Ependymomas

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Ependymomas are uncommon neoplasms of the central nervous system (CNS), and as a consequence, few randomized, clinical trials have been performed, thereby limiting treatment guidelines. A review of the literature would permit the following conclusions regarding treatment. The best management of newly diagnosed ependymoma entails a complete resection corroborated by postoperative contrast-enhanced magnetic resonance imaging (MRI). If an incomplete resection is documented, a second attempt at gross total resection should be considered, given the prognostic significance of complete resection. Small volume residual disease is best managed with involved-field radiotherapy unless postoperative staging (cerebrospinal fluid cytology, neuraxis MRI) documents metastatic disease, which is best managed by craniospinal irradiation. The role of chemotherapy is uncertain and in general would be reserved for patients having previously failed surgery and radiotherapy. Disease-free survival following recurrence is unusual (<15% at 5 years) and suggests intensification of initial adjuvant treatment may best prevent relapse.

Introduction

Ependymomas are tumors that arise from the ependymal cells of the cerebral ventricles, the central canal of the spinal cord, and cortical rests [1–6]. Although uncommon, ependymomas constitute 8% to 10% of brain tumors in children and 1% to 3% of brain tumors in adults. Sixty percent of ependymomas occur in children who are under 16 years of age and 25% occur in children less than 4 years of age [7–14,15••,16,17,18••,19,20]. The World Health Organization (WHO) classification of tumors separates ependymomas into subependymomas (WHO Grade 1), myxopapillary ependymomas (WHO Grade 1), ependymomas (WHO Grade 2), and anaplastic ependymomas (WHO Grade 3) [10,14,16,18••,19,20]. Ependymoblastomas are considered a different type of tumor, classified under embryonal primitive neuroectodermal tumors, and are not further considered in this review.

Optimal management of these tumors includes surgical resection and evaluation of the extent of central nervous system (CNS) involvement using both cerebrospinal fluid (CSF) cytology and craniospinal contrast-enhanced magnetic resonance imaging (MRI) [1–14,15••,16,17,18••,19–26,27•,28•]. Subsequent treatment depends on the extent of residual disease as defined by postoperative MRI. In instances of measurable residual disease, reoperation should be considered, as survival of patients with ependymomas is significantly improved by performance of a complete resection. In patients not considered for further surgery and with residual disease, limited-field radiotherapy is usually administered. The role of craniospinal irradiation (CSI) in patients with local disease and no evidence of metastasis is controversial because the majority of tumor recurrences are local and at the site of the primary tumor [3,7,8,10,11,16,17,18••,19,20, 27•,28•,29]. No clear role for adjuvant chemotherapy has been demonstrated [10,11,13,16,17,18••,19,20,27•,28•]. When administered, chemotherapy for ependymomas has been administered primarily to children less than 3 years of age as adjuvant therapy, and administered as salvage therapy to patients with recurrent disease who are not considered surgical candidates [9–14,16,17,18••,19,20,26,27•,28•,30,31].

Recurrent ependymomas are managed by re-operation of tumors that are surgically accessible, by radiotherapy if not previously administered, and by salvage chemotherapy [3,7,9,12,13,17,19,21,25,27•,28•,31]. The role of stereotactic radiotherapy administered as either radiosurgery or brachytherapy is unclear, as all reports are anecdotal [32,33]. Because salvage chemotherapy is not curative, no standard therapy exists and a variety of chemotherapy agents and drug schedules have been investigated.

