In 1974 the first patient presenting with skull base chordoma underwent proton irradiation at MGH/HCL. Following a first report by Austin-Seymour, et al., patient referral steadily increased. Collaborators at LBNL have treated patients with skull base tumors since 1977, but subsequently LBNL ceased its operation. In 1990, the hospital-based proton radiotherapy facility at LLUMC opened. At present, the two proton radiotherapy facilities in the United States, MGH/HCL and LLUMC, have accumulated the largest worldwide patient population treated for skull base chordomas. Treatment philosophies at both centers are similar and treatment protocols are shared.

Compared with other forms, photon radiation has the advantage of the physical properties of dose delivery—that is, dose deposition within the tumor by using a spread-out Bragg peak with sharp dose falloff downstream. Because protons do not have an exit dose, dose distributions can be designed that are highly conformal in all three dimensions. Protons are highly adaptable to irregular target volumes, and this makes them particularly useful in the skull base where tumors are likely of irregular contour and in close proximity to vital normal structures. Protons are assumed to have a slightly higher relative biological effectiveness compared with photons. A clinical working factor (relative biological effectiveness factor) of 1.1 is used in both centers to adjust the proton dose for its higher biological effectiveness. All proton data reported in this review are based on a course of fractionated radiotherapy at 1.8- to 2.0-CGE) dose per fraction. At LLUMC the majority of patients are treated exclusively with proton beam radiotherapy (five treatments per week). At MGH/HCL the proton beam system is unavailable 1 workday per week. Thus photon therapy is substituted for proton beam once per week resulting in a mixed proton–photon course (photon component < 30% of the overall radiation dose).

Having accumulated a sufficient number of patients and an adequate follow-up period, collaborators at MGH/HCL, LBNL, and LLUMC were able to identify clinical variables predictive of long-term tumor control. In this review long-term outcome data and prognostic indicators are summarized.

**LONG-TERM OUTCOME AND COMPLICATIONS**

Between 1977 and 1992 at LBNL, 126 patients with skull base tumors underwent charged particle (helium or
two cases of bilateral blindness, and four cases of unilat-
erasymptomatic brain changes, three cases of unilateral and
including 12 cases in which there were symptomatic or
chronic complications. Severe toxicities were reported in 8% of patients,
chondrosarcomas are a clinically distinct entity from chor-
domas. The MGH/HCL group recently published a report on
low-grade skull base chordomas. The 5-year local
control and overall survival rates were 63% and 75%,
respectively. In a separate analysis of 45 patients, complica-
tions in the LBNL series included three cases of unilateral
loss of vision, two of blindness, and four cases of brain-
stem injury (17%).

The MGH/HCL group recently published a report on
621 patients with skull base and cervical chordomas
or chondrosarcomas treated since 1975.14 The 519 cases of
skull base tumor included 290 chordomas (159 male and
131 female patients) and 229 low-grade chondrosarco-
mas. Prescribed doses ranged from 66 to 83 CGE, when
using a proton relative biological effectiveness value of
1.1. Daily doses were 1.8 or 1.92 CGE, respectively, given
5 days per week usually in four fractions of protons and
one of megavoltage x-rays. With increasing follow-up
time (median 41 months; maximum almost 22 years) and
increasing number of patients, a significant difference in
local control and survival rates was demonstrated between
patients with chondrosarcomas and those with chordomas.
At 5 and 10 years, the local recurrence-free survival rates
were 97% and 92%, respectively for chondrosarcomas,
and 64% and 42%, respectively, for chordomas. Analysis of
the MGH/HCL data strongly suggested that low-grade
chondrosarcomas are a clinically distinct entity from chor-
domas. Severe toxicities were reported in 8% of patients,
including 12 cases in which there were symptomatic or
asymptomatic brain changes, three cases of unilateral and
two cases of bilateral blindness, and four cases of unilat-
eral deafness.

