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Management of skull base chordoma

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Abstract Two management modalities appear to be important in treating skull base chordomas: surgery and radiation therapy. Radical resection of lesions of the distal sacrum (S3-S5) and coccyx may be curative, as total removal is often achieved. In contrast, complete resection of chordomas of the base of the skull is rarely successful because of the inability to achieve a true complete surgical resection. On the other hand, treatment of skull base chordomas by radiation therapy alone is often difficult owing to the large size of the lesion and the dose limitation imposed by the sensitivity of the adjacent structures. Local relapse is

the predominant type of treatment failure of skull base chordoma. Skull base surgery and radiation therapy have significantly improved over the last 20 years. The following papers review the most significant recent analyses of therapeutic options in treating skull base chordomas. It seems that the combination of aggressive surgery followed by combined proton-photon radiation therapy offers the best chance of long-term local control to patients harboring cranial chordomas.

Key words Chordomas · Outcome · Proton therapy · Radiotherapy · Skull base surgery

Introduction

Chordomas, which are more common in people in their twenties and thirties, are believed to develop from remnants of the primitive notochord that forms and dissolves early in fetal development. They typically occur anywhere in the axial skeleton, but are most frequently located at either end, the clivus rostrally and the sacrum caudally. Skull base chordomas present clinically when their growth in the sphenocciput results in cranial nerve compression or an obvious nasopharyngeal mass. Skull base chordomas are difficult to treat

because of their proximity to vital neurovascular structures (brain stem, temporal lobes, optic nerves and chiasm, pituitary gland, cavernous sinus, circle of Willis' vessels) and because of their propensity to diffusely invade the skull base and the structures that go through it. Skull base chordomas are not always amenable to complete surgical resection, for the origin of the tumor from the bone at the base of the skull often precludes total removal. Surgery and radiation therapy (RT) have been the mainstay of treatment of skull base chordomas, but never-

theless they have for years posed a formidable management challenge owing to their critical location, local aggressive nature, and high recurrence rate, even after radical surgical removal. In the last 15–20 years, there have been significant improvements in surgical and radiotherapeutic techniques. A critical analysis of the papers published in the last 10 years makes a powerful case for the use of a multimodality therapy using surgery and the newest radiotherapeutic techniques for the treatment of skull base chordomas.

[1] Skull base chordomas: a management challenge

J Neurosurg (1997) 86:182–189

Information. Twenty-five patients (15 female and 10 male) with skull base chordomas were treated from 1990 to 1996 at three different institutions. The mean age was 38.4 years (range 8–61). Diplopia was the most common presenting symptom (64%) followed by headache (32%), lower cranial nerve palsy (28%), facial pain and vertigo (16%), decrease in vision, nasopharyngeal mass, gait disturbance, and hearing loss (12%). Based on their skull base involvement, tumors were classified as grade I–III. Grade I tumors involve a solitary anatomical skull base area (0 cases), grade II tumors (16 cases) involve two or more contiguous skull base areas but may be removed through a single skull base approach, while grade III tumors (3 cases) involve several skull base compartments and can only be removed using two or more skull base approaches. The remaining 6 patients had recurrent tumors and were not graded.

Twenty-three patients underwent 33 surgical procedures by the senior author and were studied in detail. The surgical approaches used were the transmaxillary (8 patients), the cranio-orbitozygomatic (6 patients), the extended transsphenoidal (5 patients), the transcondylar (4 patients), the zygomatic-extended middle fossa (4 patients), and the transbasal (1 patient). The extent of tumor removal was based on postoperative magnetic resonance imaging (MRI). Ten patients (43.5%) had radical tumor removal (absence of residual tumor or the presence of a small questionable area); 11 patients (47.8%) had subtotal tumor removal (less than 10% of residual tumor); while 2 patients (8.7%) had partial tumor removal (more than 10% of residual tumor). One patient (4%) died postoperatively owing to a brain stem infarct, while 2 patients had new and permanent postoperative neurological deficits (visual field defect and III cranial nerve palsy, respectively). Various minor or temporary surgical complications were observed in 12 patients (52%) and included meningitis with or without cerebrospinal fluid (CSF) leak, oronasal fistula, facial nerve numbness or palsy, abducens paresis, dislodged tooth, and temporal muscle atrophy. Seventeen patients underwent postoperative proton-photon RT to a dose of between 60 and 72 cobalt Gray equivalent (CGE), and 1 patient was planned to have it. Two patients had already had RT prior to surgery, while 3 patients did not have postoperative RT for unstated reasons.

