



Myxopapillary Ependymomas

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15.1 Definition

Myxopapillary ependymomas (MPEs) were first defined as a distinct subtype of ependymomas by Kernohan in 1932 [1]. These tumors account for approximately 1–5% of all spinal neoplasms with an incidence of 0.0–0.08 cases per 100,000 persons annually [2, 3]. The incidence in the American population was found to be 1.00 per million person-years [4]. Fifty percent of ependymomas are spinal and—within this group—50% are MPEs [5]. Extramedullary ependymomas arise from the ependyma of the filum terminale located in the area of the conus medullaris and cauda equina. Histologically, the overwhelming majority are myxopapillary [6]. MPE is a slow-growing tumor most frequently found in adults between 30 and 50 years of age [7] and they constitute around 13% of all ependymomas and as many as 90% of all tumors in the conus medullaris [8–10]. MPEs originates from the filum terminale in the area of the conus medullaris and cauda equina [11], and are classified as a WHO Grade I Tumor. The main bulk of the tumor is located in the lumbar canal below the conus medullaris with up to one-third of the tumors extending to thoracic spine and one-fifth of these tumors extending to sacrum [6].

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The recommended treatment for patients with MPE is gross total resection, and patients undergoing subtotal resection usually also undergo radiotherapy [12]. Despite the benign histology and slow-growing nature of most MPE tumors, some MPEs behave in an aggressive manner. Treatment failure of MPE with local recurrence, distant spinal metastasis, and brain metastasis has been reported to occur in one-third of patients [13]. Signs of postoperative aggressive behavior, after either subtotal or gross total resection, are local recurrence and aggressive growth. Another sign of aggressive behavior is secondary seeding (i.e., metastasis) of an MPE to distant cranial and spinal sites or to local spinal sites after surgery [11]. MPEs have been reported to be more aggressive in pediatric patients than in adults with local rates and recurrence of 64% compared with 32% in adults [14]. The focus of our discussion will be on MPEs in adults since the topic of pediatric MPEs has been covered in another chapter of this book (Chap. 16).

15.2 Histopathology and Molecular Biology

Grossly, these tumors are well-encapsulated, reddish to purplish in color, and sausage-shaped [15]. The microscopic morphology of MPE is characterized by a papillary arrangement of cuboidal or elongated tumor cells surrounding a fibrovascular core, which contains both hyalinized blood vessels and a marked abundance of extracellular mucoid matrix [16].

It has been hypothesized that there are intrinsic molecular differences and genetic types of MPE that are currently unrecognized [11]. This could represent a spectrum of different grades of MPE, perhaps with the most aggressive tumors presenting earlier in childhood and the indolent tumors remaining clinically occult due to their slow growth and presenting later in adulthood. Also, one can speculate that in the younger pediatric population, tumor cells of the same type have a higher propensity for division [11]. There are several molecular markers of MPEs. The receptor tyrosine kinase cMET and HOXB13 gene are included in histologic and molecular analysis research of MPE. cMET may have a role in more invasive behavior of MPE since cMET activation in brain malignancy enhances cell proliferation, migration, and invasion and inhibits cell death [11]. The HOXB13 gene has been identified as a molecular signature for MPE [17]. HOXB13 is more specific for MPE while HOXA9 is more specific for ependymoma. HOXB13 was expressed equally in pediatric and adult patients with MPE [17]. MIB-1, a marker for cellular proliferation, has low expression in MPEs due to their inherent benign biological profiles [16]. Epidermal growth factor receptor (EGFR) protein expression has been shown to predict a worse clinical correlate for patients with intracranial MPEs [18] and was found in all recurrent tumors but not in tumors that did not recur [16, 19]. Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases that are capable of degrading extracellular matrix proteins, which may lead to the promotion of metastasis. Aggressive megakaryocyte-erythroid progenitor cells showed overexpression of platelet-derived growth factor receptor A (PDGFR α), MMP2 and MMP14 [16], which may be new diagnostic and therapeutic targets [16]. MPE may

be driven by a Warburg metabolic phenotype [20] with western blot analysis demonstrating increased protein expression of hypoxia-inducible factor 1-alpha (HIF-1 α), hexokinase 2 (HK2), pyruvate dehydrogenase kinase 1 (PDK1), and phosphorylation of pyruvate dehydrogenase (PDH)-E1A [20].

15.3 Classification

We have proposed a novel classification system of the MPEs. This classification is based on the location of the tumor and its correlation with extent of resection (Table 15.1). It is important to note that this classification is more an anatomical than surgical one as the biological behavior of the tumor, its aggressiveness, and its recurrence rate depends on multiple factors, which are discussed in this chapter. Figures 15.1, 15.2, 15.3, 15.4 and 15.5 demonstrate various cases of MPEs operated on by the senior author (KIA); Figs. 15.6 and 15.7 demonstrate cases of MPEs operated by primary author. Figure 15.8 shows the schematic diagram of our original classification of MPE.