Intracranial Ependymomas

The clinical presentation of intracranial ependymomas most often is composed of signs and symptoms of raised intracranial pressure (headache, alteration in level of consciousness, nausea/vomiting, diplopia, papilledema, gait instability, meningismus) either due to tumor mass effect or obstructive hydrocephalus. Intracranial ependymomas may occur in either the supratentorial or infratentorial compartment. Tumors arising in the supratentorial compartment (50% to 60% of adult ependymomas, 30% of pediatric ependymomas) most often are hemispheric or occur in relationship to the third ventricle [1,7,8,10,11,14,16,18••,19,20,34]. Tumors found in the posterior fossa (60% of pediatric ependymomas, 40% of adult ependymomas) are seen either in a midline

fourth ventricular location (40% to 50% of all infratentorial ependymomas are median tumors) or are paramedian and located in the cerebellopontine angle (50% to 60% are lateral tumors) [1,7,8,10,11,14,16,18••,19,20,34]. In either instance, infratentorial tumors may invade the brainstem or extend below the foramen magnum (seen in approximately one third of all infratentorial ependymomas). Approximately 30% of all intracranial ependymomas are anaplastic, although the prognostic significance of anaplasia is controversial and unclear [3,10,11,14,16,17,18••,19,34–36]. Part of this uncertainty relates to the lack of uniform histologic criteria for diagnosing anaplastic ependymomas. Defining tumors as anaplastic based on proliferation indices such as Ki67 staining greater than 1% may permit stratification of patients at high risk for recurrence and decreased survival [34–36].

Cerebrospinal fluid (CSF) dissemination occurs in 3% to 12% of all intracranial ependymomas and is most frequent in patients with infratentorial anaplastic ependymomas [1,7,8,10,11,13,14,16,17,18••,19,20,22,27•,34,35]. Because a small but measurable risk for CSF dissemination exists for all patients with newly diagnosed ependymoma, an extent of disease evaluation including both CSF cytology and craniospinal MRI is mandated following surgery. This staging permits stratification of patients into those with (M1) or without metastasis (M0) and patients with or without residual disease following surgery, the two most important clinical parameters affecting outcome.

Treatment of ependymomas is primarily surgical, as essentially all analyses have determined that completeness of surgical resection is the most important covariant affecting progression-free and overall survival [8,10,11,14,16,17,18••,19–21,34]. As a consequence, reoperation following initial incomplete surgery or at time of tumor recurrence is advocated, assuming that a complete resection is achievable [7,16,17,19,21]. Gross total resection is dependent both upon the operator and infiltration of tumor into eloquent areas of brain. For example, lateral infratentorial ependymomas often infiltrate surrounding cranial nerves and invade the brainstem, making complete resection technically more difficult and more likely if performed to result in significant neurologic morbidity. As a consequence, reports of achieving a gross total resection vary from 50% to 75%. Paulino *et al.* [27•], in a series of 49 patients with intracranial ependymomas, report local control rates at 5, 10, and 15 years of 75.1% following image-verified complete resection as compared with 49.2%, 41.6%, and 35.6%, respectively, following incomplete resection. Following surgery, the issue of how often to image patients is unclear. A report from Good *et al.* [15••] suggests that regular surveillance neuroimaging revealed that 43% of all recurrences were asymptomatic and that recurrences occurred with a median time of 14.5 months (range, 3 to 65 months). Regular surveillance appeared to favorably impact survival and subsequent treatment, in particular the ability to perform a reoperation with complete resection [15••].

