Meningioma as a late effect of cancer treatment

Board of the Faculty of Clinical Oncology
The Royal College of Radiologists
Summary and recommendations

Radiation-induced meningiomas

New cranial neoplasms following exposure of the brain to radiation were first recorded over 40 years ago and of these neoplasms, meningiomas are the most common. The risk of meningiomas appears to be highest in those exposed in childhood and ascertainment of meningiomas in this group increases with both time since treatment and radiation dose. After 40 years of follow-up, the cumulative incidence of meningiomas in the exposed cohort is overall more than 2% and more than 6% in those who had a first primary neoplasm of the central nervous system, which is several hundred times the incidence of sporadic meningiomas.

Radiation-induced versus sporadic meningiomas

Sporadic meningiomas, although the most common type of intracranial tumour, are rare and even rarer in children. Women are at least twice as likely as men to be affected, although there is a higher incidence of high grade tumours in men. In both sexes meningiomas are most likely to be benign on histology, although the location can make resection difficult and even dangerous. Surgery is the primary treatment with additional radiotherapy where necessary.

Radiation-induced meningiomas (RIMs) show less sex difference in incidence than sporadic tumours, are more likely to be multiple and more aggressive with consequent increased tendency to recur after resection. Management may be challenging when there has been previous therapeutic high-dose radiation treatment and therefore surgery and further radiotherapy must be given with care.

Those at risk

Patients exposed to radiotherapy affecting the brain area need to be aware that they are at risk of development of meningioma and that they should report tumour-related symptoms. Similarly, all doctors should be aware of the low but increased risk in this treated cohort.

Latency

This varies with radiation dose and length of time since treatment and is shorter the higher the dose and the younger the individual when treated. It can vary from less than ten to 40 years or more.

Care plans, long-term follow-up, lost to follow-up

The Cancer Survivors' Initiative of NHS Improvement is facilitating the national development of care plans which will be given to children and young adults after cancer treatment. These will document the risk of second neoplasms and other late effects and hopefully prompt the patient and the GP in case of subsequent symptoms. Those treated some time ago and lost to follow up are at increased risk with elapse of time. All those irradiated in childhood should be offered and encouraged to take part in long-term follow-up.

Recommendations

Although it is recognised that the risk of meningiomas is higher than expected in those exposed to cranial irradiation, particularly during childhood, we do not recommend screening for the asymptomatic patient. However, new and persistent symptoms, suggestive of an intracranial tumour in those exposed, should prompt an urgent magnetic resonance imaging (MRI) scan and subsequent discussion at a neuroscience multidisciplinary team (MDT) meeting.

Introduction

The term ‘meningioma’ was first coined in 1922 by Harvey Cushing to describe a globoid tumour arising from the arachnoid cap cells. Their ‘source and favoured seats of origin’ are the leptomeninges – the thin, protective membrane which surrounds the brain. Meningiomas were noted to grow slowly, did not metastasise and were considered to be benign. Meningiomas are extra-axial lesions, lying outside the central nervous system (CNS) but impinging onto it. The most common sites for development are the supra-tentorial convexit y dura, the falx and parafalcine regions, sphenoid ridge and planum sphenoidale. Approximately 10% are infra-tentorial and, rarely, can develop alongside optic nerve sheaths or the spinal canal.

Meningiomas are rare, although they are the most common intracranial tumour and have been reported to account for 34% of intracranial tumours in the US. In childhood they are very rare, occurring in only 0.3 per 100,000 children, increasing with age to a rate of over 40 per 100,000 in the over-85s. The cause of sporadic meningiomas is unknown but since the early 1970s an increased risk of both meningiomas and gliomas has been noted to occur after brain irradiation. Brain irradiation has been used for the treatment of fungal infections of the scalp (tinea capitis), for intracranial and head and neck tumours, for prophylaxis against CNS disease in acute lymphatic leukaemia and in allogeneic bone marrow transplant involving total body irradiation. Second primary intracranial tumours are one of many late effects of cancer treatment from which survivors of childhood cancer are at particular risk.
Incidence and aetiology of sporadic meningioma