15.4 Symptoms

MPEs are tumors with long history. Mean time between the first symptom and diagnosis was reported to range from 46 months [21] to 8 years [6]. The clinical presentation of MPEs with regard to patient age and duration of symptoms does not differ significantly from other intradural tumors that occur below the cord in the region of the filum [9]. The most common initial symptom is nonspecific back pain [6, 14, 22, 23]. Back pain, lower limb weakness, and sensory disturbances often occur together

Table 15.1 Classification of myxopapillary ependymomas (MPEs)

Type IA	Only filum terminale is involved by the MPE (rare extramedullary intradural lesion). GTR (gross total resection) easily feasible.
Type IB	Extramedullary MPE involving a lumbar nerve root with filum terminale. GTR more challenging than type I A.
Type II	Intramedullary involvement of conus medullaris and filum terminale. GTR.
Type III	Intramedullary involvement of lower part of spinal cord, conus medullaris and filum terminale (upper lumbar cord enlargement).
Type IVA	Intramedullary involvement of lower part of spinal cord and conus with solid and cystic component. No signs of hydro- or syringomyelia.
Type IVB	Involvement of entire conus and lumbar intumescencia with cystic compartment and signs of hydro- or/and syringomyelia in the upper part of the spinal cord. Slow growing, resection GTR or STR. More aggressive behavior with primary/secondary seeding.
Type VA	Tumor is located outside the lumbar part of the spinal cord but remains intradural (cervical/thoracic spine)
Type VB	Tumor is located outside the spinal canal (sacroccocygeal, mediastinal, intracranial MPE)



Fig. 15.1 Lumbar spine imaging of a 72-year-old female patient with lower back pain and bilateral leg pain and previous history of cancer. Preoperative MRI of the lumbar spine: (patient operated on by the senior author [KIA]): (a) sagittal post-contrast T1-weighted MRI shows intradural-extramedullary tumor (myxopapillary ependymoma) at L4 (arrow) confined to filum terminale without adherence to the nerve roots (Type IA); (b) sagittal T2-weighted MRI; and (c) axial T2-weighted MRI of the lumbar spine. (d) Postoperative sagittal T2-weighted MRI of the lumbar spine demonstrates total resection of the tumor

[14, 24]. Less than 10% of patients consider gait ataxia, sexual problems, or sphincter problems, although up to 50% of patients have bladder dysfunction [9, 10, 21].

Rapid worsening could indicate an intratumoral hemorrhage [21, 25, 26] with rare cases of hydrocephalus due to spinal subarachnoid hemorrhage [21]. Conus

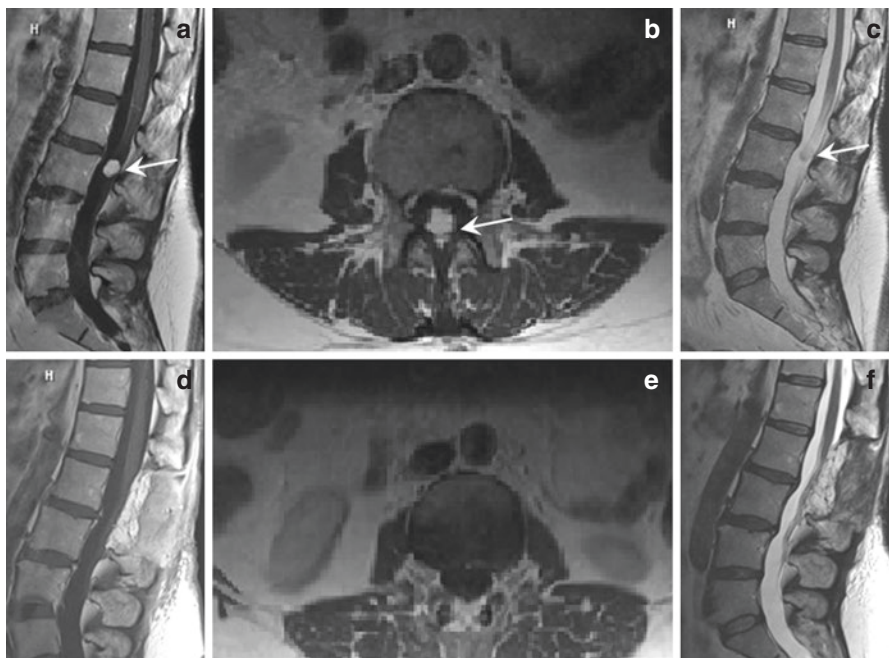


Fig. 15.2 Imaging of a 56-year-old female patient with back pain, numbness and tingling in legs with difficulties voiding. Preoperative MRIs of the lumbar spine (patient operated on by the senior author [KIA]): (a) sagittal post-contrast T1-weighted MRI showing encapsulated enhancing tumor at L3 (arrow) without involvement of filum terminale and nerve roots of cauda equine (Type IA); (b) axial post-contrast T1-weighted MRI; (c) sagittal T2-weighted MRI of the lumbar spine. Postoperative MRIs of the lumbar spine demonstrating complete tumor resection: (d) sagittal post-contrast T1-weighted MRI; (e) axial post-contrast T1-weighted MRI; (f) sagittal T2-weighted MRI. The patient recovered completely and was neurologically intact

medullaris and filum terminale lesions are located at a highly mobile segment of the spine, and the traction forces might cause disruption of blood vessels on the surface of the tumor. Histopathologic factors relate to the presence of numerous small blood vessels and loss of connective tissues in the tumor [25].

