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Overview

Radiotherapy in Craniopharyngiomas

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Abstract

The optimal management of craniopharyngioma remains controversial. Although aggressive (i.e. attempted macroscopic complete/radical) primary surgery can be associated with significant morbidity and a noticeable recurrence rate, a conservative (limited) surgical approach followed by radiotherapy has increasingly been adopted after reports of excellent local control and a significant reduction in the incidence of complications by most multidisciplinary teams. A literature review from January 1990 to May 2012 was carried out identifying 43 studies with 1716 patients treated with irradiation for craniopharyngioma. The outcome and treatment-related toxicity were analysed in relation to the timing of radiotherapy, the target volume definition and radiotherapy dose and compared with the results of radical surgery. For patients undergoing limited surgery and postoperative radiotherapy, reported 10 year local control rates ranged between 77 and 100% and 20 year overall survival was reported as high as 66–92%. Comparable progression-free survival and overall survival were reported for radiotherapy delivered at first diagnosis or at progression. Long-term toxicity of combined limited surgery and irradiation seems to be less than that associated with radical surgery. The total recommended dose prescription to achieve long-term control while minimising adverse sequelae is 50–54 Gy delivered with conventional fractionation. Care should be provided by a multidisciplinary team in a specialised centre. However, national and international prospective co-operative trials are warranted to provide robust data to define an internationally multidisciplinary accepted risk-based management strategy.

Key words: Craniopharyngioma; intracavitary irradiation; proton beam therapy; radiosurgery; radiotherapy; stereotactic radiotherapy

Statement of Search Strategies Used and Sources of Information

A review of published articles was conducted using the MEDLINE, Current Contents and PubMed databases, based on the terms 'craniopharyngioma' alone and in combination with 'radiotherapy', 'stereotactic radiotherapy', 'radiosurgery', 'intracavitary irradiation', 'proton beam therapy' and 'morbidity'.

Only studies published in English from January 1990 to May 2012 with at least 10 patients treated with radiotherapy were included; reviews, letters to the editor, commentaries, case reports and meeting abstracts were excluded. Duplicate reports regarding the same series of patients were excluded.

Introduction

Craniopharyngiomas are rare, histopathologically neuroepithelial tumours arising from the embryological remnants of the primitive craniopharyngeal duct or Rathke's pouch. Despite their histopathologically benign classification, patients suffering from craniopharyngioma frequently experience profound disabilities and uncontrolled growth remains fatal. The overall incidence of craniopharyngioma is reported as 0.13 in 100 000, constituting 5–10% of paediatric and 1–4% of adult brain tumours, respectively. There is a bimodal age distribution, with peak incidences at ages 5–14 and 65–74 years [1]. Patients commonly present with headache, nausea, vomiting, visual impairment and hypothalamic/pituitary dysfunction [2–12].

Radical surgery aiming at a macroscopic resection was the treatment of choice for several decades, with high reported rates of tumour control (65–90%) compared with limited surgery (10–50%) [2–10]. However, attempted complete removal of the tumour, usually referred to as

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radical surgery, can result in severe damage to the visual apparatus and hypothalamic–pituitary axis [2–11], secondary diabetes insipidus [2,3,7–9,11,12], hypothalamic disorders [3,4,6–8,12–17], poor functional outcomes and reduced quality of life (QoL) [17–20].

To date there is no proven role for chemotherapy in the treatment of craniopharyngioma and it remains experimental [21,22].

The most disabling toxicity associated with aggressive primary surgery is that of hypothalamic damage leading to morbid obesity, sleep and temperature dysregulation, electrolyte disturbances, cognitive and behavioural abnormalities. Given that radiotherapy is not associated with this risk upfront subtotal or partial/limited resection – and hence preserving the structural integrity of the hypothalamus – has become the preferred first surgical intervention over the last decade. In case of either substantial residual disease or progression after further follow-up, external beam radiotherapy has been given.