Twenty-one patients were followed for longer than 3 months with a mean follow-up period of 25.4 months. Fifteen of them (71.4%) had no evidence of disease, 1 (4.8%) had died of pancreatic cancer with no evidence of chordoma, 2 (9.5%) had died with recurrent tumor, and 3 (14.3%) were alive with recurrent tumor. The mean time to tumor recurrence in these last 5 patients was 14.4 months. Three patients treated with postoperative proton-photon RT (72 CGE) had clinical and radiological evidence of radiation necrosis in the temporal lobe and temporal bone (1 patient), brain stem (1 patient), and brain stem and temporal lobe (1 patient).

Analysis. This paper shows that an experienced skull base surgeon may aggressively remove skull base chordomas with low mortality (4%).

The follow-up time is short (2.4 months) considering the usual slow evolution of these neoplasms. However, it is interesting to point out that 16 of the 21 patients followed for more than 3 months showed no evidence of disease, while only 10 patients had had radical surgical removal as demonstrated by early postoperative MRI. Even assuming that all of these 10 patients remained free of disease at the stated follow-up, there are still 6 out of 13 patients (46%) who had subtotal or partial removal on early postoperative imaging whose tumor eventually disappeared on follow-up MRI, probably as a result of postoperative RT. It would be instructive to know more about these patients, for example the amount of residual tumor, the exact RT doses, the amount of surgical complications and the reasons for a subtotal or partial tumor removal.

[2] Chordomas and chondrosarcomas of the cranial base: results and follow-up of 60 patients

Neurosurgery (1995) 36:887–897

Information. Sixty patients with chordomas (46 patients) or chondrosarcomas (14 patients) of the skull base were treated at the University of Pittsburgh over a 9-year period (1984–1993). The mean age was 41 years (range 16–78). Double vision and headache were the most common presenting symptoms (60% of the patients) followed by hoarseness/dysphagia and facial numbness/pain (30–40% of the patients), while abducens nerve disorder was the most common sign followed by trigeminal nerve dysfunction (45 and 28% of the

patients, respectively). All patients underwent preoperative MRI and computed tomography (CT). The clivus was involved in 93% of the cases, while the cavernous sinus was invaded in 75% of the patients. Eighty-four percent of the tumors had a volume equal to or greater than 15 cm³. Fifty percent of the patients with chordomas and 43% of those with chondrosarcomas had had previous surgery, while 10 patients, all with chordomas, had received prior RT. The fronto-temporal and subtemporal approaches and their modifications (transcavernous and transpetrous apex approaches) were used for lesions involving the upper clivus and the cavernous sinus with a large intradural extension, while the subtemporal-infratemporal approach was reserved for paramedian tumors involving the midclivus and the petrous bone; the extended frontal approach was used when there was a significant tumor extension from the upper clivus into the sphenoidal area, and the extreme lateral transcondylar and transjugular approach was reserved for tumors involving the lower clivus and foramen magnum area. Occasionally, transfacial approaches were used. Multiple approaches were used in 52% of patients.

MRI was used to determine the extent of tumor removal. Forty-seven percent of the patients had total tumor removal (no tumor on postoperative MRI), 20% had near-total tumor removal (questionable tumor remnant), 23% had subtotal removal (10% or less residual tumor), while 10% of the patients underwent partial tumor removal (>10% residual tumor). Three patients (5%) died within 3 months of surgery; 6 patients (10%) suffered significant postoperative motor deficits (hemiparesis, tetraparesis, or gait ataxia). Forty-eight patients (80%) had a new cranial nerve deficit postoperatively, more often involving the abducens nerve, which was temporary in approximately 50% of the cases, the only exception being postoperative hearing loss observed in 15% of the patients and never temporary. Postoperative CSF leak was seen in 30% of the patients (18 patients), requiring reoperation in 55% of them (10 of 18 patients), while meningitis was observed in 33% of the patients with CSF leak (6 patients). Twelve patients (20%) underwent postoperative RT: the proton beam was used 6 times, photon beam RT 5 times, and Gamma knife once. The tumor margin doses were 50–75 CGE for proton beam, 50–60 Gy for external RT, and 20 Gy for Gamma knife. RT was used only when the tumor could be unequivocally identified on postoperative MRI scans.

