Second malignant neoplasms following treatment for primary cancer

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BACKGROUND Long term survival following treatment for primary cancer has increased significantly in the past decade. With cure comes 'survivorship'. One of the factors clearly affecting quality and length of survival is morbidity associated with treatment and the development of subsequent malignancies.

OBJECTIVE This article aims to look at the risks associated with the development of second malignant neoplasms, give some meaningful figures, and provide suggestions for follow up.

DISCUSSION The balance of heightened awareness and healthy lifestyle versus relentless surveillance and ongoing patient concern is a difficult one. We hope to make our patients aware of the small but significant risk of a second malignancy, advise on any appropriate screening investigations and encourage a life long relationship with their chosen family physician to enable detection of any future malignancy.

Current therapies to treat cancer have produced impressive cure rates. This is especially true for childhood cancer. In the past 20 years, more than 70% of children diagnosed with cancer are expected to be long term survivors. In fact, one in 900 children currently reaching the age of 20 years is a long term survivor of childhood malignancy.

Attention has now turned to the 'price of cure' and, in particular, to possible changes in existing therapies to minimise long term morbidity and mortality, including the development of a second cancer.

Incidence of second cancers

Second cancers account for up to 10% of all cancer diagnoses.[1] The following epidemiological studies have estimated the risk of a second cancer following primary cancer in adulthood:

- a study in Finland[2] of 470 000 patients with cancer over a 38 year period revealed no increased risk of a second cancer in the cohort but a 1.7-fold increase of developing a second malignancy in patients who were younger than 50 years of age at the time of first cancer diagnosis
- a Swedish cohort[3] over a similar period showed an almost 2-fold increased risk of second malignancy compared to the general population
- an American study[4] of 250 000 patients with primary cancer in adulthood showed a 1.3-fold increased risk of second malignancy
- in a comprehensive review recently published by Sklar and Bhatia[1] the cumulative risk of

second cancers following primary cancer in childhood or adolescence was:
- 2.5% at 15 years after diagnosis of first tumour
- 3.2% at 20 years after diagnosis of first tumour, and
- 3.5% at 25 years after diagnosis of first tumour.

Estimates of risk in a number of other studies range from 1.7–20% depending on the original tumour type and treatment modalities used.

Our own data reveals 50 second malignancies found in a cohort of 2716 patients who have been followed for intervals ranging from 23 months to 26 years (further analysis pending).

It is not always possible to determine if one of the more common adult neoplasms occurring in survivors of childhood malignancy is indeed related to their previous treatment. These second malignancies may be haemopoetic or solid (Table 1). Latency periods are shorter for secondary leukaemias. For solid tumours the latency period varies from 5–24 years.

Risk factors for second malignancy

Genetic susceptibility/environmental factors

There are a number of genetic conditions that are associated with an increased risk of primary cancer and, in some cases, a second cancer. Examples include:
- hereditary retinoblastoma, osteosercoma and soft tissue sarcomas
- Li-Fraumeni syndrome – brain sarcoma and breast tumours
- tuberous sclerosis – astrocytoma
- neurofibromatosis – gliomas and sarcomas
- Gardner's syndrome (familial polyposis coli) – may present with hepatoblastoma in childhood. Child and family require life long surveillance for colon cancer.

As a group, children with congenital syndromes are known to have an increased incidence of several types of malignancy, eg. Down's syndrome and leukaemia, Beckwith syndrome and Wilms' tumour. Whether these children are at increased risk of a second malignancy remains to be seen. It is thought that tumour development is the result of several genetic lesions accumulating within a cell.

