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Successful diffusible brachytherapy (dBT) of a progressive low-grade astrocytoma using the locally injected peptidic vector and somatostatin analogue [^{90}Y]-DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC)

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Summary

We present the therapeutic effect of diffusible brachytherapy (dBT), an innovative approach for the management of symptomatic low grade gliomas [1]. This protocol uses a radiolabelled small diffusible peptidic vector which is a somatostatin analogue to target somatostatin type 2 (sst–2) receptors. The stable radioconjugate [^{90}Y]-DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC) is repeatedly injected via catheters placed into the resection cavity or into tumour nodules. We report on the four year follow-up after initiation of dBT to treat progressive disease in a patient with a complex eleven year history of fibrillary low-grade astrocytoma. The radiopharmakon was not only locally injected into the resection cavity following debulking surgery, but also administered by slow infusion technique to target recurrent and infiltrative tumour zones in the subventricular region around the inferior and posterior horns.

In conclusion, peptidic vector based dBT was found to be safe, of mild and transitory toxicity, and effective in long-term tumour control.

Key words: low-grade glioma; diffusible brachytherapy; radiolabelled peptides; DOTATOC

Introduction

The natural course of a low-grade glioma (LGG) is that of an indolent and slowly growing infiltrative tumour that in some patients may persist for more than a decade, while other patients with similar histologies, for mostly unknown reasons, fare worse and die within a few years. Low grade gliomas include three prognostically distinct histological subtypes: the fibrillary and the gemistocytic variants of astrocytomas, the oligodendrogliomas and mixed oligoastrocytomas [2]. Tumours of oligodendrocytic differentiation are genetically distinct and carry a better prognosis. There is also evidence that oligodendrogliomas are more sensitive to chemotherapy than their astrocytic counterparts [3]. Patients with seizures only, aged less than 40 years, without enhancing on neuroimaging and with gross total resection are considered prognostically favourable, all others are considered unfavourable in outcome.

The variable biologic behaviour of these tumours makes the value and the timing of treatment modalities a matter of debate. Most reported series are retrospective and suffer from numerous weaknesses, e.g. small patient numbers, various imaging techniques (CT vs MRI), no postoperative imaging to discern the degree of surgical resection, short clinical follow-up, and lack of multivariate analysis. Due to the infiltrative nature of glioma cells even extended surgery is not curative. There is one randomised trial from the EORTC which compared external radiation therapy (RT) postoperatively to observation only until clinical progression in LGG. No survival advantage for early conventional RT was observed, and progression free survival was slightly prolonged [4]. How-

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ever, there might be irreversible long-term side effects from RT, mainly leukoencephalopathy and cognitive dysfunction [5]. The median survival time in adults with LGG is approximately 4 to 7 years, and the 10 year survival rate is usually less than 50% [6]. Most patients die from progression of their disease to a high grade lesion. Neurological deficits or progressive lesions on imaging usually lead to active therapeutic procedures. New nontoxic treatment options for symptomatic patients are urgently needed especially for the prevalent non-chemosensitive low-grade glioma of astrocytic lineage.

Low-grade tumours frequently express high affinity somatostatin receptor type 2 as described by Reubi et al. [7] and other researchers [8]. Receptor targeting therefore promises to be an attractive therapeutic approach. Locoregional application of a radiolabelled peptidic vector circumvents the intact blood brain barrier which seriously impairs uptake of systemically administered vectors [1, 9]. Furthermore, small therapeutic molecules are likely to target even remote cells by diffusion. We have recently published the first results of a biologically modified form of brachytherapy that uses a small diffusible peptidic vector to target sst-2 receptor positive gliomas [1]. The peptidic vector (somatostatin) can be labelled with the beta-emitting radioisotope ^{90}Yttrium, resulting in a stable chelator complex (DOTATOC) [10, 11]. DOTATOC specifically binds to sst-2 receptors in the low nanomolar range. The beta-emitting radioisotope ^{90}Yttrium delivers high energy at a low-dose rate with a mean range of 3 to 5 mm, and is therefore well suited for clinical applications. Systemic toxicity could not be observed so far in our locally treated patients. We report on an eleven year follow-up including the last four years after having initiated our brachytherapy protocol.