15.5 Imaging

On gadolinium-enhanced MRI motor evoked potential (MEPs), like their intramedullary counterparts, enhance brightly with contrast. Enhancement may be homogeneous or patchy due to small intratumoral cysts and hemorrhages [6]. MPEs differ slightly than other ependymomas in that they may appear hyperintense on T1-weighted images as well due to the proteinaceous mucoid matrix [27]. With further improvements in the resolution of MRI, even very small leptomeningeal seeding can be detected [22]. Cysts that expand cranially and caudally from the tumor as well as hydro- and syringomyelia are not uncommon. Unencapsulated tumors are more frequently seen in heterogeneously enhanced tumors on MRI than

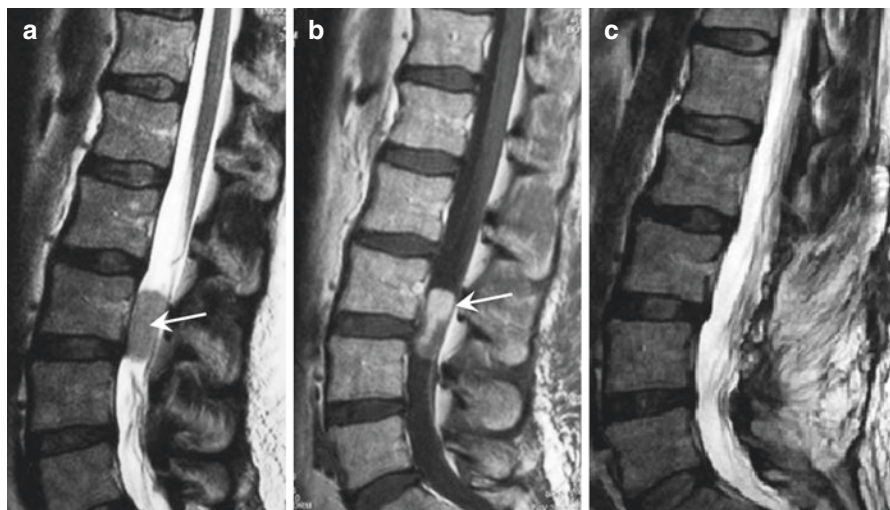


Fig. 15.3 Imaging of a 47-year-old female patient with paraparesis, L2 sensory level, and bowel incontinence (patient operated on by the senior author [KIA]). (a) Preoperative sagittal T2-weighted MRI of the lumbar spine demonstrating myxopapillary ependymoma at L3 segment (arrow) Type IB. (b) Preoperative sagittal post-contrast T1-weighted MRI of the lumbar spine. Complete resection of the tumor was performed. The patient recovered completely and was neurologically intact. (c) Postoperative T2-weighted MRI of the lumbar spine demonstrating complete resection

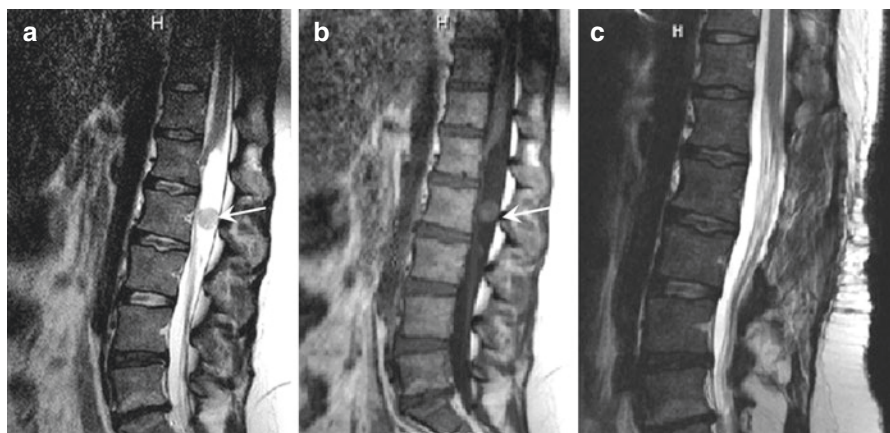


Fig. 15.4 Imaging of a 35-year-old patient with severe low back pain and urinary retention (patient operated on by the senior author [KIA]). (a) Preoperative sagittal T2-weighted MRI of the lumbar spine. (b) Sagittal post-contrast T1-weighted MRI of the lumbar spine demonstrating MPE at L2 with large cystic component, involvement of conus and lumbar intumescence, and hydromyelia (type IVB). (c) Postoperative sagittal T2-weighted MRI of the lumbar spine demonstrating complete resection with cyst drainage and resolved hydromyelia. Urinary retention resolved completely, the patient had no neurological deficits