Increasing incidence

There has been an increase in the recorded incidence of meningiomas, particularly in older age groups, over recent years. This may reflect a true increase or it may be a consequence of improvement in detection through incidental diagnosis on computed axial tomography scan (CT) or MRI scan carried out for other purposes, or because of improved reporting of meningiomas to registries. Approximately 90% of meningiomas are benign and evidence of underreporting to cancer registries has led to recent mandatory registration of 'benign' intracranial tumours in the United States. Accurate registration requires biopsy material, which has not always been available. Although a rare tumour, meningioma was the most frequently reported histology of all primary intracranial tumours in the United States Central Brain Tumour Registry 2011 report, accounting for 34% (approximately ¼ in males, ¾ in females).

Effect of age

The incidence rate increases with age, ranging from 0.3/100,000 in childhood to over 40/100,000 in the over-85s. Reflecting their extreme rarity in children, meningiomas account for only 2.5% of primary CNS tumours in childhood. Data from the UK Children’s Cancer Research Group (CCRG) registry based at Oxford records about five new cases of meningioma annually in children aged less than 15 years. Data from the National Cancer Registry of the former German Democratic Republic between 1961 and 1986 reported an incidence of 1.5 cases per million per year for the 0–19 year age range.

Known aetiological associations

Exposure to ionising radiation

Early evidence came from atomic bomb survivors and those exposed to radiation as treatment for tinea capitis. There is now evidence that survivors of childhood cancer exposed to cranial irradiation are at a significantly increased risk of developing meningiomas.

Hormones

Women develop approximately twice as many meningiomas as men, although men tend to develop a higher proportion of malignant meningiomas. Although pregnancy appears overall to have a protective effect, meningiomas that do develop in pregnancy tend to progress more rapidly in the later stages of pregnancy. The precise relationship between female hormones and risk of meningiomas remains unclear.

Chemical exposure

There is some evidence that occupational exposure to lead (Pb) increases the risk of meningiomas in genetically predisposed individuals, although the mechanism of action for this is unknown.

Family history

There is an increased risk of meningioma in certain families as well as a known association in neurofibromatosis type 2 (NF2).
Radiation-induced meningioma

Evidence suggests that radiation therapy involving the CNS is a causative factor in the development of meningiomas. An increased risk has been noted among different populations or groups including survivors of atomic bombs, children treated with irradiation for tinea capitis and those exposed to full mouth dental X-rays, as well as medically exposed populations from cranial irradiation.

Meningiomas are the most common intracranial second primary neoplasm (SPN) in survivors of primary CNS tumours and haematological malignancies. In one series, half the reported paediatric cases were discovered on surveillance scans.

Radiation – definitions of dose level

For radiation-induced meningioma, some have defined doses as: high dose (>20 Gray [Gy]), intermediate dose (10 to 20 Gy) and low dose (<10 Gy). Others have defined any dose over 10 Gy as high.

Time to development and radiation dose

The time interval between exposure and development or ascertainment is associated with the radiation dose. Following low-dose radiotherapy, such as 8 Gy for tinea capitis (this treatment was abandoned in the 1960s), the interval from treatment to diagnosis of meningiomas may reach 35 years. After high-dose radiation in childhood (>20 Gy for leukaemia or primary intracranial tumours), meningioma can occur as early as the second decade after treatment.

Groups at risk

Any child or young adult who has had cancer treatment involving the CNS is at risk. The risk is higher for those irradiated at a younger age and with a higher dose.

Changes in the management of childhood cancer make definition of at-risk patient groups difficult. Routine cranial radiotherapy for children with acute lymphatic leukaemia was common in the 1970s but discontinued in the 1980s, although since then there has been more chemotherapy CNS-directed treatment. The survival of children with primary CNS malignancies is increasing, resulting in more persons surviving to be at risk. While the use of radiation in under three year olds was abandoned for many years, focal CNS radiotherapy with photons or protons is now becoming acceptable in very young children. The brain is also irradiated when total body irradiation (TBI) is part of the conditioning for bone marrow transplant and when head and neck tumours involve the base of skull.