Radiotherapy represents the second most frequently utilized adjuvant treatment modality for ependymomas, despite the lack of a randomized, clinical trial showing benefit and the general consensus that ependymomas are radioresistant [10,11,14,16,19,27•,34,35,37]. Furthermore, there are no data regarding a dose-response relationship in ependymomas, and as such, total tumor dose has varied. By consensus, many radiation oncologists believe a tumor dose exceeding 45 Gray (Gy) is necessary, and most advocate a tumor dose of 54 to 55 Gy for ependymomas and 60 Gy for anaplastic ependymomas. Because of the possibility of CSF spread, one of the controversies regarding the radiotherapeutic management of ependymomas is the volume of brain that needs to be treated. Notwithstanding early enthusiasm for craniospinal irradiation, several recent studies support the application of limited-field radiotherapy for M0 tumors and reserve CSI for M1 tumors [16,17,19,20,27•,35,37]. Paulino *et al.* [27•], as do others, report 5-, 10-, and 15-year overall survival rates of 71.4%, 65.3%, and 63.5%, respectively, following CSI and 80.8%, 64.6%, and 64.6%, respectively, following local-field radiotherapy in patients with M0 disease. There are, in addition, advocates for observation only following gross total resection (*ie*, withholding radiotherapy) for supratentorial ependymomas; however, this suggestion is based on case series and has not been rigorously evaluated [38]. Lastly, the issue of conformal radiotherapy, including stereotactic radiotherapy, is increasingly utilized despite the paucity of studies showing benefit [33,34]. Limiting the tumor treatment volume by way of conformal radiotherapy is theoretically appealing, as irradiation of normal tissue is avoided and presumably delayed late radiation injury is mitigated. Again, however, there are no randomized trials that have demonstrated clear benefit with regard to survival or quality of life. Boost radiotherapy, wherein following conventional radiotherapy of the primary tumor additional radiotherapy is administered adjunctively, most often by way of a stereotactic methodology (for example by linear accelerator radiosurgery, gamma knife, or cyberknife), is increasingly utilized outside of clinical trials [33,34]. This adjuvant treatment is based on the assumption that radioresistance of ependymomas is relative, and that by increasing dose to the tumor, radioresistance may be overcome. Also, in that the majority of ependymoma treatment failures are local, augmenting tumor radiotherapy dose may improve long-term control. Despite an appealing construct, the lack of an established dose-response relationship for ependymomas following radiotherapy and the empiric observation that measurable neuroradiographic responses are rare suggests more is not necessarily better. A randomized trial evaluating stereotactic radiotherapies would clarify its purported benefits. Further supporting the thesis that more is not necessarily better is a report by Kovnar *et al.* [39] on using hyperfrac-

tionated radiotherapy as adjuvant radiotherapy for ependymoma showing limited benefit when compared with conventionally fractionated radiotherapy.

More controversial is the role of chemotherapy in the management of ependymomas. Robertson *et al*. [10] reported a prospective trial involving 32 children with newly diagnosed intracranial ependymoma that examined the role of adjuvant chemotherapy (CCNU, vincristine, and prednisone versus so called "8 in 1" regimen) after initial surgery and CSI. This multi-institutional Children's Cancer Group study demonstrated that both the extent of surgical resection and volume of residual disease on postoperative imaging predict progression-free survival. Chemotherapy had no impact on progression-free survival with either chemotherapy drug regimen. Five-year progression-free survival and overall survival rates were 50% and 64%, respectively. The majority of relapses were local treatment failures (71%) or concurrent local and distant CNS metastasis (21%); isolated metastatic relapse was uncommon (7%) and occurred only in the setting of M1 disease at diagnosis. The study concluded that involved-field radiotherapy results in similar outcomes as compared with CSI and, therefore, CSI is appropriately reserved for disseminated neuraxis disease (M1).

In a report of 48 infants with newly diagnosed intracranial ependymoma from the Pediatric Oncology Group, Duffner *et al*. [30,40] demonstrated a 48% response (partial and complete) to adjuvant cyclophosphamide and vincristine cycled with cis-platinum and VP-16. Furthermore, when evaluating outcome as a function of timing of radiotherapy (either at 1 year in children 2 to 3 years of age and at 2 years in children 1 to 2 years of age), 5-year survival was negatively affected by delaying irradiation (63% versus 26%). This study suggests modest efficacy of adjuvant chemotherapy following initial surgery; however, chemotherapy appears inferior to the benefit seen by administration of radiotherapy.