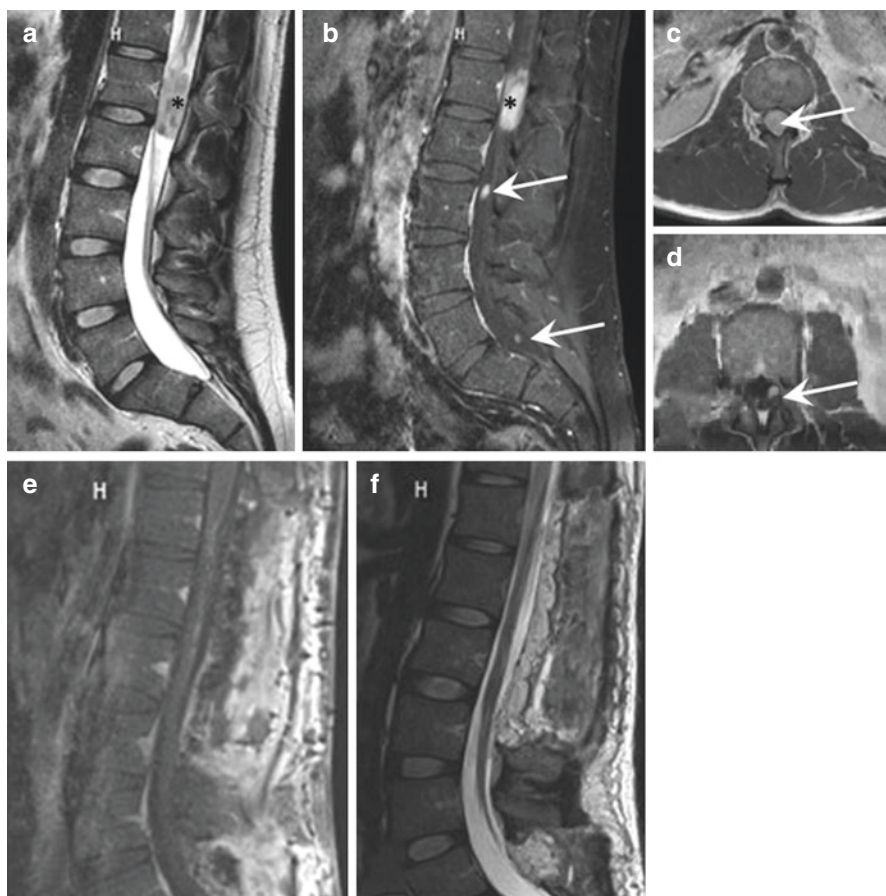


Fig. 15.5 Imaging of a 33-year-old male patient who presented with urinary retention (patient operated on by the senior author [KIA]). (a) Preoperative sagittal T2-weighted MRI of the lumbar spine demonstrating large MPE (*) at L1–L2 with involvement of spinal cord, conus medullaris and filum terminale. (b) Sagittal post-contrast T1-weighted MRI of the lumbar spine showing 2 further lesions (arrows) at L3 and S1 (type IVB). (c) Axial post-contrast T1-weighted image showing tumor at L1. (d) Axial post-contrast T1-weighted image shows the tumor at L3. Postoperative MRI demonstrates the total resection of all of the three tumors: (e) sagittal T2-weighted MRI and (f) sagittal post-contrast T1-weighted MRI. Urinary retention resolved completely. Further screening did not show the presence of secondary seeding

in homogeneously enhanced tumors [28]. Computed tomography (CT) scan is useful for demonstrating erosive bone changes that can vary from nonspecific canal widening, to scalloped vertebral bodies, to neural foraminal enlargement, and finally to osseous destruction [29].

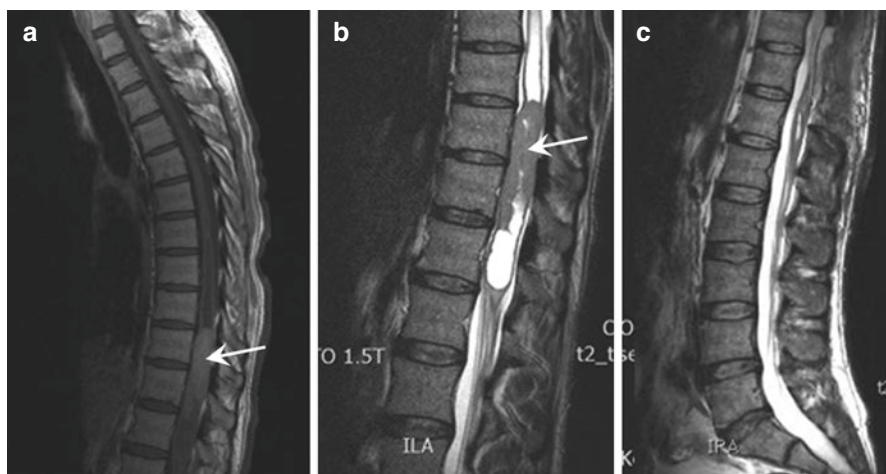


Fig. 15.6 Imaging of a 45-year-old female patient who presented with paraparesis and urinary retention (patient operated on by IO). Preoperative MRI of the spine: (a) sagittal post-contrast T1-weighted MRI showing cystic contrast-enhancing tumor (arrow) at T10-L1; (b) intratumoral cyst with syringomyelia is best seen in sagittal T2-weighted MRI (Type IV B). (c) Postoperative sagittal T2-weighted MRI of the spine showing the complete resection of the tumor with resolution of syringomyelia

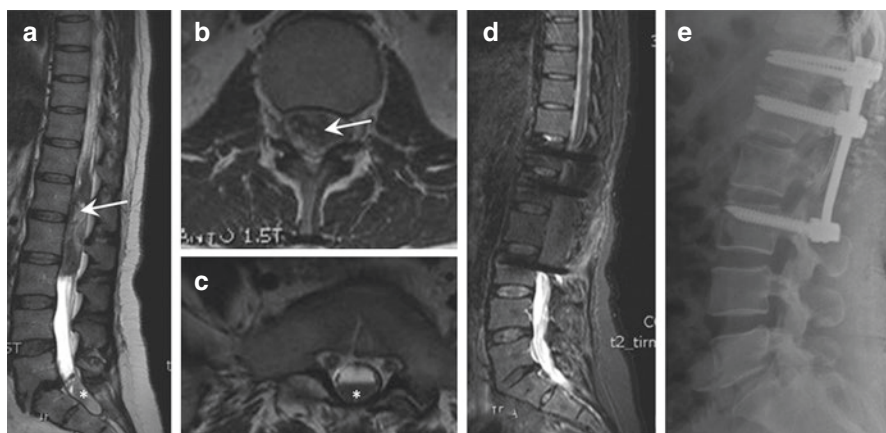


Fig. 15.7 Imaging of a 43-year-old female patient who presented with acute onset of paraparesis and urinary retention (patient operated on by IO). (a) Sagittal T2-weighted MRI of the lumbar spine revealing intratumoral hemorrhage at L1–L3 (arrow) with subdural hematoma at S1 (*) (Type IVA). (b) Axial T2-weighted MRI of the lumbar spine shows the tumor mass (arrow). (c) Axial T2-weighted MRI of the lumbar spine showing subdural hematoma at S1 (*). Complete tumor resection and evacuation of the hematoma were performed. Due to laminectomy over 3 levels, additional spinal stabilization was performed. (d) Postoperative sagittal T2-weighted MRI of the lumbar spine following tumor resection and hematoma evacuation showing complete resection without residual hematoma. (e) Postoperative sagittal X-ray of the lumbar spine demonstrating T12–L3 stabilization of the thoracolumbar transitional area