The median follow-up was 3.9 years (range 1–11). Eight patients died during the follow-up period: 6 of

them had chordomas and 2 chondrosarcomas. Five chordoma patients died either of local or metastatic disease, while 1 died of unrelated cause. The 2 patients with chondrosarcomas died of RT complications, brain stem necrosis and high-grade brain stem glioma thought to be secondary to RT, respectively. Tumor recurred in 7 patients (12%) including the 5 who died from it. The mean time to tumor recurrence was 1.9 years. Mortality was not statistically related to pathology, tumor size, extent of surgical resection or previous surgery, while patients who underwent prior RT died more frequently than those did not ($P < 0.001$). Tumor recurrence was statistically higher in patients who had had prior surgery, prior RT, patients in whom a total/near total tumor removal was not achieved, or in female patients. Tumor size or pathology were not statistically significantly related to recurrence. Recurrence-free survival was 80% at 3 years and 76% at 5 years. No patient was predicted to be alive 5 years after tumor recurrence. Recurrence-free survival was not statistically different for chordomas or chondrosarcomas even though there was a trend toward statistical significance ($P = 0.09$). Previous surgery as well as subtotal/partial resection decreased the 5-year recurrence-free survival ($P < 0.05$) in a statistically significant manner. On the other hand, patients had the same chances of having gross total/near total tumor resection irrespective of prior surgery ($P > 0.05$). Patients' functional status measured using the Karnofsky score was lower in the immediate postoperative period and at follow-up when compared with the preoperative Karnofsky score.

Analysis. This paper presents a rather detailed recurrence-free (or progression-free, given that 33% of the patients had undergone subtotal/partial tumor removal) survival analysis of patients with skull base chordomas or chondrosarcomas.

Using univariate analysis, the authors show that chordoma patients have a shorter recurrence-free survival than chondrosarcoma patients at a level approaching statistical significance ($P = 0.09$), that previous surgery impacts negatively on the recurrence-free survival ($P < 0.05$) while it has no impact on the ability to achieve a total/near total tumor resection ($P > 0.05$), and that patients with total/near total tumor resection have a longer recurrence-free survival than patients undergoing subtotal/partial resection ($P < 0.05$).

Moreover, the authors show that postoperative and follow-up Karnofsky scores are not overall better than the preoperative ones. This report also underscores the

tremendous importance of postoperative CSF leak on the postoperative degree of disability; in fact, CSF leak together with tumor size was statistically related to postoperative disability. One can assume that this is so because of postoperative meningitis, but no data are provided to support this.

[3] Radiation therapy for chordomas of the base of the skull and cervical spine: patterns of failure and outcome after relapse

Int J Radiat Oncol Biol Phys (1995) 33:579–584

Information. From 1975 to 1993, 204 patients with skull base and cervical chordomas were treated at a single institution. Sixty-three of them (31%) developed treatment failure and form the subject of the authors' study. All of these 63 patients had originally been treated with surgery and combined proton-photon radiation to a median dose of 70.1 CGE. The median follow-up from the time of relapse was 54 months. Failure was defined as local only in 49 patients (78%), distant only in 2 patients (3%), and local plus distant in 12 patients (19%).

The median interval to development of local failure alone or in combination with distant failure was 32 months; it was significantly shorter (24 months) for patients with cervical spine tumors than for patients with skull base tumors (33 months), with a P value of 0.029.