A proportion of patients with Wilms' tumour are known to carry a genetic predisposition and may be at increased risk of a second malignancy. Genetic environment interactions is an area of increasing interest. It has been found that survivors of Hodgkin's disease have an increased risk of

Table 1. Second cancers and their relationship with primary cancers[1]

Second cancers	Primary cancer	Latency (median in years)	Risk factors
Brain tumours	ALL, brain tumours, HD	9–10	Radiation: younger age
MDS/AML	ALL, HD, bone tumours	3–5	Topoisomerase 2 inhibitors, alkylating agents
Breast cancer	HD, bone tumours, soft tissue sarcomas, bone tumours, NHL	15–20	Radiation: female gender
Thyroid cancer	ALL, HD, neuroblastoma, soft tissue sarcomas, bone tumours, NHL	13–15	Radiation: younger age, female gender
Bone tumours	ALL, retinoblastoma (heritable), other bone tumours, Ewings' sarcoma, soft tissue sarcomas	9–10	Radiation: alkylating agents, removal of spleen
Soft tissue sarcomas	ALL, retinoblastoma (heritable), soft tissue sarcomas, HD, Wilms' tumours, bone tumours	10–11	Radiation: younger age, anthracyclines

Note: Acute lymphocytic leukaemia (ALL), acute myelogenous leukaemia (AML), Hogkin's disease (HD), myelodysplasia (MDS), non-Hodgkin's lymphoma (NHL)

developing lung cancer. The risk is further increased if radiation therapy was part of the original treatment. The role of environment and genetic factors remains unclear.

Environmental factors

The relationship of tobacco smoking and lung cancer is well recognised. Other environmental factors may also play a part in pathogenesis of second malignant tumours. The relationship of sun exposure contributing to the development of secondary skin malignancies in patients who have had radiotherapy for a primary tumour is an area of ongoing study.

First tumour treatment

Chemotherapy

Alkylating agents such as melphalan and topimerase inhibitors such as etoposide have particular potential to cause secondary leukaemia. It has been suggested that modification of the Hodgkin's disease chemotherapy protocol has lowered the rate of secondary leukaemia.

Radiation therapy

Radiation therapy (XRT) is associated with an increased risk of second malignancy, usually, though not exclusively, occurring in the radiation field, eg. thyroid cancer, sarcomas, brain tumours. The risk is dose dependent and the latency period is long, often decades, and appears to be higher when radiation exposure occurs at a younger age. Higher radiation dose is also associated with increased risk.

Combination therapy

Mantle irradiation is associated with an increased risk of breast and thyroid cancer. Particular associations occur with breast cancer as second malignancy in young females treated for Hodgkin's disease.

Patients treated for hereditary retinoblastoma who also have XRT as part of their therapy are at further increased risk of second malignancies.

In a recent publication we reported on the incidence of thyroid malignancy in a cohort of patients who had received direct or scattered irradiation for childhood malignancy (including cranial XRT for leukaemia). The risk of skin cancers of varying types developing in the radiation field is of particular concern in the Australian climate. The risk of secondary oral and upper gastrointestinal tumours may be further increased by smoking.

The change in delivery of radiation therapy from orthovoltage to megavoltage,[15] and a more targeted method of delivery such as stereotactic external beam techniques appears to have already lessened the risk of second malignant neoplasms although ongoing follow up is necessary.

Secondary leukaemia usually develops 1–10 years after radiotherapy, whereas an interval of greater than six years is usual for solid tumours, often decades.

Bone marrow transplantation

Second malignancies developing after marrow or peripheral blood stem cell transplantation may be related to:

- underlying disease
- immunosuppression allowing Epstein-Barr virus infection and subsequent development of post-transplant lymphoproliferative disorder
- total body irradiation
- histo incompatibility between donor and recipient as well as genetic predisposition in the host. Example, Witherspoon et al[12] reported a 7-fold increased risk of secondary malignancy in patients with Fanconi's anaemia treated with bone marrow transplant (BMT) compared to those treated for aplastic anaemia (all second cancers were squamous cell in origin).

Studies have estimated the risk of developing a second cancer following post bone marrow transplant at around 6% compared to the risk of primary cancer in the general population.[13] These second malignancies include leukaemias, squamous carcinomas and high grade brain tumours.