Case report

A male patient born in 1967 presented in 1990 with a grand mal seizure. A MRI scan revealed a mass lesion adjacent to the right ventricle (figure 1, A). One year later, biopsy was performed as the tumour was growing, disclosing a fibrillary astrocytoma WHO grade II. The clinical course was uneventful until three years later, when the patient presented with a slight left-sided hemiparesis, caused by an enlarged tumour with cystic components. At another institution ^{125}Iodine-seeds were implanted into the solid parts of the tumour (radiation dose 80 Gy). Nevertheless, the cysts became more symptomatic requiring insertion of a Rickham reservoir to drain the largest cyst located in the right frontal lobe (figure 1, B). The following two years repetitive aspirations at biweekly intervals became mandatory to decrease local pressure due to continuous production of cyst fluid. In 1997 the patient presented with frequent seizures and impaired visual fields. A cystic lesion was seen to compress the optic chiasm which again was drained by an Ommaya reservoir. Further clinical deterioration led us to stereotactically insert a port-a-cath device into the largest cyst to initiate intracystic brachytherapy (dBT). Fluid production (25–30 ml in two weeks) completely ceased after injection of 2×5 mCi [^{90}Y]-DOTATOC. Three months later the solid parts of the tumour exerted an increasing mass effect and were amenable to subtotal resection (figure 1, C and D). Histology remained unchanged to the initial diagnosis (figure 1, E). Another injection of [^{90}Y]-DOTATOC was administered four months after the patient had presented with a grand mal seizure. After injection of ^{111}In/^{90}Y–DOTATOC the diffusion of the compound could be made visible on a cranial scintigraphy (figure 1, F). Thereafter the patient went well and was able to complete his PhD thesis without much impairment. One year after subtotal resection, the tumour again progressed in less than a month's period in the periventricular zone of the right-sided inferior and posterior horns (figure 1, G and H) accompanied by clinical deterioration. No resection cavity could be created in this unresectable new lesion. Therefore, two catheters were stereotactically placed directly adjacent to the nodular structure at the subventricular subependyma. [^{90}Y]-DOTATOC was administered by slow infusion over a one hour period. This intervention halted tumour progression. Seven months later, ventriculo-peritoneal shunting became necessary to relieve hydrocephalus male-resorptivus, believed to be a consequence of tumour cell decay, cell debris obstructing CSF resorption. Two more injections of [^{90}Y]-DOTATOC followed to prevent another recurrence (table 1). No acute side effects occurred during these five brachytherapy sessions using steroids to treat perifocal oedema which lasted for several months. An obstructed ventriculo-peritoneal shunt had to be exchanged to resolve hydrocephalus male-resorptivus in December 1999. Since then no further interventions were necessary, no more seizures occurred and steroids could be completely withdrawn. The patient is now working part time as an academic. He is moderately disabled by his left-sided hemiparesis and the persisting visual deficits. The good long-term result is underlined by a Karnofsky performance status of 80%. The patient refused to undergo a neuropsychological assessment. So far no focal or whole brain radiotoxicity could be observed clinically or on MRI scans (figure I and K) four years after initial dBT and almost two years after the last locally administered dBT. The cumulative injected activity of peptide-bound ^{90}Yttrium amounts to 154 mCi delivered in five fractions (table 1).

Table 1

Activity and dose of five [^{90}Y]-DOTATOC applications.

therapy (date)	activity (mCi)	dose (Gy)[a]
5/97	10	25
11/97	15	22
9/98	30[b]	29
4/99	39	19
9/99	2×30[c]	58
total	154	153

[a] Dosimetry (absorbed dose calculations): estimates of the effective radiation dose are a function of the absorbed energy divided by the treated volume. Regions of interest were defined on scintigraphic images taken at 0, 24, 48 and 72 h after injection, and deposited energy was calculated by the integral of the activity curve. Therapeutic volume was calculated by defining the tumour extensions on the MRI acquired prior to dBT using the ellipsoid formula adding a 1cm enhancing rim that surrounds the resection cavity and residual tumour.