Surgical pathway failure was observed in only 5% of patients; the most common site of distant metastasis was the lung followed by the bone. Distant metastases were more common in patients with local failure. The 3- and 5-year survival rates after relapse were 43% and 7%, respectively. In terms of survival after relapse, there was no statistically significant difference between skull base and cervical location, between local relapse versus local and distant relapse, between chondroid versus non-chondroid tumors, between age <40 or >40, between tumor volume of < or >70 cc, or between male and female patients.

Eleven of the 60 patients with local recurrence received supportive therapy only at recurrence, while 49 received salvage therapy at recurrence. Of these 49 patients, 46 had additional surgery, (2 of them combined with RT and 2 combined with chemotherapy with or without RT), 1 had RT alone, 1 chemotherapy alone, and 1 chemotherapy and RT. The response of the

patients to salvage therapy was graded as 1 (stable or improved tumor status without subsequent tumor progression) 2 (stable or improved tumor status with subsequent tumor progression) or 3 (progressive disease). A patient should have spent at least 4 months in grade 1 or 2 following completion of therapy in order to be graded as such. Following salvage therapy 7/49 patients were in grade 1 with a median follow-up of 12 months, 26 were in grade 2 with a median interval to progression of 7 months, while 16 were in grade 3. The 2- and 5-year survival of the 49 patients treated at relapse was 63% and 6%, respectively. It compared well ($P = 0.001$) with the 21% 2-year survival of patients treated only with supportive therapy at recurrence.

Analysis. This paper confirms that the main pattern of failure in chordomas is local recurrence; however, more than 20% of patients have distant metastases as well. Once a chordoma relapses, there is no statistically significant difference in survival between patients who fail only locally versus patients who fail locally as well as at a distance. At relapse, patients may be treated effectively with at least 1 out of 7 patients enjoying good disease control for at least 1 year. However, the 63% 2-year survival of patients treated with salvage therapy at relapse and the 21% 2-year survival of patients treated only with supportive therapy at relapse must be interpreted with caution, as the authors themselves point out. In fact, those patients who were offered and accepted additional therapy at relapse were obviously in a better functional state than patients who were treated only with supportive therapy.

[4] Optimization of radiotherapy for patients with cranial chordoma

Cancer (1995) 75:749–756

Information. The dose response of 47 patients with cranial chordomas receiving postoperative photon irradiation was analyzed. The mean dose was 55.8 Gy. No dose response was observed. In addition, the survival rate was calculated for 159 patients with cranial chordomas receiving either surgery alone, RT alone, or surgery and RT. The median survival was 0.25 years with surgery alone, 7.5 years with RT alone, and >7.5 years with surgery and RT. The differences in survival were highly significant ($P = 0.011$) between the surgery alone and the RT alone groups or between the surgery alone

group and the surgery and RT group ($P < 0.0001$). The survival difference between the RT group and the surgery and RT group was not statistically significant ($P = 0.271$).

Analysis. The lack of a dose response relationship for photon RT in the 54 patients examined may be ascribed to the low delivered dose (mean 55.8 Gy). It is likely that a dose response relationship may be observed when doses of 60 Gy or higher are used. However, increasing the tumor dose may increase the RT complication rate, given the proximity of chordomas to vital structures like the optic apparatus and the brain stem. Probably higher-dose photon RT may be delivered with the newest three-dimensional treatment-planning and conformal RT.

[5] Base of skull chordoma

Cancer (1994) 74:2261–2267

Information. Sixty-two patients with skull base chordomas treated between 1979 and 1990 were analyzed. Thirty-three patients were male and 29 female. The median age was 37 years. All patients received surgery and postoperative combined proton-photon RT to a median dose of 68.4 CGE. Disease-free survival and overall survival were calculated using univariate and multivariate analysis with regard to sex, age, tumor volume, chondroid appearance, mitotic count, necrosis, prominent nucleoli, nuclear pleomorphism, and vascular invasion. The median follow-up was 69 months. Twenty-nine patients experienced local failure with a median time to local failure of 55 months for female patients and more than 143 months for male patients. The median survival was 86 months for female patients and 158 months for male patients. Univariate analysis showed that female gender, >10% necrosis, and prominence of nucleoli are associated with shortened overall survival ($P = 0.006$, 0.002 , and 0.004 , respectively). Multivariate analysis showed that female gender is associated with shortened disease-free survival ($P = 0.01$) and shortened overall survival ($P = 0.001$). Furthermore, female gender, tumor larger than 70 cc, and >10% tumor necrosis in pre-RT biopsy specimens are significant independent predictors of shortened survival time when controlling for age, mitosis, nucleoli, pleomorphism, vascular invasion, and chondroid elements.

