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Meningiomas occurring during long-term survival after treatment for childhood cancer

Elaine Sugden[1], Aliki Taylor[2], Pieter Pretorius[3], Colin Kennedy[4] and Ranj Bhangoo[5]

[1]36, North Hinksey Village, Oxford, OX2 0 NA, UK
[2]Birmingham University, Birmingham B15 2TT, UK
[3]Oxford University Hospitals, Oxford OX3 9DU, UK
[4]University Hospital Southampton, Southampton SO16 6YD, UK
[5]Kings College Hospital Foundation Trust, London SE5 9RS, UK
Corresponding author: Elaine Sugden. Email: elainesugden@doctors.org.uk

Summary

Childhood cancer is rare but improvements in treatment over the past five decades have resulted in a cohort of more than 30,000 long-term survivors of childhood cancer in the UK with more added annually. These long-term survivors are at risk of late effects of cancer treatment which replace original tumour recurrence as the leading cause of premature death. Second neoplasms are a particular risk and in the central nervous system meningiomas occur increasingly with increased radiation dose to central nervous system tissue and length of time after exposure, resulting in a 500-fold increase above that expected in the normal population by 40 years of follow up. This multidisciplinary author group and others met to discuss the issue. Our pooled information, and consensus that screening should only follow symptoms, was published online by the Royal College of Radiologists in 2013. We outline here the current knowledge and management of these neoplasms secondary to childhood cancer treatment.

Keywords

secondary meningiomas, radiation-induced secondary neoplasms, childhood cancer treatment, late effects

Introduction

Although cancer in children (0–14 years) accounts for only 0.5% of UK cancer incidence with an average of 1500 cases per year, there are now of the order of 33,000 adults in the UK who during childhood were treated for cancer and are classed as long-term survivors.[1] The majority of childhood cancers cannot be cured by local treatment (surgery and/or radiotherapy) alone and 5-year survival in the late 1960s was only 28%. Since then the addition of multiagent cytotoxic chemotherapy and the routine availability and entry to clinical trials managed by the Children's Cancer and Leukaemia Group, formerly the United Kingdom Children's Cancer Study Group, have led to serial improvement in 5-year survival for childhood cancer. Seventy eight percent of those under 15 years at diagnosis now survive at least 5 years.[2] Acute lymphatic leukaemia, the commonest malignancy in childhood and universally fatal before the use of cytotoxic chemotherapy, was the first to show improvement followed by other haematological malignancies and the solid malignancies of childhood.

The definition of 'long-term survival' varies between those alive 5 years from diagnosis and 5 years after the end of treatment. As yet, there are relatively few 50-year survivors but the number in each decade of survival continues to increase. However, the long-term survival cohort still has a shortened life span compared with the normal population. Between 5 and 10 years after diagnosis the major cause of death is from the persistence or recurrence of the original cancer. Increasingly, with lengthening time after treatment, complications resulting from the treatment itself take their toll and can affect every organ, tissue and system in the body.[3]

Second neoplasms different from the original treated cancer are the most common cause of death after recurrence and accrue steadily over time from end of treatment with a rapid increase after 30 years of follow up.[3] Breast cancer after mantle radiotherapy for Hodgkin's disease is well known and there are guidelines for screening.[4] Sarcomas are more common than carcinomas and most are associated with radiotherapy.[5] Consent for radiotherapy in children should involve detailed information about possible complications including the risk of second tumours.

The commonest site for second neoplasms in children treated in the UK is the central nervous system (CNS).[5] These follow treatment for primary CNS tumours, which as a group are the commonest solid malignancy of childhood, prophylactic brain irradiation for acute lymphatic leukaemia which was routine in the 1970s and early 1980s and after head and neck radiation impinging on the base of the brain.

In a recent study, over half (55%) of second neoplasms following brain irradiation in children in the UK were meningiomas and 30% gliomas, occurring between 5 and 52 years after treatment (mean 20.5 years).[6] After irradiation of a primary brain tumour there was a cumulative incidence for meningiomas of 6.3% by 40 years, representing a risk relative to the general population of approximately 500-fold.

Methods

As a result of this clear information a medical multispecialty working group met, sponsored by the Royal College of Radiologists. We shared knowledge on epidemiology, diagnosis and management of meningiomas and debated whether or not routine screening of those at increased risk should be advised. Current knowledge on the subject was pooled and together with our recommendations was used to create the document: 'Meningioma as a late effect of cancer treatment' published online by the Royal College of Radiologists in April 2013.[7]

What follows is a short summary of that document.