In 1999, our group reported outcome data obtained in
58 patients treated at LLUMC for low-grade skull base
chordomas and chondrosarcomas.10 Thirty-three patients
with chordomas and 25 patients with chondrosarcomas
had undergone fractionated proton beam radiotherapy to
target doses ranging from 64.8 to 79.2 CGE (mean 70.7
CGE). The dose per fraction was 1.8 CGE one fraction per
day 5 days per week. More than 90% of patients un-
derwent proton irradiation exclusively. In a mean follow-
up period of 33 months (range 7–75 months) eight (24%)
of 33 patients with chordomas experienced recurrence
compared with two (8%) of 25 patients with chondro-
sarcoma in whom the tumor recurred. Thus, in 76% of
patients with chordomas and in 82% of patients with
chondrosarcomas, local tumor control was achieved. On
actuarial analysis, these data resulted in local control rates
at 3 years of 94% for patients with chondrosarcomas and
67% for patients with chordomas. Five-year actuarial
overall survival rates were 79% for patients with chorde-
mas and 100% for patients with chondrosarcomas (Fig. 1).
Grade 3 and 4 late toxicities were observed in four pa-
tients (7%) and were symptomatic in three patients (5%).

**PROGNOSTIC FACTORS**

**Predictive Value of the Size and/or Location of Gross or
Residual Disease**

Proton beam radiotherapy has no technical size limita-
tions. In fact, most tumors treated with proton irradiation
routinely exceed the size limitations imposed in GKS.11
Data accrued at LLUMC were analyzed according to tu-
mors with volumes less than/equal to or greater than 25
ml.10 Thus, based on size, one group of tumors was poten-
tially suitable for GKS and the other (exceeding that size)
was not. In all patients with preirradiation tumor volume
not exceeding 25 ml local tumor control was achieved,
whereas in 56% of those with larger-volume tumors (> 25
ml) tumor control was achieved (p = 0.02) (Fig. 2). At
LBNL, tumors were classified as small (< 20 ml), inter-
mediate (20–35 ml) or large (> 35 ml). Significantly
higher local control rates (80% compared with 33%, re-
spectively) were observed for smaller volumes. This anal-
ysis included patients with chordomas and chondrosarco-
mas. In an MGH/HCL review the authors documented a
significant disease-specific survival difference only in
patients with large (< 70 ml) compared with very large
tumors (> 70 ml).15

In choosing the appropriate treatment modality, the lo-
cation of any residual gross tumor is at least equally
important to the actual size of the tumor. A midclival tumor
that extends into the nasopharynx or sphenoid sinus, but
without intracranial extension, is amenable to various ra-
diation treatments. However, if the midclival tumor ex-
tends intracranially and abuts or compresses the brainstem
or displaces the optic chiasm, the radiation dose deliver-
able to the tumor component in immediate contact with
these critical structures will be limited. Photon radio-
surgery and proton radiation therapy can be used to create
a sharp dose gradient in an effort to minimize the volume
of tumor not receiving the full, prescribed, tumoricidal
dose. Fractionated radiotherapy has the added benefit of
sublethal damage repair of normal tissues in between
treatment fractions, thus resulting in higher critical normal
tissue tolerance levels. The importance of resecting tumor
from critical normal tissues has been documented by the
LLUMC group.10 In 59% of their patients brainstem abut-
ment or compression was present prior to proton irradia-
tion. Local control rates at 5 years were 94% in cases
without and 53% in cases with brainstem involvement
(p = 0.04). Austin, et al.,1 reported for the MGH/HCL

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*Fig. 1. Graph showing overall survival following fractionated proton irradiation for skull base chordomas (33 patients) and chon-
drosarcomas (25 patients).*
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Fig. 2. Graph depicting local control (LC) and overall survival (OS) following fractionated proton irradiation for skull base chordomas (33 patients) and chondrosarcomas (25 patients) according to preirradiation gross tumor volume. NS = not significant.

In a limited analysis of 62 patients treated at MGH/HCL, an insignificant trend for patients older then 40 years of age was observed. In these patients worse disease-specific survival was demonstrated.