Effect of low-dose radiation

Exposure to atomic bomb

Much of the evidence on the dose–response effect of radiation is from studies of atomic bomb survivors. One study reported an excess relative risk (ERR) for meningioma of 0.6 (0.01–1.8) per Sievert (Sv).

Therapeutic radiation for tinea capitis

Extended follow-up of children treated for tinea capitis with cranial irradiation has shown an ERR for meningiomas of 4.63 (2.43–9.12) per Gy.

Dental radiographic examinations

An increased risk of meningioma after treatment with full mouth dental X-rays has been reported in women treated in childhood before 1945 (when doses were higher).
Effect of high-dose radiation

Therapeutic radiation for childhood cancer

There is a very strong dose–response effect for risk of meningiomas after cranial irradiation for childhood cancer. The relative risk (RR) of meningioma reported from the Childhood Cancer Survivor Study (CCSS) in the US is 32.8 (8.4–128.3) after exposure to radiation of at least 45 Gy and an overall ERR of 1.06 (0.21–8.15) per Gy for meningiomas.13 Equivalent results from the British Childhood Cancer Survivor Study (BCCSS) in the UK are: RR of meningiomas of 94.2 among those irradiated with doses of at least 40 Gy and overall ERR of meningioma of 5.1 (0.7–107.7) per Gy.12

Latency period

Several studies indicate that the higher the dose the shorter the time to development. A mean of 36 years was reported in those treated in childhood for tinea capitis.11 The long latency period to tumour development, after the relatively low exposure to ionising radiation in the survivors of the Hiroshima and Nagasaki bombs, led to an increased incidence of meningiomas in this group being undetected until the 1990s.22,23

After treatment which included exposure to high-dose irradiation in children, the BCCSS12,26 report a mean interval of 23 years and the CCSS13,14 a median interval of 17 years before development of meningioma. These figures are similar to a previous calculation of a mean interval of 35.2 years for low-dose exposure, 26.1 years for moderate dose and 19.5 years for high-dose irradiation.24

Age

Other studies report a variation in latency according to age at treatment with shorter latency in those treated at a younger age.30

Chemotherapy

Although there has been no previous published evidence to support an association between chemotherapy and second primary meningiomas, recently the BCCSS estimated a significantly increased risk of meningioma after intravenous treatment with methotrexate.12

Effect of growth hormone

Although growth hormone has been implicated in the development of second primary neoplasms (SPNs) of the CNS, the risk, relative to those not on growth hormone, appears to decline with longer follow-up.31

Genetics

Multiple meningiomas occur in the majority of patients with neurofibromatosis type 2 (NF2), a multisystem genetic disorder also associated with bilateral vestibular schwannomas, other cranial nerve and spinal nerve as well as peripheral schwannomas and spinal cord ependymomas.21 In addition, there appears to be an association between some cancers including breast and colorectal cancer and second primary meningioma.32

Sex ratio

Radiation-induced meningiomas still display a female preponderance but this is not as marked as in spontaneous meningiomas.12

Location

The location of radiation-induced meningiomas is primarily related to the site of exposure. For example, the Israeli tinea capitis studies showed a primarily calvarial location,33–35 whereas meningiomas that occurred after dental X-rays were predominantly skull based.24

Differences from spontaneous meningiomas

Radiation-induced meningiomas differ from spontaneous meningiomas in the age of presentation, multiplicity, World Health Organization (WHO) grade and recurrence rates.36 While the usual presentation of spontaneous meningiomas is in the fifth to sixth decade of life, the mean age in those exposed to high-dose radiation in childhood is reported to be between 29.2 to 37.9 years and after low-dose radiation 45–48 years. Multiplicity is higher in radiation-induced lesions, ranging from 4.6% to 18.7% versus 2.4% in spontaneous meningiomas.33–35 Histological atypia and anaplasia, as well as multiplicity, are more common in radiation-induced meningiomas – although still evident in only a minority of these cases.37
Diagnosis: imaging

Imaging features of secondary meningiomas

As with sporadic meningiomas, the convexities and falx are the most common locations for radiation-induced meningiomas, although the spinal canal as well as other intracranial meningeal sites are also at risk.

