Interstitial Irradiation of Skull Base Tumours

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ABSTRACT: The rationale for interstitial irradiation of tumours in and around the skull base is reviewed, and the experience accumulated with pituitary adenomas, meningiomas, and chordomas is summarized. Intracystic irradiation for craniopharyngiomas is also reviewed.

RÉSUMÉ: Irradiation interstitielle des tumeurs de la base du crâne Nous passons en revue la raison d'être de l'irradiation interstitielle des tumeurs de la base du crâne ainsi que notre expérience avec les adénomes pituitaires, les méningiomes et les chordomes. Nous discutons aussi de l'emploi de l'irradiation intracyste dans le craniopharyngiome.

The majority of meningiomas, acoustic schwannomas, and pituitary adenomas are extra-arachnoid, histologically low grade neoplasms which can be totally extirpated using microsurgical techniques. A certain number, however, because of size, location, and/or invasive biological behaviour are not amenable to gross total removal. The surgical curability of craniopharyngiomas remains controversial,[1,2] and chordomas, although rare tumours, can seldom if ever be totally removed in spite of innovative and aggressive surgical procedures.[3]

Optimal surgical resection remains the initial treatment of choice for most tumours arising in and around the skull base. There is increasing evidence that adjuvant therapy with radiation can prevent or delay the recurrence of incompletely resected meningiomas,[4-6] chordomas,[7-9] and craniopharyngiomas.[10,2,11] For pituitary adenomas, external beam irradiation has long been recognized to be an effective adjunct to subtotal resection.[12] Excellent results have been obtained with irradiation in cases of endocrine-inactive pituitary adenomas[13], prolactinomas,[14,15] Cushing's disease,[16] and acromegaly.[17] A number of different radiation techniques have been utilized in treating pituitary adenomas, including parallel opposed fields, three-field techniques, and arc rotational therapy.

The relative radioresistance of slow-growing, mitotically inactive neoplasms such as meningioma, chordoma, craniopharyngioma and schwannoma underscores the need for high tumour radiation doses in order to achieve maximum benefit.[7] However, the brain's tolerance to radiation is finite, and the cure or sterilization of any tumour (malignant or low-grade) is beyond the capability of any radiation modality that affects not only the tumour but also adjacent brain and blood vessels. We must therefore attempt to improve upon conventional teletherapy, which cannot deliver the ionizing radiation in a sufficiently well focused volume to affect only the tumour and spare the brain.

There are a number of ways of improving the therapeutic ratio between tumour and surrounding brain: 1) focused gamma radiation from numerous narrow radiation beams that are stereotactically directed to a small target volume,[18] 2) accelerated charged particles which can be focused precisely using the Bragg peak technique,[19] and 3) implantation of radiation sources within a tumour volume (i.e. interstitial brachytherapy). In this paper, we review the experience with interstitial radiation in the treatment of pituitary adenomas, meningiomas, and chordomas, and intracystic irradiation of craniopharyngiomas.

Pituitary Adenoma

A pituitary adenoma was the first intracranial neoplasm to be treated by brachytherapy; in 1911, after a trans-sphenoidal operation on a young woman with acromegaly, Hirsh inserted a radium-loaded probe through the nasal cavity into the sella turcica.[20] Other early experiences included the free-hand placement of multiple 1 mCi radon seeds into pituitary tumours, via frontal craniotomy;[21] this author stated "the results obtained are not discouraging". Since that time, an extensive experience with interstitial irradiation of pituitary adenomas has accrued.[22-25] A variety of radioisotopes have been used, but the most popular have been ^{32}P, ^{90}Y, ^{198}Au, and ^{192}Ir. Since the 1950's, the majority of cases have been done stereotactically.

Endocrinological results have been encouraging, particularly in acromegaly. Of 16 acromegalic patients treated with ^{90}Y implantation, half experienced improvement of the acrome-

galic features and headaches, while maintaining normal pituitary function.[26] In a series of patients treated with [198]Au and ^{90}Y, 60% obtained improvement of the acromegalic features, although 40% ultimately required endocrine replacement therapy.[27] In another series of 80 patients implanted between 1958 and 1967, 53% showed clinical improvement; in 45% of patients glucose tolerance tests became normal.[28] However, 59% of these patients continued to have growth hormone levels above 10 ng/ml. In his large experience, Mundinger found clinical improvement in 96% of patients with endocrine-inactive adenomas, 92% of patients with Cushing's disease, and 76% of acromegalics.[24]