Van Veelen-Vincent *et al*. [19] reported a retrospective review of 83 children with newly diagnosed intracranial ependymomas treated with surgery (73% gross total resection), limited-field radiotherapy (in all ages prior to 1990, in children over the age of 3 years from 1990 to 1995, and in children over the age of 5 years after 1995) and multiagent chemotherapy. Chemotherapy comprised seven cycles of three chemotherapy courses alternating two drugs at each course (procarbazine and carboplatin, etoposide and cisplatin, vincristine and cyclophosphamide). Considering the group as a whole, overall survival was 68% at 5 years and 47% at 10 years. Event-free survival was 48% at 5 years and 46% at 10 years, with greater than 90% of all recurrences occurring in the first 5 years after surgery. Survival after recurrence was 14% at 5 years. Extent of surgery and inclusion of radiotherapy were found on multivariate analysis to predict both for improved survival and event-free survival. A gross total resection was found to be the most important prognostic factor, as has been shown in other studies (5-year survival after complete resection was 80% compared with 51% after incomplete resection). In addition, event-free survival (sometimes referred to as progression-free survival) was 53% after gross total resection versus 33% after subtotal resection, supporting the contention that complete resection lowers the risk of recurrence. In patients treated with chemotherapy after surgery, 5-year survival was 33% compared with greater than 60% in patients treated with radiotherapy, suggesting that the role of primary chemotherapy (in lieu of radiotherapy) is not warranted and that the role of adjuvant chemotherapy is uncertain. Forty-seven percent of patients relapsed (with a mean time to recurrence of 27 months following surgery), of which 85% were local recurrences, 8% were local and distant metastasis, and in only one patient (3%) was an isolated distant metastasis seen. These data again support the position of limited-field radiotherapy in patients initially staged as M0.

Figarella-Branger *et al*. [16] reported a retrospective study of 37 children with ependymoma and reported 5-year overall and progression-free survival rates of 45% and 25%, respectively. The authors conclude that adjuvant chemotherapy (not otherwise specified and administered to 17 patients) did not affect survival, and neither did adjuvant radiotherapy in patients in whom tumor excision was complete (accomplished in a total of 15 patients). In contrast, adjuvant radiotherapy enhanced progression-free survival in patients in whom tumor excision was incomplete.

Needle *et al*. [25], in a report on 19 patients with intracranial ependymoma treated with adjuvant chemotherapy (carboplatin and vincristine cycled with ifosfamide and VP-16 for a total of four cycles) following surgery and involved-field radiotherapy, suggest a benefit with the addition of chemotherapy based on a progression-free survival rate of 74%. In this small, single-arm study, extent of surgical resection was not a significant prognostic factor. This study has not been replicated and its conclusions are contrary to the previously mentioned larger trials.

The management of recurrent ependymoma has not received much attention in the literature despite the fact that nearly 50% of patients will recur. Goldwein *et al*. [14] reported on 36 patients with recurrent intracranial ependymoma in which 33 were treated with reoperation, 12 received radiotherapy (prestereotactic radiotherapy), and all received chemotherapy. Median time to recurrence was 2.8 years, and in the majority relapse was either local (78%) or local with concomitant distant metastasis (14%). Twenty-nine patients (79%) of the initial cohort had a second relapse, in which a local component to the relapse was seen in 80%. Two-year overall survival and progression-free survival were 29% and 23%, respectively. Considering only first relapse, 2-year actuarial survival was 39% and median survival was 17 months. Median progression-free survival was 12 months. Among 36 evaluable patients and 37 chemotherapy regimens, there was one partial response (3%), seven stable disease patterns (20%), and 29 disease

progressions (77%). In responding or stable disease patients, median duration of response was 9 months (range, 3 to 23 months). Cisplatin was felt to be the most active agent among the four commonly used chemotherapeutics (cisplatin, procarbazine, CCNU, and vincristine).

In a single institution retrospective review by Chiu *et al.* [8] from the M.D. Anderson Cancer Center, 12 children with recurrent ependymoma were treated with a variety of chemotherapy regimens, including PCV (procarbazine, CCNU, vincristine) and MOPP (mechlorethamine, vincristine, prednisone, procarbazine). All but two patients progressed in less than 6 months. Two long-term responding children were described, both of who responded to PCV.