[b] application through slow infusion

[c] two fractions, one week interval

Figure 1

(A) The initial axial T_1-weighted MRI (with Gadolinium) is shown with an irregular enhancing mass lesion in the right periventricular region without oedema and mass effect.

(B) A large secretory cyst in the frontal lobe (with a catheter in situ) is shown which shrank after 10mCi ^{90}Y-DOTATOC (not shown).

(C) A coronal T_1-MRI shows an irregular solid tumour mass, in addition perifocal cysts and oedema in the right periventricular zone causing prominent mass effect with subfalcial herniation to the left.

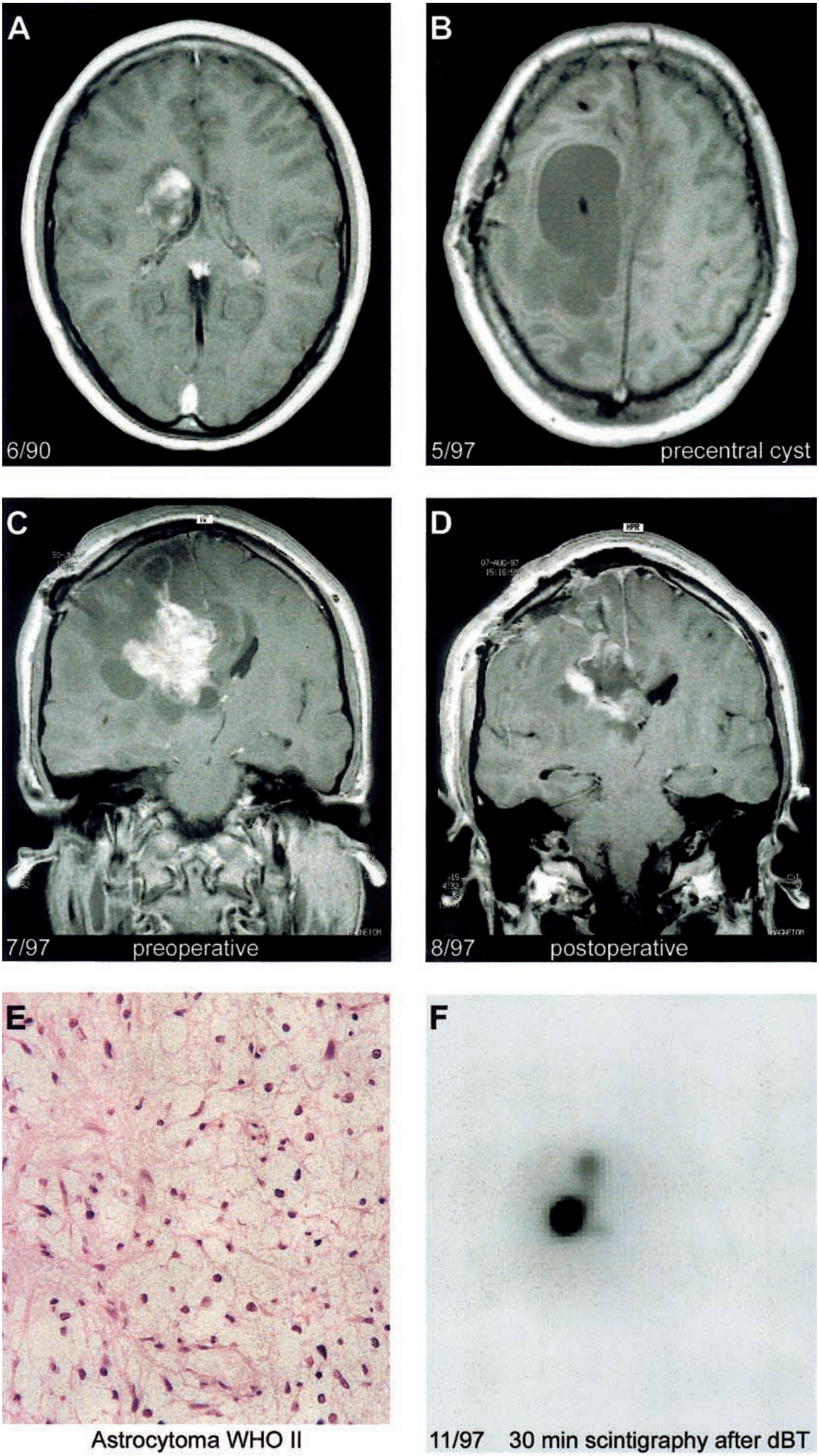
(D) Postoperative imaging displays a marked reduction of the enhancing tumour mass.

