage girls. Cranial radiation often leads to temporary hair loss, and the degree of permanent effect relates to total dose and concurrent chemotherapy

The lens is prone to cataractogenesis from both radiation (even very low dose) and steroids.[15] Anterior chamber exposure increases the risk of late glaucoma.[16]

Both surgery and radiotherapy to the hypothalamus can lead to hypothalamic-pituitary axis dysfunction, including hypothalamic obesity or metabolic syndrome. Late radiotherapy effects occur at a median time of three years post therapy. The thyroid stimulating hormone (TSH) is usually affected first, followed by growth hormone, the sex hormones and less commonly adrenocortocotropic hormone (ACTH), leading to Addisonian syndromes. The thyroid gland itself may suffer primary failure if it is in the radiation field. Central infertility may also result, however this may be negated by the use of gonadotrophic releasing hormone agonists to induce gonadal stimulation.[17-20]

The most devastating long-term effect is the functional neurological compromise suffered by patients who have had brain tumours.[21] Merchant et al have demonstrated that IQ decline is proportional to the volume and dose of brain irradiated, especially the temporal lobes.[22] Palmer et al found that there appeared to be a constant decline until age 12, after which the IQ remained stable. There is a progressive reduction in short-term memory and concentration span through the teenage years.[23] Some evidence suggests medications such as dexamphetamine and/or cognitive remediation programs may improve academic performance and overall quality of life in these patients.[24-27] Similar, but not as profound effects can be seen in patients who have had intrathecal methotrexate, especially if cranial radiotherapy is also given.[26] In adults, radiation "ages" the brain which may accelerate concentration and memory decline in later years.

There is also a small risk of focal radionecrosis in high dose regions,[27] and an increased risk of strokes. Radiation to the neck and mediastinum can increase the rates of cerebrovascular disease.[28] Thus, an aggressive approach to management of hypercholesterolemia, hypertension and other reversible risk factors for cerebrovascular disease is taken.

Cardiac effects

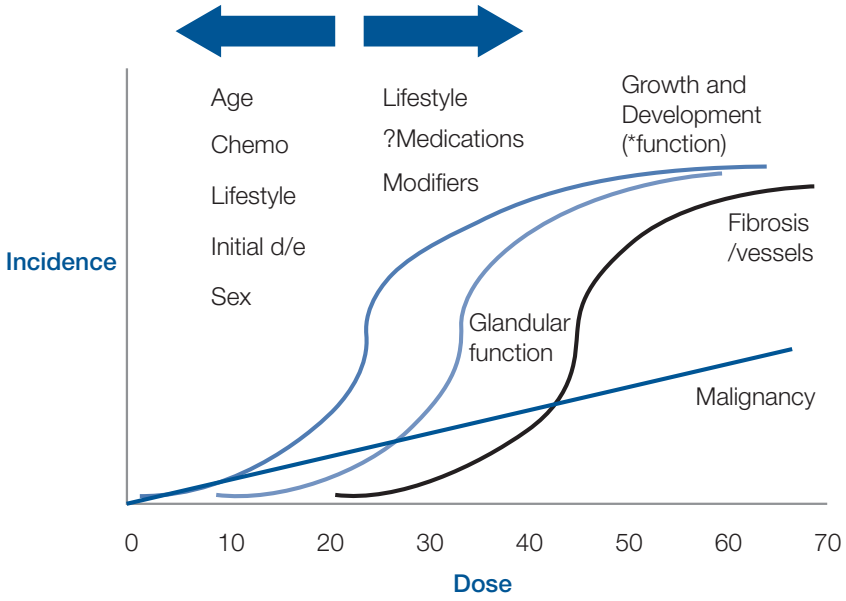
Radiotherapy and chemotherapy have significant impacts on cardiac function. Radiation itself can cause myocardial fibrosis leading to late cardiac failure. This is in addition to the effects of high-dose anthracyclines (eg. > 350 mg/m2 doxorubicin).[29-31] Cardiac failure may be unmasked during pregnancy, thus women with a history of cardiac irradiation or anthracycline chemotherapy should undergo cardiac function assessment during pregnancy and monitoring during labour and delivery. Radiotherapy to the chest increases the risks of ischaemic heart disease by 2-5%.[13,32] These patients also have an increased rate of valvular abnormalities – usually presenting with stenotic rather than incompetent valves. Renal irradiation may cause cortical scarring or fibrosis, increasing the risk of Angiotensin converting enzyme driven hypertension, aggravating both the cerebral and cardiac risk profile.[33]

Other effects

Radiation doses > 20 Gy induce variable degrees of pulmonary fibrosis in the radiation field, which may lead to a restrictive pattern on lung function testing and a decrease in overall diffusing capacity.[32,40] These problems are aggravated by Bleomycin chemotherapy, tobacco and marijuana smoking, so smoking cessation is essential.[34,35]