In a phase 2 study of daily oral etoposide in children with recurrent brain tumors, Needle *et al.* [41] reported that of five children with ependymoma who were treated with etoposide, there was one complete response, one partial response, two stable disease patterns, and one disease progression. In a similar study, Chamberlain [9] reported on 12 patients with recurrent ependymoma treated with chronic oral etoposide. Two patients demonstrated a radiographic response (all partial) and four demonstrated stable disease for a median duration of response of 7 months.

In the largest study of dose-intensive chemotherapy with autologous bone marrow transplantation, Grill *et al.* [18••] reported on 16 patients using a regimen of high-dose busulfan and cyclophosphamide. Toxicity, mainly gastrointestinal and cutaneous, was severe and resulted in one toxicity-related death. Of 15 patients evaluated, there were no radiographic responses, and 10 (66%) patients had a stable disease pattern. Median duration of stable disease was 7 months (range, 5 to 8 months).

Lastly, Mason *et al.* [13], in a study from the Children's Cancer Group, treated 15 children with recurrent ependymoma with dose-intensive chemotherapy (thio-TEPA, etoposide, carboplatin) followed by autologous bone marrow transplantation. Five children died of treatment-related complications, eight children died of progressive disease (median survival post-transplant of 6 months), and one child died of unrelated causes. Only a single child remains alive and without tumor progression.

These studies indicate that chemotherapy has a modest effect in the setting of recurrent disease and that no chemotherapy regimen has clear superiority over another. Furthermore, dose-intensive chemotherapy offers no advantages over conventional-dose chemotherapy in the treatment of recurrent intracranial ependymomas.

Because recurrent ependymoma is difficult to manage, and multiple recurrences after intervention with further surgery or chemotherapy is common, Stafford *et al.* [33] treated 12 patients (with a total of 17 tumors) with recurrent ependymoma and stereotactic radiosurgery. Eleven of the 12 patients had previously been treated with external beam radiotherapy and all patients had undergone previous resection. The median marginal tumor dose was 18 Gy (range, 12 to 24 Gy). The median overall survival was 3.4 years (range, 1.4 to 5 years) with two in-field, one marginal, and two distant failures. Two patients developed treatment-related complications after radiosurgery. These results are as good or better than salvage chemotherapy and indicate that this modality of therapy may offer the best palliation in patients with recurrent ependymoma not otherwise considered for reoperation.

Newton *et al.* [42] reported on the rare occurrence of extraneural metastasis in patients with recurrent ependymoma (seen in <1% of all recurrences). Potential sites of metastasis include lung, lymph nodes, and bone. Management of patients with extraneural metastasis is particularly problematic, as reoperation is rarely a consideration and as a consequence, the majority of such patients will be treated by therapeutic default with salvage chemotherapy.

Spinal Cord Ependymomas

Spinal cord tumors are uncommon primary malignancies of the CNS and constitute 5% to 10% of all primary CNS malignancies [1,4–6,23,24,26,43–50]. Approximately 60% of all primary spinal cord tumors are intradural extramedullary in location and are either meningiomas (50%) or peripheral nerve sheath tumors (10%). Intradural intramedullary spinal cord tumors constitute only 30% to 40% of all primary spinal cord tumors, of which ependymomas comprise 60% in adults and 30% in children [1,4–6,23,24,26,45–50]. Two distinct spinal cord ependymomas occur. The myxopapillary histiotype accounts for 50% of all spinal cord ependymomas and is located in the cauda equina, with occasional extension into the conus medullaris [1,4–6,23,24,26,43,45,47,48,50]. The second ependymoma histiotype is the cellular ependymomas found in the spinal cord proper and which account for 50% of all spinal cord ependymomas [1,4–6,23,24,43,47,48,50]. These latter tumors are most often located in the cervical or thoracic spinal cord.

