Radiotherapeutic Management of Medulloblastoma

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The prognosis for patients with newly diagnosed medulloblastoma has improved dramatically over the past several decades. In contrast to the dismal results of treatment during the first half of the 20th century, current 5-year survival rates of better than 50% are now being reported, and certain subsets of patients have more than a 70% chance of long-term disease-free survival.[1,2] Although neurosurgeons and radiation oncologists have proposed that this improvement is due to advances in their respective specialties, probably multiple factors are involved.

The prognosis for patients with newly diagnosed medulloblastoma has improved dramatically over the past several decades. In contrast to the dismal results of treatment during the first half of the 20th century, current 5-year survival rates of better than 50% are now being reported, and certain subsets of patients have more than a 70% chance of long-term disease-free survival.[1,2] Although neurosurgeons and radiation oncologists have proposed that this improvement is due to advances in their respective specialties, probably multiple factors are involved. These include:

1. decreased operative mortality and morbidity due to improvements in surgical technique, allowing for more extensive resection of the primary tumor, advances in anesthesia, the use of perioperative corticosteroids, and better supportive care;
2. advances in radiation therapy equipment, namely, the introduction of supervoltage radiotherapy;
3. improved noninvasive diagnostic imaging modalities, such as CT and MRI, which allow for earlier diagnosis, better assessment of tumor extent, accurate assessment of disease beyond the posterior fossa, extent of tumor resection, and response to therapy;
4. increased use of MRI, CT, and cerebral spinal fluid (CSF) cytology studies for staging and identification of high-risk patient subgroups; and
5. increased use of chemotherapy, which may be improving disease-free survival in certain subsets.

Improvements in Radiotherapy
As Paulino has detailed so well, improvements in radiation therapy practice (namely, the advent of supervoltage equipment) and technical advances now allow for the administration of an accurate, uniform high dose to the cranio-spinal axis. This is one of the most important factors accounting for the improvement in prognosis. As he emphasizes, this more favorable outcome has been associated with the use of whole craniospinal axis irradiation, as opposed to radiotherapy just to the posterior fossa plus or minus the spinal cord.

However, equipment alone is not sufficient. There must be proper technique and accurate placement of the radiation portals to avoid shielding the cribriform plate region and to ensure adequate coverage of the lower spinal cord. The junction of the portals used for cranial irradiation and the posterior spinal portal must be determined and placed accurately in order to avoid overdosage or underdosage to the upper cervical cord.

Prior to the availability of CT, relapse in the supratentorial region as a first site of failure was certainly under-reported. This lack of appreciation for the supratentorial region as a frequent site of failure prompted several unsuccessful attempts to eliminate supratentorial irradiation from the treatment of medulloblastoma.[3-5] Even though Cushing recognized the propensity for medulloblastoma to disseminate via the CSF pathways, it was not until 1975 that thorough staging with myelography and CSF cytology studies were suggested for all newly diagnosed patients with medulloblastoma.[6] By using thorough staging procedures, evidence of dissemination beyond the posterior fossa was demonstrated in over 40% of newly diagnosed patients, even though very few had symptoms suggestive of dissemination at diagnosis.

The M-stage is probably the most important predictor of prognosis in patients with medulloblastoma.
Other factors considered to be important are T-stage, extent of resection, and age at diagnosis. Using such factors, many investigators have divided the medulloblastoma population into "good-risk" and "poor-risk" subgroups.

**Is High-Dose Craniospinal Irradiation Needed?**

With the improvement in long-term survival associated with high-dose craniospinal axis irradiation has come the appreciation that radiotherapy may cause severe late sequelae, such as neurocognitive and learning disorders, lower IQ scores, endocrine dysfunction, and interference with normal growth and development. These late sequelae are related mainly to irradiation of the craniospinal axis and are dependent upon dose factors and age at treatment.

The problem of late sequelae from craniospinal radiotherapy, as well as several retrospective reviews that questioned the need for high-dose craniospinal axis irradiation, prompted the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) to evaluate a lower dose of neuraxis irradiation, 2,340 cGy/13 fractions, vs a standard dose, 3,600 cGy/20 fractions, with both arms receiving a posterior fossa dose of 5,400 cGy/30 fractions. This study was carried out in the low-stage (T1-T3, M0), prognostically favorable group of medulloblastoma patients. In neither arm was chemotherapy used. The study was terminated in 1990 after an interim analysis demonstrated an increased risk of early relapse overall and in the neuraxis among patients receiving the lower neuraxis dose.

As Paulino states, most published series cite relapse in the posterior fossa as the most common site of failure. However, when patients are followed with CT scans of the head and MRI of the spine, the incidence of recurrence beyond the posterior fossa, often clinically silent, increases. A series reported in 1988, in which staging was attempted in all patients at relapse, demonstrated an incidence of supratentorial and cord involvement about equal to the incidence of relapse in the posterior fossa. Even in the recently completed CCG-POG study carried out in a relatively good-risk population with low T-stage and no evidence of dissemination, less than one-half of all relapses involved the posterior fossa, both in the total randomized population and completely eligible patients.

**Important Unanswered Questions**

Several important questions about radiotherapy for medulloblastoma remain:

1. Would low-dose neuraxis irradiation plus chemotherapy be equivalent or perhaps even better than standard-dose neuraxis irradiation for a good-risk, M0 population?

2. What is the role of radiotherapy in infants? Chemotherapy alone after surgery achieves a 3-year disease-free survival rate of less than 25% in infants. Should all infants receive craniospinal axis irradiation when they reach a specified age, perhaps 3 years? Should radiotherapy be reserved just for relapse in the infant population? Hopefully, relapse would be detected relatively early by intense surveillance.

3. Would it be possible to increase the cure rate in the infant population by using a very low dose of craniospinal axis irradiation in children who are rendered clinically and radiographically disease-free by surgery and chemotherapy? Perhaps radiotherapy just to the posterior fossa would be adequate for a large proportion of infants who have M0 disease. For the infant who has been treated with postoperative chemotherapy alone and who still has detectable disease, there are still unanswered questions concerning the proper radiation dose and the volume to be irradiated.

4. Would hyperfractionation improve on or at least be equivalent to the results of standard-dose irradiation while decreasing the incidence and severity of late effects? A current CCG study is gathering data on hyperfractionation after intense chemotherapy in a poor-risk population of patients with medulloblastoma or supratentorial primitive neuroectodermal tumor. Although the data on the relationship between hyperfractionation and late sequelae are rather incomplete, I tend to use hyperfractionated radiotherapy for craniospinal axis irradiation in children under age 7 years.

5. Lastly, will advances in chemotherapy allow even the poor-risk patient to be treated with a lower dose of craniospinal axis irradiation, thus reducing late sequelae and hopefully also improving outcome?

Over the next decade, it will be important to determine optimal radiation regimens for good- and poor-risk medulloblastoma patients and to determine the optimal integration of radiotherapy with chemotherapy.
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