Recently, Al-Mefty, collaborating with Borba and colleagues, suggested that chordomas behave more aggressively in the pediatric population. For the MGH/HCL group, Benk, et al., reported 18 pediatric patients in whom tumors were treated with doses ranging from 55.8 to 75.6 CGE. The 5-year actuarial overall survival rate was 68% and the local recurrence-free survival rate 78%. The author treated 10 pediatric patients with skull base chordomas between 1992 and early 1999 at MGH/HCL and LLUMC. Patient age ranged from 2 to 19 years at time of diagnosis. The average prescribed tumor dose was 74 CGE (range 70–79 CGE). Local tumor control was maintained in six (60%) of 10 patients. The author of the present report is aware of three children who developed tumor recurrence whereas only one of five boys experienced recurrence. The cause for this sex difference is unknown. Preliminary estrogen and progesterone receptor studies in adult patients were thus far inconclusive.

**Predictive Value of Age or Sex on Increased Biological Aggressiveness**

In summary, analysis of available data indicates a local control and survival benefit, in previously resected large- or small-sized tumors if they can be debulked and freed from critical normal structures.

**Relation of Higher Radiation Doses to Improved Outcome**

In conventional radiotherapy the radiation dose to the tumor is limited according to the maximum dose that nearby critical normal tissues can tolerate (for example, brainstem optic nerves and optic chiasm). This strategy has resulted historically in fractionated total radiation doses ranging from 50 to 60 Gy. Rarely was a dose of 60 or 65 Gy exceeded. Recurrence rates as high as 50 to 100% have been reported after conventional megavoltage irradiation. Local control and survival curves follow a continued downward slope.

Proton radiotherapy in which the authors applied mean doses of 71 CGE (LLUMC series) and doses up to 83 CGE (MGH/HCL series) has resulted in increased tumor control. Almost all patients undergoing proton radiotherapy received doses greater than 66 CGE. In a multiinstitutional study, involving MGH/HCL, LBNL, and later LLUMC, the investigators divided patients into low-risk and high-risk groups. Low risk cases were defined as male or female patients with chordomas, as well as male patients with skull base chondrosarcomas; high-risk cases were female patients with skull base chordomas, as well as male and female patients with cervical chordomas and chondrosarcomas. Patients in the low-risk group were randomly assigned to receive treatment with either 69.6 CGE or 75.6 CGE; patients in the high-risk group were randomly assigned to receive treatment with either 75.6 CGE or 82.9 CGE. Overall 328 patients were enrolled. This is the largest randomized study ever conducted in patients with skull base chordomas and chondrosarcomas. An interim report is expected soon.

**Effects of Delayed Proton Irradiation on Tumor Control**

Unfortunately, in the largest series of patients (those treated at MGH/HCL), the authors did not include the variable of treatment for primary compared with recurrent disease in any recent analysis. Previously, the LBNL had found a higher 5-year local control rate for patients undergoing helium or neon radiotherapy at the time of initial diagnoses (78%) compared with recurrent disease (33%). No difference in outcome was demonstrated in the
LLUMC study in patients undergoing radiotherapy for recurrent or primary disease.

A diagnosis of chordoma spans a wide variety of natural history and range of biological aggressiveness. In patients with documented several-year histories of slowly progressive symptoms, a policy of watchful observation following initial resection appears sometimes justified. Our knowledge of the true rate of long-lasting tumor control following modern microsurgical, gross-total resection is limited. Thus, it is difficult to develop general treatment recommendations.

Although currently we have limited evidence that delayed radiation treatment will effect the overall outcome negatively, it has to be kept in mind that tumor regrowth might occur at an unfavorable location, causing potentially irreversible neurological nerve damage. Additionally, repeated resections limit the tolerance of normal tissue to definitive high-dose proton irradiation. Debus, et al.,9 have reported that repeated surgical procedures are an independent prognosticator for severe brainstem toxicity after proton radiotherapy.

DISCUSSION

In using proton radiation, practitioners have pioneered the concept of high-dose fractionated radiotherapy for skull base tumors. Three-dimensional conformal irradiation in the base of skull was also introduced by users of proton beam radiotherapy. Radiation doses in excess of 70 Gy, previously considered unsafe, were safely achieved, and valuable information on partial organ tolerance doses obtained.