The risk of haemopoetic disorders is highest in the first two years post-transplant, whereas solid tumours usually occur six or more years after transplant. Risks are greatest for those patients who received prolonged immunosuppression for graft versus host disease, and for patients who received pretransplant conditioning with total body irradiation.

In data produced recently from the Seattle Marrow Transplant Program, the records of 4713[12] patients who had BMT for a variety of conditions, predominantly malignancy, but also including conditions such as aplastic anaemia were examined. Second malignancies developed in 103 patients. Kaplan Meier probability risks were:

- 3% at 5 years post-transplant
- 6% at 10 years post-transplant
- 12% at 15 years post-transplant
- 17% at 20 years post-transplant.

The median time range from transplant to diagnosis of second malignancy was 4.3 years with a longer latency period for solid tumours (median 6.6 years) compared to leukaemia/myelodysplasia (median 7.3 months). The study also looked at the risk of second malignant neoplasms in this population compared to the risk of developing a primary malignancy in the general population. Transplant recipients had a 5.99 times increased risk of developing a second malignancy.

Hodgkin's disease

Patients treated for Hodgkin's disease (HD) seem to have a particular sensitivity to developing second malignancies. This may be related to more prolonged immunosuppression though mechanisms remain unclear. A number of studies[7,8,10] have shown an:

- increased incidence of leukaemia/NHL cited as 1.5–10% peaking somewhere between 4–8 years after primary diagnosis. Relative risk compared to the normal population is estimated to be 20–40 times
- increased incidence of solid tumours especially breast, lung, sarcoma, head and neck tumours (including thyroid) and gastrointestinal tumours.

The risk of breast malignancy in females treated for HD with radiotherapy vary, with the relative risk estimated to be up to a 30-fold increase for women under 30 years of age at the time of treatment. Bhatia et al[1] give an actuarial cumulative probability of breast cancer of 35% at the age of 40 years.

An interesting recent study by Diller et al[9] investigated patient awareness of breast cancer risk and patient screening behaviour in female survivors of HD. The study concluded that practitioners caring for women after completion of treatment for HD needed to educate patients regarding their risk and begin early screening.

Another recent study looked at the long term risk factors for second malignancy in this group of patients and discussed the need for ongoing analysis. They concluded that: 'The relative risk and absolute excess risk of second malignancy were 4.6 and 89.3 per 10 000 person years in a group of patients with a median follow up of 12 years'. Overall, this translates to a 4.6-fold risk of developing a cancer compared with the general population, and almost 1% excess risk per person per year. The excess risk increased with follow up time'. The relative risk was significantly higher with combined chemotherapy and radiation therapy than with radiation alone' as found in some other studies.

Survivors of HD appear to face a 2–4% excess risk of second malignancy per person per year. Changes have been made to the therapy for HD to minimise risks of second malignancy. There has been a decrease in the radiation dose (and sometimes the radiation field) and modification of chemotherapy protocols.

Retinoblastoma

Heritable retinoblastoma (RB) is associated with a significantly increased risk of second nonocular tumours particularly in patients who had radiation therapy as part of their treatment.[6]

Retinoblastoma is often caused by an inherited mutation of the RBI tumour suppressor gene. Most patients (80%) with hereditable mutations have bilateral disease, with 30–40% of case, including all bilateral cases, being transmitted in autosomal dominant pattern with 90% penetrance. However, it should be noted that most children presenting with bilateral RB have no positive family history of RB.

Familial RB is the result of an inherited germline mutation. The rate of second cancers in a number of studies tend to cluster around:

- 10% at 20 years follow up
- 15% at 30 years follow up
- 26% at 40 years follow up.

This figure (26%) is similar to the expected lifetime cumulative mortality from all cancers combined in the general population.

Second cancers were further increased in patients with RB who received radiotherapy. Most second cancers occur in bone, soft tissue, brain and skin (melanoma). These cancers are more often in the radiotherapy field but may occur in other areas of the body. Some studies suggest rates of second malignancy to be as high as 50%.