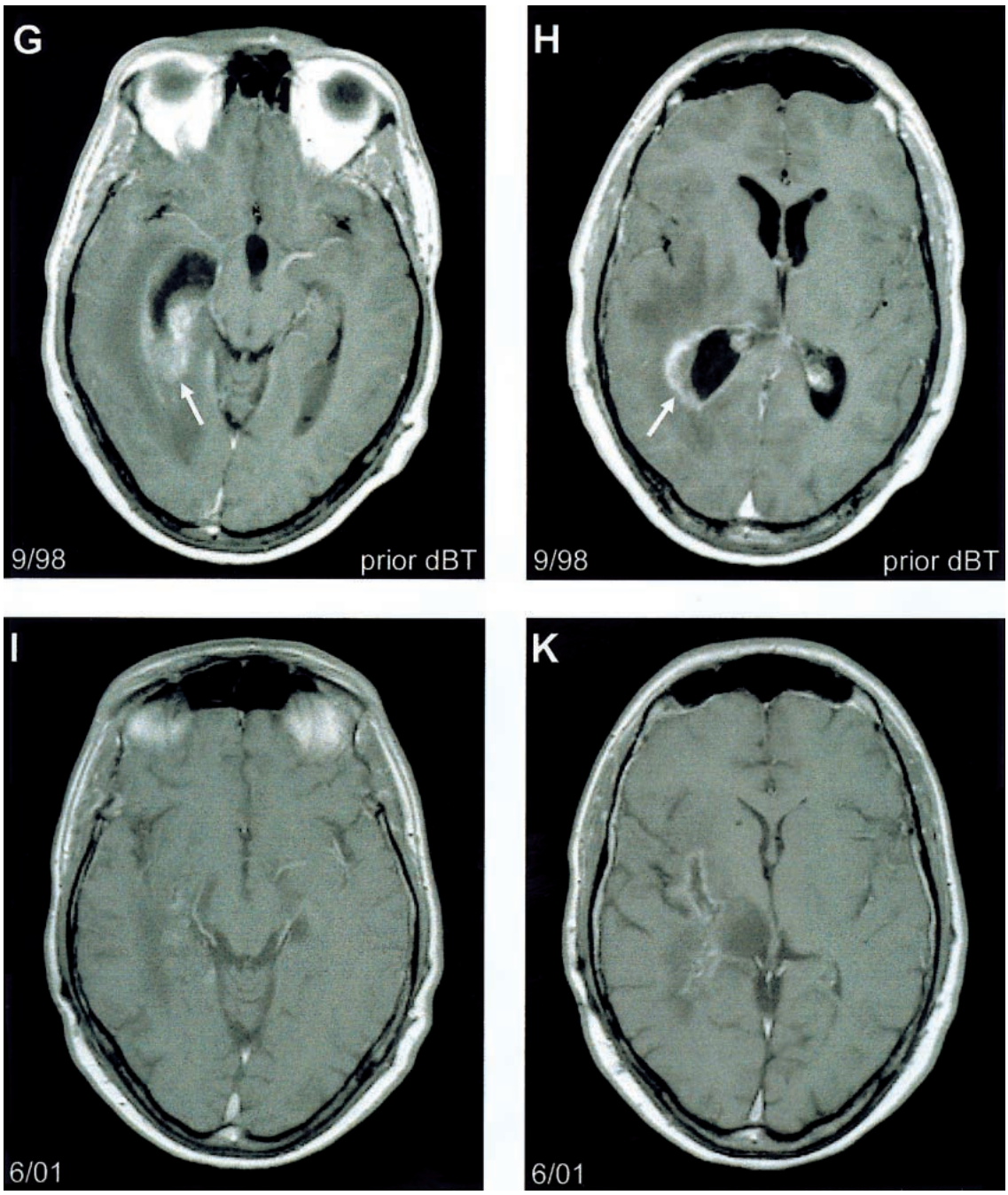
(E) The histology disclosed a fibrillary astrocytoma WHO II.