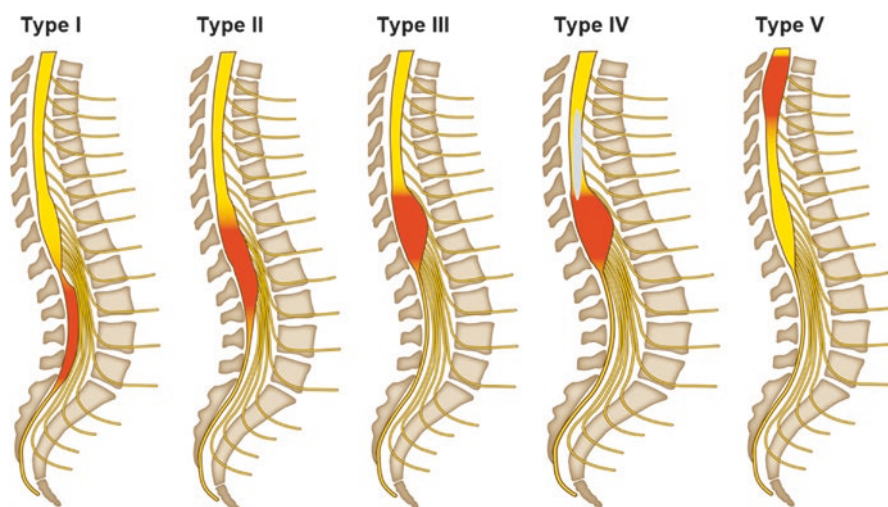


Fig. 15.8 Schematic diagram of the classification of myxopapillary ependymomas (from Omerhodzic, Pojski and Arnautović 2018)

15.6 Rare Locations

Myxopapillary ependymomas can occur in ectopic sites, such as the sacrum and in presacral tissue where ependymal cells may be found. These ectopically located tumors have a worse prognosis and a higher rate of extraneural metastasis. Sacrococcygeal [30–32], intracranial [33], and soft tissue myxopapillary ependymomas have been described, as well as extraneural metastases in the lungs, pleura, liver, and thoracic and abdominal lymph nodes [34]. Case series on extradural ependymomas showed higher local recurrence rate (60% for presacral and 25% for tumors on the dorsal aspect of sacrum) compared with classical MPEs, with a mortality rate of up to 50% in one case of local recurrence [29] and a 100% 5-year mortality if metastases occur. Giant sacral MPEs may require resection, lumbopelvic reconstruction and fusion, followed by radiotherapy [31]. Intradural lumbosacral ependymomas can spread throughout the central nervous system (CNS) but rarely metastasize beyond it, whereas extradural ependymomas seldom disseminate within the CNS but pose a significant risk for systemic metastases [35].

15.7 Surgical Technique

Removal of ependymomas in the lumbar and sacral region may be quite difficult as these tumors are well-vascularized and may not display a capsule, so that they may completely encase nerve roots of the cauda equine [9]. Nerve roots and the spinal cord may be very adherent to—or even infiltrated by—the tumor [36], and surgical

morbidity for these tumors is considerably higher compared with other extramedullary pathologies [37].

Both microsurgical technique and spinal cord monitoring are indispensable to achieve total removal of MPEs and to obtain improvement of neurological recovery [38]. Based on plane of dissection and intraoperative neurophysiological monitoring (IONM), GTR should be always the goal. Tumor resection can be safely achieved, if the tumor is encapsulated. However, as the tumor grows, tumor encapsulation can be lost and adherence to cauda equina can inhibit or make complete resection more difficult and induce new deficits after surgery [39]. Complete resection without capsular violation—the so called marginal en bloc resection—can be curative, and is often simply accomplished by snipping the filum above and below the mass. Nevertheless, this technique can be technically difficult based on tumor size, shape, and anatomical relation to the cauda equina or spinal cord.

The details of the surgical resection of MPE is demonstrated in our surgical videos (Video 15.1). Positioning of the patient needs to fulfill two important goals: first, to provide an optimal working angle, and second, to keep the operative field well above the level of the heart with minimal obstruction of the venous flow, the latter being an important point in keeping the intraoperative bleeding at minimum [40]. (For technical details on prone positioning for resection of spinal cord tumors, refer to Chap. 12, Spinal Cord Astrocytomas.) An alternative to the full prone position described there, some authors recommend the use of the kneeling or so-called “praying to Mecca” position [40].

Arms are properly padded and the head is placed either in straight neutral position or turned to side so that there is an even pressure distribution on the face with the eyelids carefully shut [40]. Intraoperative neurophysiological monitoring—MEPs, somatosensory evoked potential (SSEPs), and free-running electromyography (EMG) are performed routinely for resection of these lesions and it are of vital importance in identifying the filum terminale. Intraoperative fluoroscopy with a C-arm is a good way to determine the cranio-caudal extent of the lesion in the lumbar and cervical region in lateral projections, and in the thoracic spine in anterior-posterior projections.