High dose irradiation may induce scarring in the bladder, causing reduced bladder volume with resultant frequency and urge incontinence. It reduces uterine blood flow, and above 16-20 Gy may induce hypoplasia and fibrosis, resulting in miscarriage or inability to carry a pregnancy to term. Radiotherapy doses of 2-4 Gy to the testes and 4-6 Gy to the ovaries may induce sterility, and at higher levels (~20 Gy) may result in loss of hormonal function.[36-39]

Figure 1: *Schematic representation of the late effects of radiotherapy.*



As depicted in figure 1, the threshold dose for hypoplasia induced by radiation appears to be about 16 Gy, with the plateauing of effect seen at about 25 Gy. If there is inhomogeneity across growth plates asymmetric growth may lead to impaired cosmetic outcomes, such as kyphoscoliosis, facial asymmetry and pelvic tilt. Impaired growth may also be due to decreased GH production. Radiation can lead to late osteoporosis in field and in some cases radionecrosis in high dose areas aggravated by steroids.

Second malignancies

One of the most concerning complications of cancer treatment is second malignant neoplasms.[40-49] Some primaries are associated with an increased risk of other malignancies, such as retinoblastoma or lymphoma. The second malignancy risk from radiotherapy has a dose response, with the exception of thyroid cancers (plateauing at ~15 Gy). Concurrent chemotherapy, particularly doxorubicin, increases the risk of developing a radiation induced second malignancy.

Mediastinal radiation increases the risk of breast cancer;[44] and cranial radiotherapy causes meningiomas or rarely gliomas in the central nervous system, especially with concurrnet antimetabolite maintenance chemotherapy.[49] Retinoblastoma patients who have had irradiation have a significant risk of osteosarcomas in the field, and the prognosis from these tumours is grim. Eighty per cent of secondary malignancies are either in or at the margins of the field, strongly implicating radiation in their pathogenesis.[40-49]

Psychological and social effects

Having had cancer can have a profound impact on psychosocial development. Survivors of cancer in childhood or adolescence are much less likely to marry, hold a job, reach the same socioeconomic status, hold insurance or complete tertiary education.[50-54] The most obvious impacts relate to failure to socialise due to brain injury. Damaged frontal lobe function often impacts on group play, and children may be ostracised as a result. More subtle impacts are seen when children lose touch with their peers during long absences caused by treatment. They are also often caught between wanting to be 'normal', yet having a life-changing event acknowledged in some way.

School absence can result in poor grades and if they need to repeat a year of school worsening social isolation.[55] Having a healthy body image and self-esteem relies on accepting physical appearances, which in the maelstrom of surgery, chemotherapy and radiotherapy, is hard for young people to achieve, especially with altered responses from peers. Permanent side-effects such as hair loss, amputation, scarring and fatigue can result in reactive depression, anxiety and in some situations post-traumatic stress disorder.[56,57] Increased prevalence of somatic symptoms, depression and/or anxiety, attention deficit and anti-social behaviour among young cancer survivors has been documented in many paediatric malignancies.[57,58]

Central nervous system patients in particular may have profound and often debilitating fatigue, which inhibits ability to work and socialise. In some patients, exogenous growth hormone or stimulants such as dexamphetamine may be useful. Of course, screening for hypothyroidism is an important part of surveillance. Other causes of fatigue may be an early sign of more significant issues such as a reactive depression, post-traumatic stress disorder or general anxiety, which many patients have about their health.[57] The wait for results can be particularly onerous, and returning to the same institution where their treatment was given can bring flashbacks or responsive nausea and vomiting. Often minor symptoms can bring on marked

agitation about the possible cause, and the caring team must put the risks of long-term problems in perspective. In other cases, patients may want to completely ignore what they have been through and refuse further follow-up. The extreme of this is to engage in risk taking behaviour such as tobacco and alcohol excess or illicit drug use.

Financial effects

Cancer survivors often find long-term consequences in later life that are not directly related to the direct physical effects of chemotherapy or radiotherapy. In many countries (such as Australia), there are enormous hurdles to cancer survivors joining the military and developing further trade opportunities that could carry on into civilian life. Short-term memory impairment and concentration span problems reduce patients' ability to complete tertiary education or vocational training.[50-54] More subtle issues such as altered cosmetic outcomes or personality affects may deny survivors promotion prospects or other advancement in their fields.

Life insurance policies are often very difficult to obtain, frequently an issue when they start their own families. Many policies exclude any malignancy, even if it were to develop outside the treatment field and have no obvious link to the treatment given or the primary condition. Likewise, health insurance may be difficult to obtain and in many regions assisted fertility (eg. IVF) is not covered in public health programs. In regions where there is no universal health coverage, this can carry significant implications for patients, both for future health issues as well as the need for routine surveillance for long-term treatment related effects.

The increasing use of molecular genetics in the diagnosis of the primary tumour raises the spectre of future employers requesting the results as part of the employment process, potentially allowing discrimination. This is of most concern in jurisdictions where part of the employment conditions involves employer funded health insurance.