Meningiomas have a characteristic appearance on CT and MRI (well circumscribed, dural based, contrast-enhancing mass with or without associated brain oedema and/or hyperostosis of the adjacent skull). Other neoplasms can mimic this appearance such as dural metastases and haemangiopericytomas but in the vast majority of cases the radiologist can be confident about the diagnosis.

Reliable distinction between benign (WHO grade I), atypical (WHO grade II) and anaplastic (WHO grade III) meningiomas is not possible on imaging.

Clinical presentations

Meningiomas can present in a number of ways, including a new neurological deficit, seizures, symptoms of raised intracranial pressure, proptosis, cavernous sinus syndrome or a lump on the skull.

Most of these presentations are non-specific and in the context of previous treatment for CNS or haematological malignancy can signal any of the following: recurrence of the primary CNS malignancy; metastasis from an extra cranial solid tumour; a second primary neoplasm (SPN) of the skull, meninges or brain; non-neoplastic parenchymal brain changes secondary to radiotherapy or chemotherapy; hydrocephalus such as due to failure of cerebrospinal fluid (CSF) diversion by shunt or ventriculostomy.

Imaging in symptomatic patients

Any of the presentations listed above is an indication for urgent imaging. The modality (CT, MRI or both) and anatomical coverage chosen (for example, brain, spine, orbits) will depend on the specific case. An unenhanced CT scan will confirm or exclude hydrocephalus but for most other indications MRI is preferable. An MRI protocol that includes axial T1, T2, diffusion-weighted images (DWI), axial or coronal fluid attenuated inversion recovery (FLAIR) and axial, coronal and sagittal gadolinium-enhanced T1-weighted images is ideal. A lesion involving the skull base and/or orbits should be further evaluated using high-resolution gadolinium-enhanced MRI.

When an extra-axial lesion with bony skull involvement is identified on MRI, a CT scan with bone algorithm image reconstructions may help to distinguish between a meningioma and other possibilities, such as a sarcoma or a metastatic or lymphoma deposit in the skull or meninges. Review of previous neuroimaging studies is often useful in deciding on appropriate further imaging and in the interpretation of new scans.

Follow-up scans after treatment involving the brain in asymptomatic patients

Neuroimaging following treatment for most types of CNS tumour is standard practice. Follow-up scans, usually annual over several years, are done to monitor residual disease or to detect recurrence. Gadolinium-enhanced MRI is usual and will detect incidental SPNs including meningiomas (see examples in Appendix 1), although that is not the primary reason for follow-up.
Diagnosis: pathology

Primary (sporadic) meningiomas

Most meningiomas occur sporadically without a known aetiology, while others arise in the context of NF2 or in rare non-NF2 families. Spontaneous multiple meningiomas are a signature lesion of NF2 and inheritors of this gene have a very high risk of meningioma development.21

Cytogenetic changes in spontaneous meningiomas

Monosomy of chromosome 22 (loss of one chromosome) is the most common alteration in sporadic grade I meningiomas. Deletion of chromosome 22q (which includes the tumour suppressor NF2 gene) is less common.38

Histopathological classification of spontaneous meningiomas

The current WHO classification of tumours of the CNS (2007) distinguishes 13 histological subtypes of meningiomas and three grades (WHO I, II, III). There is a significant amount of inter-observer variability in terms of classification of meningiomas, although it is agreed that most histological subtypes correspond to WHO grade I (benign). This implies a low growth rate.

Any histological subtype may present with, or progress to, atypical (WHO grade II) or anaplastic (malignant) (WHO grade III) meningioma.