Analysis. This is one of the few chordoma papers that try to disentangle the relative weight of several variables on disease-free and overall survival by performing a multivariate analysis. It is intriguing that female patients not only fare worse than male patients, but also that postmenopausal women tend to have a shorter survival than premenopausal women, raising the possibility that the hormonal changes taking place at menopause may modify the biological behavior of the tumor.

[6] Intracranial chordomas: a clinicopathological and prognostic study of 51 cases

J Neurosurg (1993) 78:741–747

Information. Fifty-one patients with intracranial chordomas treated between 1960 and 1984 form the subject of this report. The median age was 46 years. The median time from symptom-onset to diagnosis was 10 months. Diplopia (49%) and headache (24%) were the most common presenting symptoms, while abducens deficit (57%) and sensory trigeminal deficit (27%) were the most common presenting signs.

Eleven tumors (22%) were biopsied, while 40 (7.8%) were subtotally removed. Thirty-nine patients received postoperative RT to a median dose of 50 Gy. Subtotal tumor removal was achieved in 74% of the patients who did and in 92% of the 12 patients who did not receive postoperative RT. The median follow-up was 8.3 years (range 5.6–29.7).

The overall survival at 5 and 10 years was 51% and 35%, respectively, while disease-free survival at 5 and 10 years was 33% and 24%, respectively. The value of multiple prognostic factors, including but not limited to age, neurological function, duration of symptoms, diplopia, sex, histology (chondroid versus non-chondroid), biopsy versus tumor resection, and postoperative RT on overall and disease-free survival was assessed using a uni- and multivariate statistical analysis. Patient age (<40 years) and diplopia were associated with increased survival in a multivariate analysis, while age (<40 years) and tumor resection were associated with a longer survival in a univariate analysis. Also, younger patients (<40 years of age) survived longer than their older counterparts when they received tumor removal and postoperative RT.

Analysis. This is a good study performing a multivariate analysis of those factors affecting overall and disease-free survival in patients with cranial chordomas. As in many other neoplasms, including primary brain tumors, age was found to be important in determining survival. This is independent of functional status, which was the same in younger and older patients. It is true that younger patients received tumor removal and RT more often than older patients, but in the authors' material neither tumor removal nor RT were related to survival in a multivariate analysis. The presence of diplopia may be related to longer survival because of earlier tumor diagnosis or favorable tumor location.

In conclusion, this paper makes a strong case for the importance of age and diplopia on overall and disease-free survival of patients with cranial chordomas.

[7] Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull

J Neurosurg (1989) 70:13–17

Information. Sixty-eight patients with skull base chordomas or low-grade chondrosarcomas were treated with fractionated proton beam radiotherapy after biopsy or subtotal tumor removal between 1974 and 1986. Forty

patients had chordomas and 28 had low-grade chondrosarcomas. There were 33 female and 35 male patients. The median age was 33 years (range 7–75). All patients had evidence of residual local disease, while none of them had evidence of metastases. The median follow-up was 34 months (range 17–152). The median tumor volume was 45 ml (range 2–282). The RT was delivered using a combination of photons and protons, with the proton component of the treatment ranging from 40 to 100%. The median tumor dose was 69 CGE (range 56.9–75.6), given with a daily dose of between 1.8 and 2.1 CGE in 31–41 treatments. At 5 years, the actuarial local control rate was 82%, while the 5-year actuarial disease-free survival rate was 76%. Nine patients (13%) developed some degree of pituitary insufficiency requiring replacement therapy, while 3 patients (4%) developed severe visual complications. Multivariate analysis showed that larger tumors had a worse outcome ($P = 0.01$); the combination of larger tumors and female sex also had a worse outcome ($P = 0.02$).