Ependymomas constitute 4% of all primary CNS malignancies in adults, of which 30% occur in the spinal cord [1,4–6]. Assuming 17,000 new cases of adult primary CNS tumors per year in the United States, approximately 227 new cases of spinal cord ependymoma are seen yearly. Of this number, only 50% (124 new cases per year) are intradural intramedullary ependymoma, indicating the relative rarity of these tumors. As a consequence, clinical trials directed at the treatment of spinal cord ependymomas have been nonexistent.

Spinal cord ependymomas may arise at any age but present most frequently in adults 20 to 40 years of age. Ependymomas arise from or extend into the cervical cord in greater than 65% of cases [1,4–6,48,50]. Greater than 90% of spinal cord ependymomas have a benign pathology, are slow growing, and although unencapsulated, tend to compress adjacent cord parenchymal rather than infiltrate it [23,24,47–50]. Approximately 50% of tumors span three or more vertebral levels. Pain is the most common presenting symptom and is seen in greater than 70% of

patients. Sensory disturbance is the second most common presenting symptom, seen in greater than 60% of patients. Limb weakness and bladder/bowel dysfunction are symptoms in 50% and 35%, respectively. Objective neurologic signs are seen in greater than 70% of all patients at presentation. These signs include hyperreflexia (in >65% of patients), motor dysfunction (in >65%), a sensory level (in 35%), and spasticity (in 35%).

A general consensus regarding management of spinal cord ependymomas has emerged based on institutional experience [23,24,47–50]. Extent of surgical resection is the strongest covariant predicting survival in patients with spinal cord ependymomas. Gross total removal of a spinal cord ependymoma (achievable in >70% of patients) may be safely attempted as ependymomas do not appear surgically to infiltrate adjacent neural tissues, and accordingly, a surgical interface is present. Surgical outcome is dependent upon the premorbid neurologic status. Patients with good preoperative status not only encounter less surgical morbidity, but also have less neurologic dysfunction postoperatively. Radiation therapy does not appear necessary following gross total resection of the tumor, as 5- and 10-year survival in excess of 80% is expected in patients with completely resected tumors. In the event of tumor recurrence, reoperation with attempted gross total removal should again be considered. Lastly, subtotally resected spinal cord ependymomas may be palliated by the administration of limited-field radiotherapy. Five- and 10-year survival rates of 60% are reported following radiotherapy [4–6,43,44,51,52].

Less clear is the management of recurrent spinal cord ependymomas having previously failed surgery and radiotherapy. Because salvage therapy chemotherapy is not curative, no standard therapy exists and, therefore, investigative trials are warranted. A variety of regimens have been utilized for recurrent intracranial ependymomas, including the "8 in 1" regimen, etoposide, carboplatin, PCV, MOPP alternating cyclophosphamide plus vincristine with cisplatinum plus etoposide, and autologous bone marrow transplantation [26,31,53–56]. These studies indicate that chemotherapy has a very modest effect in the setting of recurrent intracranial ependymoma and that no chemotherapy regimen has clear superiority over another. How to extrapolate this data to recurrent intradural intramedullary ependymomas is problematic.

Begemann and DeAngelis [31] reported on the chemotherapy treatment of 23 recurrent spinal cord and 25 intracranial ependymomas. Of this group, seven were treated with carboplatin alone and six received a variety of multi-agent regimens. The abstract is, however, unclear on how many patients treated with chemotherapy represented recurrent spinal cord ependymomas. In this brief report, the authors conclude that single-agent carboplatin was better tolerated than multi-agent regimens and may provide meaningful palliation (median progression-free survival of 7.5 months). Chamberlain [56] reported on 10 consecutive adult patients with recurrent intramedullary spinal cord ependymoma, all of who were treated with chronic oral etoposide. Four had previously been treated with single-agent carboplatin or PCV. Two patients showed a partial radiographic response and five had stable disease for a median duration of response of 15 months and median overall survival of 17.5 months.