Histological features of the three grades are listed in Table 1.37

Table 1. Histological features of the three WHO grades

<table>
<thead>
<tr>
<th>WHO classification</th>
<th>Description</th>
<th>Reported recurrence rate</th>
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<tr>
<td>Grade I</td>
<td>Meningiomas, with low risk of recurrence and/or low risk of aggressive growth</td>
<td>7–25%</td>
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<tr>
<td>Grade II</td>
<td>Atypical meningiomas, with increased mitotic activity or three or more of the following features: increased cellularity, small cells with high nucleus-to-cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of spontaneous or geographic necrosis</td>
<td>29–52%</td>
</tr>
<tr>
<td>Grade III</td>
<td>Anaplastic (malignant) meningiomas exhibit frank histologic features of malignancy far in excess of the abnormalities present in atypical meningiomas. The tumour can invade rather than push and compress other structures. Can metastasise outside the CNS; eg, to lung</td>
<td>50–94%</td>
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Table 1 is based on World Health Organization (WHO) classification for meningiomas.37

The diagnosis of WHO grade II meningioma implies a statistically higher risk of local recurrence and WHO grade III lesions are associated with rapid recurrences, seeding and high mortality.
Hormone receptor expression

Eighty-eight per cent of primary meningiomas express progesterone receptors (PR), 40% express oestrogen receptors (ER) and 39% express androgen receptors (AR). Atypical and anaplastic meningiomas are more likely to express ER or AR compared to grade I meningiomas. Expression of PR positivity with ER negativity has been found to be favourable for clinical and biological outcome, but so far no benefit has been shown from tamoxifen or other hormone treatment.

Spontaneous meningiomas in childhood

The proportion of clinically aggressive and histologically higher grade subtypes of spontaneous meningiomas (WHO grade II/III) appears to be greater in children, particularly the very young, and varies from 7–38% based on small observational retrospective case series. Published incidence figures are difficult to interpret since the histopathological classification of 'high-grade meningioma' varied over time, often including other pathological entities associated with meninges; that is, meningeal sarcomas which feature prominently among young children.

Radiation-induced meningiomas

Cytogenetics of radiation-induced meningiomas

These may be genetically different from the sporadic entity with more frequent involvement of chromosome 1p and rarely involvement of chromosome 22q.

Histopathological classification of radiation-induced meningiomas

Radiation-induced meningiomas (RIMs) are classified and graded according to the same system as sporadic meningiomas. Studies of the histological and genetic features of RIMs are limited and it remains to be seen if the phenotype and genotype of RIMs following low-dose irradiation are the same as that following high-dose irradiation. Some studies suggest that RIMs are more aggressive than their sporadic counterparts; however, the majority still corresponds to grade I. It is possible that the histological grading criteria developed for sporadic meningiomas may not have the same predictive value when applied to RIMs. There are indications that an increased frequency of recurrence may occur even in the context of a grade I lesion. The current view expressed in the most recent WHO classification scheme (2007) is that as a group RIMs are more commonly multifocal, atypical and proliferative than their sporadic counterparts. Recorded grades of the 137 cases of post-radiation meningiomas from the BCCSS study were: 57 benign (grade I), seven atypical (grade II) and eight anaplastic (grade III).
Management

There is no specific Improving Outcomes Guidance (IOG) or National Institute of Health and Clinical Excellence (NICE) Guidance for either sporadic or radiation-induced meningiomas, reflecting the lack of randomised controlled trials. However, the need for organisation of care by a neurosciences MDT, taking into account signs, symptoms, patient fitness and site and size of the tumour, is stressed and locally agreed protocols for follow-up are recommended.43

Guidelines for the management of meningiomas generally in children and young people have been produced by the Children’s Cancer and Leukaemia Group (CCLG).4

The management of meningiomas – surgery

Surgery remains, as in Cushing's day, the mainstay of treatment and this is reflected in the fact that after WHO grading the most important predictor of meningioma recurrence is the degree of resection as characterised by Simpson in 1957.44

Surgical limitations in radiation-induced meningioma

Complete and safe resection is often not possible because of the multiple, invasive and atypical or malignant nature of many radiation-induced meningiomas.36,45

Surgery is further complicated by the frequent involvement of the venous sinuses, which both limits resection and increases mortality and morbidity.44,46,47

Previously irradiated skin

Perhaps most important of all for the surgeon dealing with RIM is the problem of thin, atrophic skin and alopecia following irradiation. Care is required to prevent the very real risk of wound breakdown with resulting cerebrospinal fluid (CSF) leak and catastrophic infection. To limit this possibility, curvilinear rather than traditional horseshoe flaps are preferred and the use of haemostatic clamps and diathermy to control scalp bleeding are discouraged.36 Skin closure requires similar care, usually a single layered nylon as opposed to a multi-layer closure using vicryl and clips.