Visual impairment has also improved following brachytherapy of pituitary adenomas. In one large series, 87% of patients had stabilization or improvement of vision; patients treated for endocrine-inactive adenomas did slightly better than acromegalic patients.[24,29]

Among the complications of this technique are cranial nerve palsies, reported by Molinatti et al (1962)[26] in 13%, and diabetes insipidus, seen in 38% of their cases. Other complications encountered include CSF rhinorrhea, pituitary abscess, and visual impairment.[27]

Stereotactic gamma radiosurgery has also been employed successfully in treating endocrine-inactive adenomas and prolactinomas[31] and Cushing's disease.[32] Bragg peak proton radiation has similarly been utilized with excellent results in acromegaly, Cushing's disease, prolactinoma and endocrine-inactive pituitary adenomas[33] treatment with alpha particles (helium ions) has also been used since 1957 in a series of acromegalics.[34]

In summary, interstitial irradiation of pituitary adenomas has proved effective in controlling the endocrinopathy in over half of patients with acromegaly and Cushing's disease; experience with prolactinomas has been less extensive, due to the present high rate of surgical curability, and effective drug therapy with bromocriptine. Visual symptoms and signs can be corrected or stabilized in most patients. Interstitial brachytherapy of pituitary adenomas is at present more popular in Europe than it is in North America.

Craniopharyngioma

Interstitial irradiation has been used to control recurrent cyst formation in craniopharyngiomas by introducing radioisotopes into the cyst cavity. This technique was pioneered in the early 1950's and applied stereotactically by Leksell and Liden (1952).[35] The initial agent used was phosphorus-32[36,37] but other isotopes have been introduced (Table 1). The ideal isotope for intracystic therapy would have a half-life of several days, beta energy low enough to ensure minimal tissue penetration, and no or minimal gamma emission. Yttrium-90 is probably the

most ideal isotope available at present,[38,39,40,41] but recent work shows rhenium-186 to be promising.[25,42,43] Advances in disimetry and methods of administration have also rekindled interest in gold-198 for intracystic irradiation.[40,44]

Intracystic isotope treatment is limited to those craniopharyngiomas with a medium to large thin-walled cystic component; intracystic therapy will have no beneficial effect on solid portions of tumour, or on thick or calcified cyst walls. The optimum dose to cause collapse of a cyst is yet to be determined; Bond et al concluded that the effective intracystic dose of [198]Au is 10-15 mCi of colloidal gold.[45] Another study with ^{32}P and ^{90}Y determined that the dose delivered to the cyst surface must exceed 100,000 rad to collapse the cyst.[46] The method of calculation of the cyst wall dose depends on whether one assumes a uniform distribution of the colloidal isotope throughout the cyst volume, or uniform deposition of the isotope along the inner wall of the cyst, as demonstrated in Figure 1.[36,40]

Results of intracystic isotope therapy have been encouraging. Kobayashi et al injected [198]Au or ^{32}P via an Ommaya reservoir into the cyst in eight patients. The cyst volumes ranged from 5 to 120 mL, and cyst wall thickness varied from 0.5 to 7.0 mm. Isotope dosages were 10-20 mCi of [198]Au and 2.3 - 5.0 mCi of ^{32}P; cyst wall doses were 6,000 - 100,000 rad. Results were considered excellent in six cases, and good in two, with a mean follow-up of 71 months. Only one complication was reported, an oculomotor nerve palsy in the patient with an accumulated cyst wall dose of 100,000 rad.

In summary, intracystic irradiation remains an effective and relatively safe means of controlling craniopharyngioma cysts; this technique might be particularly valuable in a patient who has received a course of conventional external beam radiation and develops a recurrent symptomatic cyst refractory to surgical management. Solid craniopharyngiomas have not been considered amenable to interstitial irradiation, although a limited experience using ^{125}I and ^{192}Ir implants has been reported.[47] As
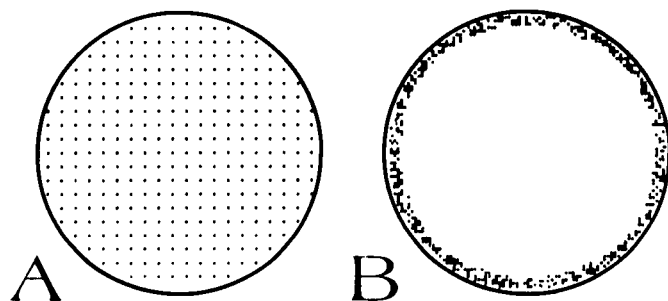

Figure 1 — Models of distribution of colloidal radioisotope in a cystic tumor, for mathematical calculations of dose to cyst wall. A. uniform suspension, B. layering-out along cyst wall.