Modern stereotactic radiotherapy and radiosurgery techniques allow the dose to be tightly conformed to the target tumour, permitting structural sparing of adjacent critical structures such as the optic apparatus, hypothalamus, temporal lobes and pituitary gland. Fractionated stereotactic radiotherapy (FSRT), including using fixed beam arrangements, intensity-modulated radiotherapy or arcing techniques, combines the high precision of stereotactically guided radiation dose delivery with the possible biological advantages of conventional fractionation. FSRT allows the treatment of larger tumours and those sited close to or abutting the optic pathways.

This review aims to analyse the role of radiotherapy in the treatment of craniopharyngioma, focusing on the role of modern conformal techniques and their effect on morbidity and outcome.

Materials and Methods

A review of published articles was conducted using the MEDLINE, Current Contents and PubMed databases, based on the terms 'craniopharyngioma' alone and in combination with 'radiotherapy' [4,6,10,23–64], 'stereotactic radiotherapy' [32,38,50,51], 'radiosurgery', [31,33–35,39,40,53,54,56,57,59,60], 'intracavitary irradiation' [24,28,42,49,59], 'proton beam therapy' [46,47,62–64] and 'morbidity' [4,6,10,23–61].

Only studies published in English from January 1990 to May 2012 with at least 10 patients treated with radiotherapy were included; reviews, letters to the editor, commentaries, case reports and meeting abstracts were excluded. Duplicate reports regarding the same series of patients were excluded.

In total, 43 clinical studies [4,6,10,12,23–61] were identified, including a total of 2292 craniopharyngioma patients, of whom 1710 received irradiation with reported clinical outcomes.

The MEDLINE research identified only three prospective studies, mainly reporting on paediatric patients only (St Jude Children's Hospital [47], a German multicentre study [10] and Necker–Enfant Malades Hôpital [12]), with the remainder being mixed retrospective single-centre series. Moreover, three dosimetric studies were identified [62–64], which included 34 craniopharyngioma cases, previously treated with radiotherapy, aiming to compare proton versus conventional radiotherapy, reporting on dosimetric data, but not on clinical outcomes.

Results

Clinical Role of Radiotherapy

Radiotherapy has been clinically used for the management of inoperable and progressive craniopharyngioma for decades. Yet given the low incidence of craniopharyngioma and the lack of consistent multidisciplinary teams in the last century, management has been inconsistent and published series reflect this heterogeneity. In 1996, De Vile *et al.* [4] showed that the addition of irradiation was found to be a positive prognostic factor with a significant reduction in the risk of disease progression ($P = 0.004$). A 3 year follow-up multivariate analysis of treatment variables in the prospective German multicentre trial KRANIOPHARINGEOM 2000 [10] reported that irradiated patients had an 88% lower risk of recurrence/progression compared with patients treated without/before irradiation ($P < 0.001$).

Published long-term local control and survival rates after postoperative radiotherapy or primary radiotherapy alone seem similar to those obtained by radical surgery, as reported in comparative studies and in exclusive radiotherapy series (Table 1) and recently confirmed in a prognostic univariate analysis on 122 patients published from the University of California [61].

Particularly for patients undergoing limited surgery and postoperative radiotherapy, reported 10 year local control rates were 77–100% and 20 year overall survival 66–92% (Table 1).

When the primary surgery group comprised both gross and subtotal resections, local control after the addition of postoperative radiotherapy was significantly improved compared with surgery alone [27,37,41,52].

Several authors analysed clinical outcomes with respect to the timing of radiotherapy (immediate postoperative radiotherapy/primary radiotherapy alone versus radiotherapy at recurrence) and found no significant difference in progression-free survival (PFS) or overall survival (Table 1) [30,44,45,52].

The data do not suggest that patient age, excluding infants with craniopharyngioma, should influence the decision whether or not to use radiotherapy. Publications where results were stratified according to age group, no suggestion of significant differences in terms of local control [25,36,43–45,59] and no significant differences [43–45,59] or conflicting data [25,26,43] could be found. In two series which included only children or young adults treated with different treatment modalities, age was not found to have an effect on local recurrence [41,52] or mortality rates [41]. One series observed a higher risk of recurrence in younger