The management of meningiomas – radiotherapy

Radiotherapy in sporadic meningioma

For benign tumours with subtotal resection, postoperative radiotherapy has an established role in reducing recurrence. Local control is improved over a five to ten year period from 66% to 85–97% for both intracranial and skull base lesions.48,49

In adult sporadic meningioma, where surgery is not possible, radiotherapy can be used as a primary treatment.50 It should also be considered for all atypical and anaplastic (malignant) meningiomas where recurrence rates after surgery alone are in the region of 40–100% at five years (see Table 2).50–52.)
Table 2. Local control benefit of radiotherapy in adults

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient group</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Nutting et al\textsuperscript{51}</td>
<td>82 patients with benign skull base meningiomas treated with surgery followed by radiotherapy</td>
<td>5 and 10 year progression-free survival 92% and 83% Overall survival 71% at 10 years</td>
</tr>
<tr>
<td>Debus et al\textsuperscript{50}</td>
<td>189 patients with benign skull base meningiomas treated either immediately after surgery or at recurrence</td>
<td>Local control 98% at median follow up 35 months. Overall actuarial survival 97% at 5 years</td>
</tr>
<tr>
<td>Estall et al\textsuperscript{52}</td>
<td>128 patients receiving radiotherapy for meningiomas</td>
<td>Median follow-up 5.3 years. Local control rates 93% for grade I, 45% grade II, 82% grade III</td>
</tr>
</tbody>
</table>

The aim of radiotherapy is to achieve or improve local control, while limiting dose to other structures, and so favours techniques which minimise the treated volume.

The decision to use adjuvant radiotherapy must take into account the patient factors of choice and co-morbidity and tumour factors such as the extent of surgical resection and tumour grade or histological subtype.\textsuperscript{48,51}

In children and young adults, radiotherapy is usually withheld unless the meningioma is threatening vital neurological functions, such as vision or the cavernous sinus, and no further surgical options are available.\textsuperscript{3} A recently published meta-analysis of paediatric meningioma therapy suggested no survival benefit from radiotherapy.\textsuperscript{53}

The dose of fractionated radiotherapy

The dose of fractionated radiotherapy for benign meningiomas is usually of the order of 50 Gy in 1.67–1.8 Gy per fraction with higher doses for higher grade tumours.\textsuperscript{52} A current European Organisation for Research and Treatment of Cancer (EORTC) Phase II study is investigating the effect of doses up to 70 Gy in patients with atypical and malignant (anaplastic WHO III) meningioma.

Stereotactic radiotherapy or stereotactic surgery

These precise focal treatments are useful for benign (grade I) well-demarcated tumours with a treatment volume ≤2 cm; its use in larger lesions (up to 3.5 cm) is now entering practice. Compared to conventional fractionated radiotherapy, the superior immobilisation and beam quality of fractionated stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS) reduces the added margin around visible tumour required for the final treatment volume. SRT uses the same fractionated protocol as conventional radiotherapy; SRS aims to deliver a single larger dose where size and position of the tumour in relation to other organs at risk (OARs) allows.

Radiation-induced meningioma

Further irradiation would not seem the best option for meningiomas within a previously irradiated area. However, when radical surgery is impossible because of location, it has to be considered. SRT can reduce the volume of normal brain irradiated so reducing the risk of brain necrosis with re-irradiation and permitting cumulative doses in a higher range than would otherwise be possible with standard conformal radiotherapy.\textsuperscript{54}

Intensity-modulated radiation therapy

Intensity-modulated radiation therapy (IMRT) has a potential role in the treatment of meningiomas where dose escalation is required or where retreatment is envisaged in the setting of local or multifocal relapse. Selected volumes can be spared but only at the expense of higher dose to other areas.