Table 1: Radioisotopes used for Intracystic Irradiation

Isotope	Half-life (days)	Maximum beta energy (MeV)	Mean beta energy (MeV)	Beta half-value in tissue (mm)	Gamma energy (MeV)
Gold-198 ([198]Au)	2.7	1.37	0.32	0.4	0.41
Phosphorus-32 (^{32}P)	14.3	1.71	0.69	0.8	—
Rhenium-186 ([186]Re)	3.7	1.07	0.36	0.4	0.14
Yttrium-90 (^{90}Y)	2.7	2.27	0.93	1.1	—

well, stereotactic gamma radiosurgery has been tried in a series of nine patients, eight of whom had predominantly solid tumours.[30]

Meningioma

Experience with interstitial irradiation of meningiomas has been very limited. The first radioactive implantation of a meningioma was performed around 1918 by Frazier who reported that his results with "endotheliomata" were more encouraging than with gliomas;[48] the largest experience has been reported by Mundinger.[49,47] Most of the cases were implanted either because of unfavourable pathology (angioblastic or malignant features) or because of incomplete surgical resection, and the isotope used was either ^{192}Ir or ^{125}I, implanted intraoperatively. It was Mundinger's impression that brachytherapy caused the tumours to shrink and become better demarcated (as documented at repeat craniotomy).

Currently, one of the authors (PHG), is conducting a clinical trial of reirradiation of recurrent tumours of the skull base with interstitially implanted ^{125}I sources. Since March 1981, seven patients with recurrent, life-threatening, inoperable, basal meningeal tumours have been treated (two meningiomas, three malignant meningiomas, two meningeal sarcomas). All patients had previously received maximal surgical resection and external radiation (5,000 - 6,000 rad). Five patients were treated with multiple (9 to 36) permanent, low-activity seeds implanted at open craniotomy; total doses delivered to the periphery of the lesions were 8,000 to 15,000 rad. Two patients with recurrent malignant meningiomas of the falx were stereotactically implanted with removable high-activity ^{125}I sources to produce peripheral tumour doses of 5,000 and 11,000 rad. Of the seven patients, two developed regrowth of the tumour outside the treated volume, and one other deteriorated from radiation necrosis one year following implant. The other four, and the patient operated on for focal radiation necrosis have remained stable during a mean follow-up of 24 months after brachytherapy. As part of the same trial, two recurrent meningeal neoplasms have been treated with charged particles (helium and neon); one patient developed radiation necrosis at 16 months and the other had tumour recurrence at 19 months.

Chordoma

Experience with interstitial irradiation of chordomas is even less extensive than with meningiomas. The first reported chordoma treated by this method was in Montreal in 1938.[50] A chordoma extending into the nasopharynx was implanted with six 1 mCi radon seeds combined with 4,000 rad external radiation. A few months later, four more 1 mCi radon seeds were implanted, ultimately resulting in the shrinkage of the nasopharyngeal portion of the tumour to one fifth its original size. The first stereotactic implantation of an intracranial chordoma was performed following stereotactic biopsy of a clivus lesion in a young man with headaches and cranial nerve palsies.[51] Five ^{90}Y seeds (each 5 - 6 mCi) were deposited in the tumour and at follow-up nine months later, the patient was symptom free. Intraoperative implantation of permanent radioisotope sources has also been employed as adjuvant therapy in a few cases of spinal chordoma.[52]

In the current trial cited above, one of the authors (PHG) has implanted five recurrent clivus chordomas with multiple permanent, low-activity (0.5 mCi) iodine-125 sources to deliver estimated peripheral tumour doses of 5,000 - 15,000 rad. Two patients developed tumour recurrence 19 and 28 months after treatment; two others died of other causes but their tumours were not progressing, and one patient died early of progressive tumour growth outside the irradiated volume. Recurrent clivus chordomas have also been treated with helium ion irradiation[53] and protons.[8]

Acoustic Schwannoma and other tumours

In 1914, Frazier implanted 85 mg of radium into an "inoperable tumour of the pontile angle", and then removed the radium 15 hours later; this may represent the first implantation of an acoustic schwannoma.[48] Since then, there has been little interest in interstitial irradiation of these tumours, but stereotactic radiosurgery of these lesions with focused gamma beams[54,55] has recently been reported; particle beam therapy has also been tried.[56] In the series reported by Noren et al, 14 acoustic schwannomas were given doses up to 125,000 rad. The results were encouraging in that eight (57%) had radiologically documented decrease in tumour size; one patient experienced improvement in auditory acuity. Cranial nerve complications were significant: two patients had trigeminal nerve, and five had facial nerve dysfunction. Barcia-Salorio et al reported 16 patients who received tumour doses of 72,000 - 90,000 rad. Reduction in tumour size was documented radiologically in six (38%), the response being better in patients with tumours smaller than 3 cm diameter. Only one side effect occurred — a case of trigeminal neuralgia which responded to medication.