We routinely harvest fat from the paraumbilical area in the supine position, which will be later utilized to obliterate “dead space” after laminectomy and for CSF leak prevention. After the skin incision, the subcutaneous fat is entered. Diathermia is preferred with meticulous hemostasis throughout the approach, which prevents oozing blood from obstructing the operative field. The exposure is tailored according to the length of the lesion in a cranio-caudal direction. We use hemilaminectomy for smaller lesions and laminectomy for larger lesions (e.g., >3 cm), and where the multilevel decompression is needed. Laminectomy is performed with high-speed diamond drill and Kerrison rongeurs. Laminectomy with three or more segments may be accompanied with spinal fusion following the tumor resection, particularly at the thoracolumbar junction. In other locations, with >three levels involved, laminoplasty is utilized.

The exact extension of the tumor is then demonstrated by ultrasonography before opening the dura. Dura is opened in the midline and tacked to the surrounding

muscle tissue with dural tacking sutures. The arachnoid is opened separately with micro-scissors or a micro knife and delicately freed from the posterior or lateral spinal cord, keeping it intact for closure at the end of surgery. Ligaclips are applied to hold the arachnoid membrane to the dura.

Tumors are usually well-demarcated, grayish, and sausage-like encapsulated structures that displace the cauda equine nerves laterally [41]. The rostral part of the tumor is first mobilized to allow visualization of the attachment of the tumor that arises from filum terminale, which usually has a distinctive white color from a striated pial membrane compared with the yellow tan of the cauda equine nerve roots. Proximal and distal attachment of the filum terminale is then microsurgically dissected off the tumor and isolated for any nerve roots in order to prepare for the resection. Lateral tumor margins are mobilized and freed from any attachments [41].

We recommended transecting the filum terminale first at its proximal end to avoid upward retraction. Prior to coagulation and division of filum terminale, we stimulate it with a probe nerve stimulator to make sure it is not mistaken for a nerve. The key step in the resection of MPE is the transection of filum terminale, which presents the tumor origin. Intraoperative neurophysiological monitoring plays a key role in this surgical step. The modalities that are in standard use are transcranial electrical stimulation and direct root stimulation. Both consist of recorded muscle motor evoked potentials (mMEP) that were evoked by either transcranial electrical stimulation (TES) or by direct stimulation of nerve roots in the surgical exposed area. The bulbocavernosus reflex (BCR) is a third IONM modality to monitor the sacral sensory roots and neural circuitry [42]. Furthermore, free-running electromyography (EMG) monitoring of the lower-limb muscles, external anal sphincter (EAS), and external urethral sphincter (EUS) is routinely performed for monitoring of bladder and anal sphincter function [43]. Direct spinal stimulation has been used to exclude motor function of the surgically identified filum terminale or other tethered structures, whereas TES-mMEP was recorded for monitoring the integrity of sacral motor roots and neural circuitry in the lower spinal cord [42]. Direct nerve root stimulation for identification and mapping of vital nervous tissue is performed by the surgeon. A monopolar and/or a bipolar probe is used applying 200 μ s voltage pulses, and when the voltage threshold is over three-times the voltage threshold of a prior stimulated nerve root in the operating field, the structure can be resected [42]. Subsequently a TES-MEP stimulus can be applied in order to reassess the responses of the vital neural tissue after the transection of filum or detethering [42]. The mean electrical threshold for EMG response during stimulation of the filum terminale was 37.1 v (range, 15–100 v) in one series. In comparison, the lowest threshold obtained by direct stimulation of the ventral nerve roots was a mean of 1.46 v (range, 0.1–7 v) [44].

The isolated proximal filum terminale is then coagulated and divided. Gentle traction on a divided filum terminale stump allows for anterior, inferior, and lateral tumor margins to be delivered out of the tumor bed. After transecting the filum, the tumor can be dissected away from the neural structures and completely extirpated. Lifting the proximal end of the filum together with the remaining tumor allows the nerve roots on the ventral side to be mobilized, and additional cotton pledgets can

be placed to keep them separated from the remaining lesion. The cranial pole of the tumor needs to be dissected free in order to follow the ventral tumor side caudally to identify the exact position of the conus. The tumor is gently delivered and rotated from the tumor bed. Attachments of the nerve roots on the tumor surface are carefully isolated and released. Preservation of small sacrococcygeal roots is important to reduce the incidence of postoperative urinary dysfunction [41]. Finally, after completely releasing the tumor from the surrounding nerve tissue, the filum can be transected immediately below the conus to achieve a complete tumor resection (i.e., GTR) [7]. Again, particular care is exercised to avoid violation of the tumor capsule and possible dissemination of tumor cells.

The first step in the resection of an infiltrative MPE is microsurgical debulking of the tumor using micro-scissors and bipolar instrument (mostly without any coagulation). Resection without any violation of the tumor capsule might be difficult in some cases. Capsule rupture has been found in many MPEs extending over three vertebral levels, suggesting that these tumors grow over time and eventually penetrate the capsule [39]. To prevent any subarachnoid spreading of tumor particles during debulking, small cotton patties are positioned around the entire tumor before starting the resection [7]. Fine forceps, micro-dissectors, or sharp dissection with micro-scissors or micro-knife can be used to create a plane between the tumor and the normal spinal cord tissue. Once the tumor mass had been removed inside the capsule, the filum terminale needs to be identified, coagulated, and cut [7].