Superior local tumor control and overall survival achieved using fractionated proton irradiation, compared with conventional photon radiotherapy, are attributed to superior dose localization characteristics of protons that result in higher doses delivered.

Over the past decades, we have witnessed a revolution in the application of photon radiotherapy. Rapid advancements in computer software as well as hardware have resulted in fractionated stereotactic radiotherapy (intensity-modulated radiation therapy) and LINAC-based radiosurgery. Thus, the ability to deliver a conformal photon radiation dose has greatly improved. In addition, indications for GKS have been expanded to include use in malignant skull base lesions. For small tumors with some distance from normal critical structures, there appears to be little difference between high-dose isodose target coverage between three-dimensional conformal photons and similar proton techniques. However, in larger lesions in immediate proximity to normal critical structures and in highly irregularly shaped tumors, proton radiotherapy has consistently been demonstrated, in comparisons with other modalities in terms of target planning and delivery, to maintain an advantage.10 The fact remains that proton irradiation does not have an exit dose. Therefore, the integral volume of normal tissues receiving radiation will always be smaller compared with that when using photons. This is of particular importance in the pediatric patient in whom even small to moderate amounts of radiation can lead to major cosmetic and life-long functional impairments. A principal, philosophical difference exists between single-fraction radiosurgery and fractionated proton irradiation: in general, only gross tumor volume and a limited microscopic target volume are targeted with either single or multiple isocenters in radiosurgery. Any additional microscopic disease beyond this target will be irradiated concentrically in the dose falloff region. In contrast, in using proton irradiation, it has been always our policy to identify separately a clinical target volume, with distinctly different shape and size compared with the gross tumor volume. This clinical target volume is defined as any area of risk for microscopic disease, in general including the entire operative bed and anatomical compartment of initial extension. The clinical target volume will receive a separately prescribed microscopic target dose in fractionated fashion. This concept has proven to be successful because the majority of any failures after proton radiotherapy occur within the gross tumor target volume itself and not in the operative bed.

The routine use of postoperative radiotherapy is controversial. To judge the potential benefits of adjuvant radiation therapy, we need to accrue long-term data on permanent tumor control rates since the introduction of modern microsurgical techniques to achieve total or near-total tumor resection.

In dose-escalation trials charged particle therapy continues to be studied. We await the results of the recent randomized study in which doses up to 83 CGE were used. Developments in proton radiotherapy include intensity-modulated therapy and the introduction of beam-scanning techniques. These should further increase the degree of dose conformity.

In the foreseeable future, the use of protons will remain limited to major centers only. Proton radiotherapy has provided a standard of long-term tumor control with acceptable morbidity rates. Most skull base centers either have GKN or LINAC-based systems available and/or modern three-dimensional conformal radiotherapy (intensity-modulated radiation therapy) capabilities. It is the hope of the author that other centers will combine their efforts in prospective trials to evaluate the benefits of radiosurgery or stereotactic fractionated photon radiotherapy techniques. Early results of stereotactic fractionated radiotherapy as reported by Debus, et al.,9 are encouraging. Additional data on local tumor control following either GKS or LINAC radiosurgery are expected to be published soon to add to the available data reported by the Pittsburgh group.16

A very interesting development is the use of carbon ion therapy at the Heavy Ion Research Facility in Germany. Carbon ion therapy combines the physical advantages of protons with the differential increase in biological effectiveness of particles in tumors compared with normal tissues. In a preliminary analysis of the first 13 patients with skull base chordomas and chondrosarcomas in whom this therapy was applied, the authors did not find any evidence of increased acute toxicity.18

In summary, following a historically, almost fatalistic approach to skull base chordomas, recent refinements and new advances in microsurgical techniques, as well as introduction of various radiation therapy modalities, offer patients with skull base chordomas a realistic chance of long-term local tumor control and hopefully prolonged survival. Prognostic factors have been identified to guide...
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physicians and patients in choosing the most appropriate management approach. Further developments are needed to improve the survival chances of patients in whom poor risk factors are present.

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