(F) Scintigraphy 30 min after dBT depicts rapid distribution of the radioconjugate. Since Yttrium-90 is a pure beta emitter the diagnostic radionuclide Indium-111 was admixed for imaging.

(G, H) The two axial MRI slices (with Gadolinium) show a heterogeneous enhancing subependymal mass along the posterior and inferior horns (arrows) on the right with perifocal oedema.

(I, K) Twenty two months later, corresponding slices with a slightly different angulation show a normalized ventricular system and faint enhancement deeply within the temporo-occipital white matter extending into the basal ganglia. Residual tumour cannot be differentiated from post-interventional changes.





Discussion

Prognosis of a low-grade glioma seems largely determined by the inherent biology of the tumour and the patient's age at diagnosis. General management of these tumours remains controversial since no treatment modality so far offers cure to this infiltrative disease which harbours the potential to transform into more malignant variants in more than 50% of cases. The fundamental question is whether upfront therapy without long-term adverse effects is of any benefit versus a wait and see strategy or intervention in symptomatic patients only. The extent of surgery seems to play a role in prognosis of LGG but due to the infiltrative nature of glioma cells and due to eloquent tumour location, surgical procedures are always incomplete. Conventional radiation therapy is not well established in LGG, which can lead to significant long-term cognitive dysfunction in one third of the patients [12]. Similarly, chemotherapy is not generally advocated in LGG.

This young patient presented with an indolent LGG which did not demand any intervention at the time of diagnosis. Four years later the tumour enlarged and became symptomatic. After the implantation of ^{125}I- seeds at another institution, he experienced three years of repetitive interventions with concomitant clinical deterioration and frequent seizures because of cystic transformation of the tumour. In 1996, [^{90}Y]-DOTATOC became available at our institution which we administered

through port-a-cath devices in five fractions. The calculated dose deposited by the peptidic vector was 154 Gy, total dose was 233 Gy when considering ^{125}I- seeds treatment. Dosimetry and radiation biology of beta-emitting radionuclides is not well understood and might significantly differ from conventional RT since the upper level of the standard external dose of 60 Gy is clearly transgressed. Since the last intervention almost two years ago, the patient improved steadily and is now able to work part time. He is off steroids, and without seizures for more than one year. This favourable outcome would not have been possible with surgery alone. After conventional external radiation therapy long term cognitive side effects might manifest [5], but have not occurred so far in this locoregional [^{90}Y]-DOTATOC protocol. The only toxicity observed in this patient was secondary perifocal oedema which lasted for nearly six months but could be controlled with oral steroids. We therefore propose regionally delivered dBT as a novel therapeutic option to control progressive sst-2 receptor positive LGG. Future controlled trials will ask whether upfront postoperative dBT has any impact on time to disease progression, and if it can be delivered without long-term side effects. The effect observed in this case and in additional patients treated with this approach allows the initiation of a prospective study to evaluate the contribution of this treatment modality to disease management. Theoretically, dBT after extensive surgical debulking would have a number of advantages such as a lower tumour burden, a lesser degree of tumour cells infiltrating normal brain tissue, and a better Karnofsky performance status. In contrast to external radiation therapy, dBT intervention can be repeated many times wherever a new lesion might arise. Theoretically, biologically targeted radiotherapy could be curative if all tumour cells were covered with a tumour specific target sparing normal cells. To this end, more specific radioconjugates have to be developed with a narrower range of energy dissipation by using low energy beta and alpha emitting radionuclides limiting neuro-toxicity.