In the brain tumour survivor cohort who have suffered significant neuro-cognitively injury from the tumour or treatment, there is the heart-rending situation where patients are reliant on their now ageing parents for many of their activities of daily living. These parents often struggle with the issue of who will care for their children when they die or become unable to do it themselves.

Finally, one of the more insidious and common problems faced by patients is their, and their doctors, lack of knowledge about late-effects. There needs to be a balance between knowledge of risk and causing unnecessary concern. Many patients feel that they are a 'time bomb' waiting to develop a second cancer or other significant complication, when in fact most won't. The risks mandate an appropriate screening regimen, but an understanding of the risk is critical for peace of mind. In a busy oncology clinic, the needs of acutely unwell and newly diagnosed patients take precedence over those who are cured and healthy. In our practice, we find that a consult in our dedicated late effects clinic – with the same patient and the same room – is profoundly different in the scope of issues covered than in an acute clinic. We often see a correspondence trail between their GP asking for advice about issues and the oncology team answering that it is not related to their cancer and thus not appropriate for them to address. How should these patients be cared for now?

Future care models

At one end of the spectrum is where a patient is deemed cured and they are discharged into their GPs care. The other end is regular detailed follow-up in a multidisciplinary long-term follow-up clinic. The problems with the first option are that it places a lot of reliance on the family doctor to keep up-to-date with a wide range of potential issues for a small number of patients. Compounding this is the mobile nature of the young adult population and their own lack of knowledge about their treatment, let alone the likely toxicities. The second creates its own issues. A dedicated paediatric late-effects clinic can reach a steady state when patients that are discharged when they reach adulthood (18 years old), are replaced by patients entering the long-term follow-up period – a revolving door concept. However, an adult clinic is more like a bucket. Patients enter the clinic either directly from their oncology team or from the paediatric long-term follow-up unit and, due to the high cure rates and low mortality from late effects and with no ongoing plan, will stay there. Our own clinic initially ran alternate monthly, 10 years later is now a fully booked clinic every week.

Clearly a shared care model is appropriate.[59] The model that we are developing is based on a stratified shared care system. On entry to the clinic patients will be assessed as low, intermediate or high risk. Low risk patients would include such groups as a stage I Wilms tumour treated with surgery and simple chemotherapy. They would be discharged into their family physician's care with important provisos. The first is that the patients are given a survivorship care plan which outlines the treatment they have received, the risks identified as a result of the treatment and the recommended screening investigations and lifestyle modifications. This would enable a patient to change doctors without compromising their ongoing care, and would also give the family doctors guidance. The second proviso is the need to have a feedback loop so that the long-term follow-up clinic knows who the local doctor is, what tests have been ordered and what the results are. This is necessary to ensure that the appropriate care is being delivered and to allow contact with both the patient and the family doctor should new information about potential late-effects become apparent. In a survey of GPs from the Netherlands, 97% of GPs were willing to participate in the long-term care of survivors, and indeed 64% felt that it was their responsibility.[60]

The intermediate risk group would be patients who need regular surveillance and imaging, but not on an annual basis. This would include any patients who had had radiotherapy, high dose anthracyclines or endocrinopathies. Again, a passport and management plan is essential as is the feedback loop to a robust database. For instance, structural imaging for second malignancy surveillance or echocardiograms for delayed cardiotoxicity may be done every two to three years and subsequent review in a multidisciplinary could alternate with yearly bloods, blood pressure checks and lifestyle modification counselling by the GPs.

The high risk group would be those who need annual multidisciplinary review in a tertiary centre. Again, the passport and database would be essential to inform the GPs for care between visits to the long-term follow-up clinic. Patients in this group would include brain tumour/ cranial irradiation patients and bone marrow transplant recipients.

In the Netherlands survey, GPs felt that to participate in a shared care program they needed availability of guidelines (64%), sufficient information about the patient's medical history (37%) and short communication lines (45%).[60] The main barriers to participation were felt to be workload (16%), lack of knowledge (15%), and lack of communication from the parent institution.

The challenge remains to plan the long-term care of cancers with high survival rates. Hopefully, a working model for childhood and adolescent cancer survivors will extrapolate easily to the appropriate care of cured adults such as breast, GI and head and neck tumours. It is often suggested that new techniques may reduce late-effects (eg. IMRT/protons) and hopefully this will be the case. However, a reduction in toxicity allows dose escalation to improve cure rates resulting in an isotoxic treatment.

As a profession we have only been curing childhood cancers reliably for only 30-40 years. This is the span of many of our senior colleagues working life. We need to provide robust and thorough follow-up, both for our current patients' sakes, and through surveillance and research, our patients that are yet to come. It may well be that in 200 years, our professional descendents look upon our crude therapies much as we look on the gross surgeries performed without anaesthesia 200 years ago. The question for us is how we will be viewed with regard to the care we have provided for our patients.

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