Epidemiology

Meningiomas, tumours of the meninges, the thin-layered membrane surrounding the brain, occur sporadically in the absence of known aetiology and overall are the commonest brain tumour. Their apparent incidence is increasing as more are registered and more are found incidentally with scanning and an ageing population. The most recent statistics from the United States Central Brain Tumour Registry[8] confirm their rarity in childhood (0.1/100,000) and a strikingly increased incidence with age reaching 49/100,000 in over 85 year olds. Women have an approximately double incidence and there is an association with neurofibromatosis type 2.[9] Since 2004 it has been mandatory to register unbiopsied tumours diagnosed on scanning; 98% of meningiomas in the most recent report were given a non-malignant code.[8]

An increased incidence with radiation exposure has been recognized since the 1970s and has been seen in atomic bomb survivors,[10] after scalp irradiation for tinea capitis,[11] after full mouth dental X-rays (when doses were higher than now)[12] and after cranial or spinal irradiation.[6,13] Higher radiation doses and longer interval after irradiation increase the risk of meningioma development.[6]

Diagnosis

Symptoms are of new neurological deficit, seizures, raised intracranial pressure, proptosis, cavernous sinus syndrome or a lump on the skull. These prompt a scan (CT or MRI) which shows a well-circumscribed dural-based contrast enhancing mass; multiple lesions can occur. The radiological appearance is usually characteristic although histopathology is necessary to distinguish between benign WHO grade I with low recurrence risk, atypical grade II with increased cellularity and mitoses, and anaplastic grade III with frank features of malignancy and the ability to invade other structures.[14]

Specific features of radiation-associated meningiomas

While both sporadic- and radiation-induced meningiomas are usually benign, those associated with radiation show behaviour which reflects the finding that 20–40% of radiation-associated meningiomas compared with <10% sporadic meningiomas demonstrate atypical or malignant features.[11,15,16] They are more likely to be invasive and to recur than sporadic ones and in addition are more likely to be multiple (5–15% vs. <5%).[15] Both sporadic- and radiation-associated meningiomas can recur even after apparent total resection.

Cytogenetic differences are also seen. Deletions of chromosome 1 have been reported in over 75% of radiation-associated meningiomas compared with the more usual deletions of chromosome 22 seen in sporadic forms.[15] Most series of radiation-associated tumours show a lower female preponderance than control groups[11,15] and a younger mean age at presentation (30–40 years after radiation for solid tumours,[16] 65 years for sporadic tumours[8]).

Management

The options include watch and wait with serial scanning for asymptomatic cases picked up incidentally,[17] surgery for accessible and radiotherapy for inaccessible sites. Complete and safe resection is often not possible because of the tendency for radiation-induced meningiomas to be multiple, invasive and atypical or malignant.[11,16] In addition, surgical healing can be compromised when prior radiotherapy has left a relatively avascular scalp.[16] When re-irradiation is necessary newer techniques such as stereotactic radiotherapy[18] and intensity-modulated radiation treatment[19] and alternative radiation modalities (e.g. Protons)[20] might benefit.

Long-term follow-up after childhood cancer

While two-thirds of survivors of childhood cancer have one or more late effects and one-third are

significantly affected,[21] historically only about half were followed up beyond 5 years after the end of treatment.[22]

Ongoing care of those who have been treated for cancer in childhood is recommended. The British Childhood Cancer Survivors Study has questionnaire information on 10,000 long-term survivors, with details on physical and psychological wellbeing.[23]

This, together with a similar, though USA hospital based, Childhood Cancer Survivors Study has provided solid information on the incidence and severity of late effects.[3,24]

In 2008, NHS Improvement launched a Survivors' Initiative to address long-term follow-up in survivors of childhood and adult cancers.[25] The Scottish Intercollegiate Guidelines Network has recently updated its recommendations on long-term follow-up and this SIGN guidance number 132 has been adopted by the National Institute for Clinical Excellence for the whole of the UK.[26]

Personal treatment summaries containing known risks of late effects and access to multidisciplinary long-term follow-up clinics for childhood cancer survivors are now expected. All survivors of childhood cancer will be provided with a contact number and will be contacted. Those at substantial risk will be invited to be seen by a nurse or doctor every year or less frequently as appropriate. (Children who are still growing need to be seen three or four times a year by an endocrinologist to ensure optimal final height.)

Should routine scanning be suggested?

The group debated long and hard about formal screening with MRI scans for those at risk of meningioma development.

We agreed the importance of survivors being made aware of their risks and that symptoms should be reported. However, we concluded that the physical risks of a new neurological disability or healing problems associated with surgery, in addition to the psychological risks from knowledge of an asymptomatic but not easily resectable lesion, from repeated waits 'in limbo' for scan results and from finding indeterminate white matter changes which often follow radiation, outweighed any advantage in the early detection of an asymptomatic lesion.

In addition, although gliomas would also be detected by scanning there has been no demonstrable benefit from intervention when asymptomatic.

Declarations

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