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References

1 Merlo A, Hausmann O, Wasner M, Steiner P, Otte A, Jermann E, et al. Locoregional regulatory peptide receptor targeting with the diffusible somatostatin analogue ^{90}Y-labelled DOTA^{0}-D-Phe^{1}-Tyr^{3}-octreotide (DOTATOC): a pilot study in human gliomas. Clin Cancer Res 1999;5:1025–33.
2 Kleihues P, Cavanee W. WHO Classification of tumours, pathology and genetics, tumours of the nervous system, IARC Press, Lyon 2000.
3 Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, et al. Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendroglioma. J Natl Cancer Inst 1998;90: 1473–9.
4 Karim AB, Cornu P, Bleehen N, Afra O, DeWitte S, Schraub F, et al. Immediate postoperative radiotherapy in low grade glioma improves progression free survival but not overall survival: preliminary results of an EORTC/ MRC randomized phase III study [abstract]. Proc Am Soc Clin Oncol 1998;17:400a.
5 Surma-aho O, Niemelä M, Vilkki J, Kouri M, Brander A, Salonen O, et al. Adverse long term effects of brain radiotherapy in adult low grade glioma patients. Neurology 2001;56:1285–90.
6 McCormack B, Miller D, Budzilovich G, Voorhees G, Ransohoff J. Treatment and survival of low grade astrocytoma in adults 1977–1988. Neurosurgery 1992;31:636–42.
7 Reubi J-C, Horisberger U, Lang W, Koper J, Braakman R, Lamberts S. Coincidence of EGF receptors and somtatostatin receptors in meningeomas but inverse, differentiation dependent relationship in glial tumors. Am J Pathol. 1989;134:337–44.
8 Held-Feindt J, Kirsch B, Mentlein R. Molecular analysis of the somatostatin receptor subtype 2 in human glioma cells. Mol Brain Res 1999;64:101–7.
9 Merlo A, Jermann E, Hausmann O, Chiquet-Ehrismann R, Probst A, et al. Biodistribution of ^{111}In–labelled SCN-BZ-DTPA-BC-2 MAB following locoregional injection into glioblastoma. Int J Cancer 1997;71: 810–16.
10 Otte A, Jermann E, Béhé M, Götze M, Bucher HC, Roser HW, et al. DOTATOC, a powerful new tool for receptor mediated radionuclide therapy. Eur J Nucl Med 1997;24:792–5.
11 Otte A, Mueller–Brand J, Dellas S, Nitzsche EU, Herrmann R, Maecke HR. Yttrium^{90} labelled somatostatin-analogue for cancer treatment. Lancet 1998;351:417–8.
12 Olson JD, Riedel E, DeAngelis LM. Long-term outcome of low-grade oligodendroglioma and mixed glioma. Neurology 2000:54;1442–8.

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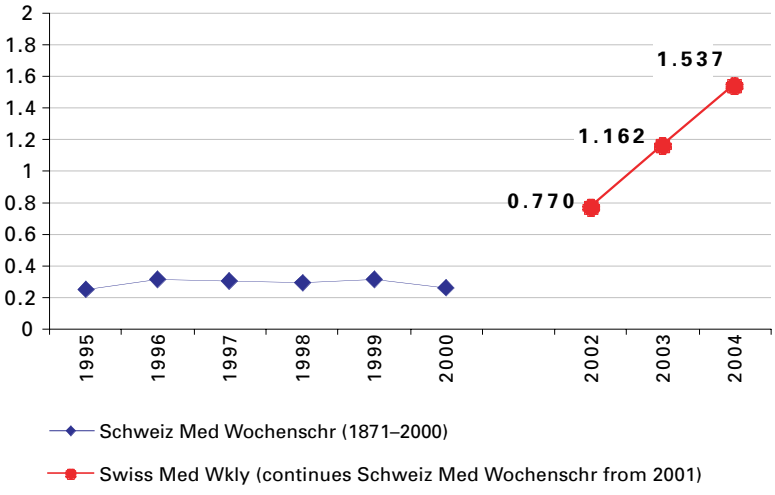

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