Screening[13,14]

In adults who have been treated for a primary cancer, long term follow up varies among centres. Annual physical examination is strongly recommended. Certain investigations may be performed depending on the original disease and treatment.

Table 2. Future directions

Primary prevention

- Modification of existing protocols, eg. adolescent girls with HD usually now receive chemotherapy alone. Radiotherapy to chest is only given if there is a high risk of relapse
- Genetic testing may be used to identify patients with particular enzymes which may activate other enzymes leading to an increased risk of second cancer. Modification of therapy may be possible
- Identification of familial cancer syndromes and development of appropriate surveillance. There are a number of familial cancer clinics now operating across Australia

Secondary prevention

- Healthy lifestyle
- Targeted screening, eg. breast screening in female survivors who have had mantle irradiation. Thyroid screening in patients who have had direct or scatter irradiation
- Avoidance of excessive sun exposure
- Avoidance of known risk factors, eg. smoking
- Patient education regarding past diagnosis and future risks
- Physician education of known risk factors for second malignancy
- Ongoing reporting of second malignancies which may help identify high risk populations who could benefit from more intensive screening and prevention programs
- Ongoing research into innovative trials of treatment
- Modulation of immune system or tumour cells to improve elimination is the subject of ongoing research
- New vaccines for viruses such as the herpes virus may have a role in tumour prevention

For example, females who have had mantle radiotherapy are at significantly increased risk of breast cancer as a second malignancy. The risk is particularly high for women treated at a young age with some studies estimating the risk to be as high as 30–40%.

Regular breast self examination, yearly physician examination and annual or bi-annual mammogram and/or ultrasound have been recommended. For women who have had a first primary breast cancer suggested screening involves 3–6 monthly physical examinations for the first three years (postoriginal diagnosis) followed by 6–12 months for two years, then yearly.[16] Initial mammography is performed at six months then yearly postoriginal diagnosis. Regular pelvic examination is also recommended. Our current practice is to begin mammography screening at the age of 25 years or 10 years postcompletion of treatment for HD (whichever is sooner).

At the Long Term Survival Clinic, annual thyroid function tests, neck examination and thyroid ultrasound are also recommended in all patients who have had direct or scattered irradiation to the thyroid area. Some screening tests in themselves may increase the risk of carcinogenesis, eg. yearly mammograms for long periods of time.

No other particular screening tests for a possible second malignancy are recommended at this time unless there are other risk factors such as family history, hereditary conditions such as familial polyposis coli, or conditions known to be associated with malignancy, eg. neurofibromatosis.

It is unknown if early detection will improve rates of successful treatment of a second malignancy.

Table 2 indicates future directions in primary and secondary prevention.

Conclusion

The quality of life of survivors and the ability to put the 'cancer' experience behind them is of equal concern. As patients recover and resume their

normal activities a balance needs to be struck between living with the constant fear of relapse or, more remotely, a second cancer, and embracing life and 'survivorship'.

The frequency and type of surveillance for survivors of cancer remains controversial and may differ in different centres. Age at time of first malignancy as well as type and treatment for that malignancy will influence ongoing care.

Our aim at the Long Term Survival Clinic is to encourage the young people who have been in our care to develop an ongoing relationship with a family physician who can monitor their health and address any concerns they may have. Part of this 'transfer' of care entails education of patients and general practitioners on the possible long term effects of treatment. We develop an individual patient record and surveillance plan and provide an information package to the treating GP. Oncology staff are always available to answer any patient or GP queries.

Conflict of interest: none declared.

SUMMARY OF IMPORTANT POINTS

- More than 70% of children diagnosed with cancer are expected to be long term survivors.
- Second cancers account for up to 10% of all cancer diagnoses.
- Genetic susceptibility, environmental factors, and first tumour treatment are all risk factors for a second malignancy.
- Survivors of HD face a 2–4% excess risk of second malignancy per person per year.
- Age at time of first malignancy, and type and treatment for that malignancy will influence ongoing care.
- A life long relationship between patient and practitioner is essential to assist with the early detection of future malignancies.

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