Other low-grade or histologically benign tumours have occasionally been implanted with radioisotopes. These include hemangioblastoma,[57] choroid plexus papilloma of the fourth ventricle,[58] epidermoid,[59] germinomas,[60] and teratoma.[25] As well, intra operative ^{125}I implants of the skull base have been employed to control invasive or recurrent oropharyngeal and parotid malignancies.[61]

DISCUSSION

A dose-response relationship has been demonstrated in conventional teletherapy of malignant gliomas;[62] cohorts of patients who received higher doses of radiation had longer median survivals than cohorts of patients who received smaller doses. There may also be a dose-effect response in radiotherapy of certain low-grade skull base tumours.[7,63] It seems desirable to deliver as large a dose as is deemed safe to the tumour volume in order to prevent or delay recurrence, and this goal may be achievable using interstitial radioisotope implants. Considerable experience has now accrued with interstitial brachytherapy of gliomas.[49,64,25,47,65,66]

Interstitial brachytherapy provides an enhanced therapeutic ratio between tumour and normal tissue, because of the favourable radiobiology of low dose-rate radiation, and the radiophysics of intratumoral location of the radioactive source.[64,65] Low dose-rate radiation from interstitial implants (<10 rad/minute as compared to 200 rad/minute in conventional cobalt teletherapy) is better tolerated by normal than neoplastic tissue because the ongoing repair of sublethal radiation damage is performed more effectively by normal than neoplastic cells.[67] Furthermore, the inverse-square law which applies to any point source of radiant energy, and tissue attenuation of radiation, both cause a rapid fall-off of radiation dose outside the target volume; therefore, a radioactive source placed directly into a tumour can deliver a

maximum therapeutic dose to the tumour, with relative sparing of the surrounding normal tissues. This normal tissue sparing is of great importance, since the major normal-tissue complications of therapeutic irradiation appear to be dose-related.[68,69]

What conclusions can be drawn from the experience accumulated with interstitial irradiation of low grade neoplasms, in and around the skull base? For pituitary adenomas, both endocrine-active and -inactive, this modality is effective and has an acceptable complication rate in most series. However, due to advances in microneurosurgical techniques, improved drug therapies, and the excellent results with conventional external beam radiation, the role of interstitial irradiation in the treatment of pituitary adenomas is uncertain. Perhaps it is most appropriate in invasive, aggressive adenomas which recur after surgery and external beam teletherapy.

For craniopharyngiomas, there is a definite role for the administration of intracystic radioisotopes for control of recurrent cysts which are compressing neural structures, and are refractory to surgery and external irradiation.

Evaluation of interstitial irradiation in the treatment of basal meningiomas and chordomas is difficult because of the somewhat variable and unpredictable biological behaviour of these lesions. When a meningioma or chordoma recurs after maximal surgical removal and external irradiation, the options for treatment are limited. Repeated surgical decompression becomes difficult and dangerous with progressive distortion of surgical anatomy, and further external beam teletherapy carries a high risk of damage to normal tissue. Interstitial radiation provides an alternative treatment. However, during surgical exposure of these difficult tumours, the surgeon cannot predict the exact tumour volume and therefore correctly place the radioactive sources. Dosimetry planning can be greatly improved by stereotactically placing high-activity removable implants into a CT-defined target volume, but the skull base area is relatively inaccessible to the stereotactic surgeon. If inadequate doses are delivered to the entire tumour volume, tumour recurrence will likely occur; on the other hand, if normal tissue is included in the target volume, serious radiation necrosis may ensue.[68,66] The consequences of damage to normal tissue in the skull base region are greater than in the supratentorial compartment because of the presence of many large arteries and cranial nerves. The indications and methods of interstitial irradiation for recurrent basal tumours therefore remain unresolved, but the theoretical and practical advantages of this technique will hopefully result in more extensive clinical trials which should help to define them more precisely.

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