Analysis. This paper shows that a substantial disease-free (or progression-free) survival (76%) may be achieved when high-dose proton RT is given after surgical resection of skull base chordomas or chondrosarcomas. The multivariate analysis underscores the importance of a substantial surgical removal of the tumor in local tumor recurrence/progression.

Synthesis

Chordomas are slow-growing tumors. In order to assess the impact of any management strategy on overall survival, disease-free and progression-free survival, it is important to have a median follow-up of at least 3 years. In fact it is by that time that the survival curves generated by the papers reviewed start to differ from each other.

Two management modalities are important in treating chordomas: surgery and RT. Chemotherapy is generally not used; its value has not been assessed in any systematic way with a large enough number of

patients and therefore cannot be commented upon. The goal of surgery is the removal of as much tumor as possible while at the same time maintaining or improving the functional status of the patient. The papers by Al-Mefty and Borba [1] and Gay et al. [2] (who reported on Dr. Sekhar's patients) set the benchmark of what may be achieved using modern skull base surgery. Approximately 50% of the patients may expect to have total tumor removal with a mortality rate of about 5% and a major complication rate of about 10%. CSF leak may be expected in

about 30% of the patients, giving a figure similar to that observed in other major skull base procedures. In order to achieve this total tumor removal in 50% of the patients, multiple skull base approaches are necessary in 16–50% of the patients. These results were generated between 1984 and 1996 and represent a dramatic improvement compared to the 78% subtotal tumor removal and 11% biopsy rate reported by Forsyth et al. [6] in patients treated between 1960 and 1984. The 5-year recurrence-free survival after this aggressive skull base surgery is about 76%.

This recurrence-free figure seems to be more of a progression-free survival because it is apparent that many patients still have residual disease, albeit controlled. The detailed analysis of functional status performed by Gay et al. [2] is important to highlight the fact that after aggressive state-of-the-art skull base surgery, the postoperative functional status is not better than the preoperative one.

It is hard to deny the role of RT in the treatment of skull base chordomas. In fact, it is difficult to discount the meta-analysis of Tai et al. [4], showing that the median survival was 0.25 years with surgery alone and 7.5 years with photon RT alone. The results of fractionated proton beam therapy reported by Austin-Seymour et al. [7] in 1989 are of paramount importance in highlighting the efficacy of radiation, provided that tumor localization is accurate and that the dose to surrounding structures is limited. These authors show a 76% 5-year disease-/progression-free survival rate with a 69 CGE median tumor dose. As surgery has significantly improved over the last

20 years, so has RT in terms of precise localization and types of radiation. Clearly, the proton beam computerized multidimensional treatment-planning system or the newest conformal inverse planning systems cannot be fairly compared with conventional external beam photon therapy. Furthermore, gamma knife radiosurgery may have a role in a selected group of patients with small tumors (<30 mm in diameter) more than 5 mm away from the optic nerves/chiasm. In fact, Kondziolka et al. (1991) demonstrated no progression with a short follow-up when such tumors were treated with 20 Gy to the tumor margin.

Regarding the multiple factors that affect overall and progression-free survival, it seems that female sex has a negative impact. This is of extreme interest, also because postmenopausal women fare worse than premenopausal ones. The fact that age >40 years is associated with a worse survival than age <40 years is not surprising because this is shared by many other neoplasms. It also seems that the existence of the so-called chon-

droid chordoma is doubtful and certainly does not seem to have a survival advantage over typical chordoma.

When chordomas recur or progress, they do so mainly locally (78%), even though about 20% fail locally and at a distance. Once there is a failure, the 5-year survival rate is less than 10%. However, there is a subgroup of patients probably with a good functional status and perhaps with a more indolent tumor in which aggressive multimodality therapy at recurrence/progression with surgery and additional radiation may be of benefit in terms of improved survival (63% survival rate 2 years after recurrence/progression).

In conclusion, it seems that the combination of aggressive surgery followed by combined proton-photon RT offers the best chance of long-term control to patients suffering from cranial chordomas. The enthusiasm of aggressive surgery should, however, be tempered by the knowledge that even in subtotally removed tumors, postoperative proton-photon RT may afford a very substantive progression-free survival.

Papers reviewed

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Further reading

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