Protons

Radiotherapy treatment with protons has the theoretical advantage of limiting the volume of normal brain irradiated. This treatment modality, as yet only available overseas and without full efficacy and follow-up information, could be particularly useful for retreatment. Indications for treatment with protons are expected to change over time.

Adjuvant hormones or cytotoxics

The anecdotal use of tamoxifen and hydroxyurea has proved to be disappointing in tumour control.
Prognosis

As most meningiomas (spontaneous or radiation-induced) are benign, prognosis is favourable: five-year survival of all grades combined is approximately 80%. Survival to five years of 137 patients with meningiomas following CNS radiation in childhood was 84% in males and 82% in females with a significant negative effect of higher grade and meningioma-associated syndromes. Malignant meningiomas have a poorer prognosis: RARECARE estimated relative survival to be 65% at five years for malignant meningiomas.
Surveillance

Long-term follow-up

The NHS has put huge investment into cancer treatment in children and aims to keep them fit and well for as long as possible.

Treatment summaries, care plans and arrangements for indefinite long-term surveillance after childhood and adolescent cancer are expected to be mandated by the government in the near future and will inform survivors of potential long-term morbidity.

Screening for second neoplasm

The increased risk of new tumours in the previously irradiated CNS raises the question of screening for the ‘at-risk’ population.

The main premise of a screening programme is that there should be a useful intervention which will improve quality of life and survival.

There is no robust evidence for or against intervention for an asymptomatic meningioma or glioma (the other most frequently induced neoplasm in this context). Anecdotal experience provides proponents on both sides. Not all meningiomas are in surgically accessible sites; some are solitary and show no change over five years while others are multiple, which makes management more complex.

Potential benefits of screening

The increased risk of meningiomas following cranial irradiation, coupled with the reasonable assumption of better surgical outcomes in patients with smaller tumours, has prompted some clinicians to advocate imaging surveillance for survivors of childhood leukaemia.58

Patients are made aware of the definite possibility of developing a second neoplasm.

Potential disadvantages of screening

Early diagnosis can, in the asymptomatic, produce unnecessary psychological morbidity from knowledge of an abnormality.

Surgery in the asymptomatic patient has to be weighed against any possible new neurological disability as well as problems of healing in previously irradiated sites.

Scanning will reveal the white matter and vascular changes seen in about half of brains after surgery, chemotherapy and radiotherapy, even at low dose.59 Knowledge of these can provide another area of concern for patients.

Patients often focus so much on a recent scan that their life can seem to be ‘on hold’ waiting for the result; only if the result will alter management in a positive way should scanning be undertaken. Knowledge of an abnormality which cannot be corrected is unlikely to be helpful.

Who should be scanned?

There should be a low threshold for imaging of the patient, previously exposed to radiotherapy and/or chemotherapy directed against or involving the central nervous system, who has new and persistent symptoms. The long latency for development makes it unlikely that a meningioma will be found earlier than 10–15 years after initial treatment. It is worth remembering that teenagers are often beginning to default from clinic attendance or are discharged before this. It is important that both patient and GP are aware that the risk, although small, is real and remains lifelong.

When a patient, concerned about second neoplasms, insists on a scan, they should be made aware of the disadvantages of finding an abnormality which might not be treated. A strong desire for a scan, in spite of understanding the disadvantages, should be taken as a ‘symptom’ which can prompt a scan.

Pregnancy

A small number of published case studies report meningiomas increasing in size and presenting during pregnancy. Pregnancy should not be considered the explanation for symptoms in a woman who has received cranial radiotherapy. MRI scanning is safe during pregnancy and the same low threshold for imaging should apply.60
**Modality**

Gadolinium-enhanced MRI is preferred; it has a high sensitivity and specificity and does not involve ionising radiation. Meningiomas as small as 0.5 cm in diameter are easily detectable.