Further chemotherapy trials for recurrent spinal cord tumors are warranted and novel therapies would be a welcome addition to the limited therapeutic options presently available. A potential new option would utilize the cyberknife, a stereotactic radiotherapy technique applicable to the spinal cord.

Subependymomas

Subependymomas are slowly growing expansile tumors usually encountered as an incidental autopsy finding within the ventricular system [57–61]. The frequency of subependymomas, both incidental and symptomatic, among intracranial neoplasms is 0.2% to 0.7%. These tumors are characterized by a distinctive microscopic appearance of cellular nests with intervening hypocellular fibrillary regions.

Scheithauer [57] and Lombardi *et al*. [59] first recognized these tumors as a separate pathologic entity and proposed the subependymal plate as the origin of these tumors; however, this is still a controversial issue. When symptoms do occur, they are secondary to their location and size (usually greater than 4 cm in size) rather than a change in biologic behavior.

In the largest series, Scheithauer [57] reported the mean age of symptomatic patients was 49 years and that 80% of subependymomas occurred in men. Approximately 71% are infratentorial (located in the fourth ventricle), 25% are supratentorial (located in the lateral ventricles), 2% are thalamic (located in the third ventricle), and 2% are spinal (most often located in the cervicothoracic region). Among supratentorial tumors, tumors arise from either the walls of the lateral ventricle (80%) or septum pellucidum (20%). Fourth ventricular subependymomas may arise from the floor (47%), the roof (41%), or lateral recess (12%) of the fourth ventricle.

Greater than 85% of all patients with symptomatic tumors present with raised intracranial pressure secondary to obstructive hydrocephalus. Symptoms are often episodic and of comparatively long duration (median of 30+ months). Tumors arising in the thalamus or fourth ventricle may, in addition, present with focal signs and symptoms, most often hemiparesis or cranial neuropathies.

The radiographic appearance of subependymomas consists of a well-demarcated, slightly lobulated tumor appearing isodense with minimal enhancement (50%) and frequent dystrophic calcification (50%) on cranial computed tomography scans [57–61]. On MRI, the tumors are isointense on T1-weighted and slightly hyperintense on T2-weighted images. With gadolinium enhancement, subependymomas demonstrate marked contrast enhancement.

When possible, complete tumor removal is recommended. Not dissimilar to spinal cord ependymomas, image-verified gross total resection is curative [57–61]. Therefore, in instances of subtotal resection, consideration for reoperation should be entertained with the goal of complete resection. The efficacy of postoperative radiotherapy for incompletely resected subependymomas is unclear and, in general, not advised. If complete surgical excision is not possible (*eg*, in tumors that invade the brainstem) with symptomatic residual tumor or for patients who develop tumor progression or recurrence, irradiation is often employed. Again, the role of radiotherapy for such circumstances is uncertain. There is no evidence that chemotherapy is effective and, as a consequence, its role as a salvage therapy is poorly defined.

Conclusions

Ependymomas are uncommon tumors found throughout the neuraxis. Essentially, all investigators concur that complete resection is the most important prognostic variable predicting for event-free survival. The survival benefit from image-verified complete resection has led many to conclude that a second surgery be performed in the event of an incomplete resection and the possibility of achieving a complete resection based on tumor location and risk of reoperation. Radiotherapy for resected intracranial ependymomas appears beneficial, particularly for incompletely resected tumors. Limited-field radiotherapy is administered to M0 tumors and CSI to M1 tumors. The issue of total tumor dose is uncertain, and limited data suggest a potential benefit may be seen with boost radiosurgery following conventional radiotherapy. Radiotherapy has a very limited role in the treatment of spinal cord ependymomas and subependymomas regardless of location. Chemotherapy is not advocated as primary treatment and at present is best utilized as a salvage therapy in patients having failed surgery and radiotherapy.

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