Following resection, the subarachnoid space is irrigated with warm saline solution. After hemostasis, the pial closure (if applicable) is done with 7-0 Prolene, and arachnoid closure is done by approximating edges with bipolar coagulation. Dural closure is performed with 4-0 Nuroton stitches with application of previously harvested fat graft to prevent CSF leak [45].

15.8 Extent of Resection

Reported extent of resection in surgical series has increased since the introduction of microsurgery. In the literature, the reported incidence was 40–78.9% [7, 10, 21–23, 36, 46, 47]. Table 15.2 provides the literature review of the studies that evaluated patients with spinal MPEs. GTR was achieved in 77.7% of cases in the series by Klekamp, with subtotal resections in the remainder of largely unencapsulated MPEs [7]. There are two possible explanations for the relatively low GTR rates [16]. First, MPEs have a histological feature of myxoid degeneration. The myxoid matrix that accumulates between the tumor cells and blood vessels renders the GTR challenging. Second, the nerve roots of the cauda equine may be embedded in the neoplastic tissue, so the manipulation of the intertwined tumor and nerve tissue may cause irreversible neurological morbidities. Under such circumstances, aggressive removal may not be the preferred option [16]. Some of the complications associated with surgery include postoperative CSF leaks, wound infections, cyst and syrinx formation, declining Franklin grade, tethering of the spinal cord, paraplegia, pulmonary embolism, kyphosis, and scoliosis [60].

Table 15.2 Literature review on main (recent) studies evaluating spinal myxopapillary ependymomas (MPEs)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Chan et al. [15] 1984 Retrospective study Single institution 1919–1981	N = 7	5 surgery alone 2 surgery plus RT	2 patients were long term survivors (3 and 7 years) 2 patients with STR plus RT survived 1 and 17 years.	3–17 years. follow-up	MPE is not uncommon during childhood but has a good prognosis. All patients with this tumor require prolonged follow-up for tumor recurrence after operation and irradiation.
Someland et al. [9] 1985 Retrospective study Single institution 1924–1983	N = 77 Male = 49 Female = 28 Mean, 36.4 (range, 6–82)	All patients underwent surgery	GTR had a recurrence rate of 10%, piecemeal (34%), or STR (41%) had recurrence rates of 19%	GTR resulted in longer survival of 19 years, STR 14 years.	Radiotherapy may be of particular benefit to patients whose tumors are not amenable to intact total removal.
Ross et al. [48] 1993 Retrospective study Single institution	N = 77	6 patients had total resection of encapsulated lesions; GTR, and 4 had STR. 12 received postoperative RT	12 patients are well and disease-free 2 patients have had recurrences after surgery and RT	Mean follow-up of 80 months.	Patients with MPEs should be followed indefinitely because of the potential for late recurrence, even after aggressive therapy.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Celli et al. [10] 1993	N = 28 Male = 17 Female = 11 Median age, 38 (range, 13–64)	20 patients (71%) underwent GTR	8 patients improved, 7 unchanged and 11 deteriorated 7 patients died—5 deaths were related to tumor	Mean follow up of 18 years.	Factors having a positive influence on the prognosis (risk of recurrence) were the following: Clinical history >1 year, confinement of tumor to the filum terminale, and total tumor removal. Postoperative RT had no appreciable effect on outcome. The mode of the tumor growth is cardinal factor in prognosis.
Akyurek et al. [3] 2006	N = 35 Median age, 35 years. (range, 14–63 years.) Male to female ratio was 2.5:1.	21 (60%) patients underwent GTR 13 (37%) underwent STR 1 (3%) underwent biopsy only 22 (63%) also received adjuvant RT.	10-year OS, PFS, and LC rates for the entire group were 97%, 62%, and 72%, respectively Of 11 patients, 5 (45%) who had undergone GTR alone had recurrence Total of 12 (34%) patients had disease recurrence	Median follow-up was 10.7 years.	Long-term patient survival duration for MPE managed with surgery and adjuvant RT is favorable. Regardless of the extent of resection, adjuvant RT appears to significantly reduce the rate of tumor progression. Failures occurred exclusively in the neural axis, mainly at the primary site.
Pica et al. [49] 2009 Retrospective study Multicenter	N = 85 Male==50 Female==35 Mean age, 45.5 years. (range, 14–88)	38 (45%) underwent surgery 47 (55%) received postoperative RT	5-year. PFS was 50.4% for surgery only and 74.8% for surgery plus RT	Median follow-up was 60.0 months. (range, 0.2–316.6)	Age < 36 years, absence of neurologic symptoms at diagnosis, tumor size >or = 25 mm, and postoperative high-dose RT were variables predictive of improved PFS.