**Imaging interval**

If an asymptomatic meningioma is detected on imaging, repeat imaging at increasing intervals (for example, six months, then one year, then two years) could be performed to assess growth rate and help inform surgical decision-making.6

**Recommendations**

With the current state of knowledge, the working group does not recommend scanning for the asymptomatic patient, but would support a prospective study that included cost-effectiveness and quality of life as well as incidence, stage and outcome of any intervention.

Approved by the Board of the Faculty of Clinical Oncology: 2 November 2012

Reviewed by the CCLG Radiotherapy Group and the CCLG Late Effects Group
References


Appendix 1. Case studies

Case study 1

A 28-year-old man who underwent cranial radiotherapy in early childhood following partial resection of a pilocytic astrocytoma of the left temporal lobe presented with recent onset of progressive right-sided weakness and numbness. Review of previous MRI scans confirmed that a small residual or recurrent tumour nodule had been present in the left temporal lobe for at least six years. A right occipital extra-axial tumour in keeping with a meningioma had also been present for at least six years and remained unchanged in size over that period.

An MRI scan was performed to investigate the new symptoms. Axial contrast-enhanced T1-weighted images confirmed that the residual pilocytic astrocytoma (arrow in Figure 1) and the presumed meningioma (arrowhead in Figure 1) remained unchanged compared to previous scans.

![Figure 1](image1.png)  ![Figure 2](image2.png)

A partially necrotic, peripherally enhancing mass was identified in the left side of the pons (arrow in Figure 2). This lesion was not evident on an MRI scan performed five months previously. In the light of the rapid clinical deterioration, the imaging appearances were most in keeping with a glioblastoma. A decision was taken at MDT to biopsy this lesion and histology confirmed a glioblastoma.

Case study 2

MR imaging follow-up in an asymptomatic 19-year-old man treated with cranial irradiation for a pituitary region germinoma at age of seven showed a left convexity meningioma (Figure 3). A further follow-up scan two years later showed significant growth in the tumour despite the patient remaining asymptomatic (Figure 4). The tumour was therefore resected and histology confirmed a WHO grade I meningioma.
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### Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>BCCSS</td>
<td>British Childhood Cancer Survivors’ Study (population-based study in Britain)</td>
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<tr>
<td>CCSS</td>
<td>Childhood Cancer Survivor Study (hospital-based study in United States)</td>
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<tr>
<td>CCLG</td>
<td>Children’s Cancer and Leukaemia Group</td>
</tr>
<tr>
<td>CCRG</td>
<td>Childhood Cancer Research Group</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed axial tomography scan</td>
</tr>
<tr>
<td>MDT</td>
<td>Multidisciplinary team (meeting)</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging scan</td>
</tr>
<tr>
<td>ERR</td>
<td>Excess relative risk: the excess risk attributable to the exposure and equals the odds ratio (OR) minus 1 (ERR=OR−1)</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray: a measure of absorbed radiation dose – one Gy is the dose given by one joule of energy per kilogram (1 Gy = 1 J/Kg)</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity-modulated radiation therapy</td>
</tr>
<tr>
<td>IOG</td>
<td>Improving Outcomes Guidance</td>
</tr>
<tr>
<td>NF2</td>
<td>Neurofibromatosis (NF) type 2</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute of Health and Clinical Excellence (based in UK)</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>OAR</td>
<td>Organs at risk</td>
</tr>
<tr>
<td>RIM</td>
<td>Radiation-induced meningioma</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SPN</td>
<td>Second primary neoplasm</td>
</tr>
<tr>
<td>SRT</td>
<td>Stereotactic radiotherapy</td>
</tr>
<tr>
<td>SRS</td>
<td>Stereotactic radiosurgery</td>
</tr>
<tr>
<td>Sv</td>
<td>Sievert: a measure of radiation received from environmental exposure – one Sv is the equivalent of one Gy of absorbed radiation dose</td>
</tr>
</tbody>
</table>