Kucia et al. [50] 2011 Retrospective study Single institution 1983–2006	N = 34 Male = 14 Female = 20 Mean age, 45.5 years. (range, 14–88)	27 patients (80%) had GTR alone 7 (20%) had STR plus RT	The overall recurrence rate was 10% (3/34 patients)	N/A	The goal of surgical treatment of MPE is resection to the greatest extent possible with preservation of function. In cases of STR, postoperative RT may improve outcome. If neurological function is maintained at treatment, these indolent lesions allow years of good function.
Al-Habib et al. [51] 2011 Retrospective study Single institution 1972–2005	N = 18 Male = 7 Female: 8 (age range, 18–71)	GTR 4 out of 7 cases in which conus was not involved, Only 1 of 10 cases involved conus	No patients with GTR developed recurrence All patients survived at long-term follow-up.	Median postoperative follow-up was 56 months.	MRI is very sensitive (100%) and moderately specific (67%) in detecting direct anatomical contact between conus and MPE tumors.
Aghaie et al. [52] 2013 Retrospective study Single institution 1984–2010	N = 16 Mean age, 16.8 (range, 12–21)	All patients received surgery (GTR or STR) 50% followed with RT	LC at 5 and 10 years. was 62.5% and 30%, respectively for surgery alone vs. 100% for surgery and adjuvant RT	Median follow-up of 7.2 years. (range, 0.75–26.4 years.)	50% of the patients receiving surgery alone had local failure.
Tsai et al. [53] 2014 Retrospective study Single institution 1968–2007	N = 51 Mean age, 35 years. (range, 8–63)	22 patients (39%) had surgery alone, 30 (59%) had surgery plus RT, 1 (2%) had RT only	10-year OS, PFS, and LC were 93%, 63%, and 67%, respectively 19 patients (37%) had recurrence, mostly local (79%)	Median follow-up of 11 years. (range, 0.2–37 years.)	Postoperative radiotherapy after resection of MPE was associated with improved PFS and LC.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Kukreja et al. [54, 55] 2015 Systematic review Multicenter	N = 337	N/A	Patients in GTR group had better PFS and OS. Patients in older age group (>35 years.) had better PFS	N/A	Overall, PFS did not improve if RT was combined with surgery compared with surgery alone; however, the adjuvant RT benefited patients aged ≤35 years.
Weber et al. [13] 2015 Retrospective study 11 institution	N = 183 Male = 108 Female = 75 (range, 19–51)	97 patients (53.0%) underwent surgery without RT 86 (47.0%) were treated with surgery and/or RT	Treatment failure in approximately 1/3 of patients.	Median follow-up was 83.9 months.	Recurrence pattern was mainly local. Younger patients and those not treated initially with adjuvant RT or not undergoing GTR were significantly more likely to present with tumor recurrence/progression.
Abdulaziz et al. [56] 2015 Retrospective review 2 institutions 1990–2013	N = 58 Male = 31 Female = 27 Mean age, 40.8 years. (range, 7–68)	27 patients En block resection (46.5%), GTR 20 (34.5%), STR 11 (18.9%)	12 patients (20%) underwent adjuvant RT following either STR or GTR Overall recurrence rate was 13.8% (N = 8), 5-year PFS was 81%.	Median follow-up was 51.5 months. (range, 12–243 months)	A strong correlation between capsular violation and recurrence was found following removal of MPE. Adjuvant radiotherapy in cases of capsular violation showed a trend toward improved PFS.
Khalatbari et al. [57] 2016 Retrospective study Single institution 2003–2010	Overall: 22 M:14 F:8 (range, 11–66)	22 patients underwent surgeries (14 adults, 8 children)	N/A	N/A	En bloc resection or piecemeal resection with radiotherapy were associated with satisfactory outcome without recurrence.

Chen et al. [16] 2016	N = 27 Male = 13 Female = 14 Median age, 32 (range, 7–57)	GTR achieved in 18 patients (66.7%) STR achieved in 9 (33.3%)	MPE recurrence rate was 4 in 27 (14.8%) with a median time of 26.5 months. (range, 17–83 months.) Patients who received GTR had a lower recurrence rate (11.1% vs. 22.2%), although not statistically different	Mean follow-up period was 49.8 months. (range, 13–122 months.)	Extent of resection and age are major factors related to tumor recurrence. PDGFR α , MMP2 and MMP14 may be new diagnostic and therapeutic targets, and EGFR may be a potential predictor of improved prognosis for MPE.
Bagley et al. [14] 2009	N = 52 Male = 34 Female = 18 Mean age, 31.8 years.	44 patients underwent surgery (40 adults, 12 children)	Pediatric patients had higher rates of LC and dissemination (64% vs. 32%) Median time to disease recurrence was 88 months. For the entire group OS after 11.5 years follow-up was 94%	Mean follow-up time was 6.1 years. (range, 0.6–33 years.)	Excellent outcomes may be obtained, however, with the use of aggressive surgical techniques. No clear benefit for adjunctive chemotherapy, and radiation therapy was demonstrated
Klekamp et al. [7] 2015	N = 42 Male = 25 Female = 17 Mean age, 38 \pm 14 years. (range, 11–73 years.)	34 four patients underwent 36 operations for 39 tumors 27 operations were performed to treat de novo tumors and the remainder were undertaken on recurrent tumors	GTR achieved in 28 operations (77.7%) and STRs in the remainder RT was employed after 6 operations on unencapsulated tumors, with 5 of these also demonstrating subarachnoid seeding	Mean follow-up 10 years. (127 \pm 100 months.)	Despite their delicate location and often enormous size, surgical morbidity in experienced hands is low with good chances for postoperative clinical improvements and very low recurrence rates after GTR for encapsulated tumors. The role of postoperative radiotherapy remains controversial. RT may be considered after incomplete resections of unencapsulated tumors and/or for patients with subarachnoid dissemination.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Chao et al. [58] 2011	N = 37 Male = 15 Female = 22 Median age, 33 years.	25 (67.6%) GTR 9 RT	16 patients (43.2%) were found to have a recurrence with a median time to recurrence of 7.7 years Mean survival time was 12 years.	N/A	Radiotherapy improved time-to- progression following first relapse, not up front. Less aggressive resection to maintain functionality and delaying RT at the time of recurrence is a reasonable approach. This may maximize patient quality of life by delaying any sequelae from aggressive surgery or side effects from radiation.
Kraetzig et al. [22] 2018	N = 19 Male = 9 Female = 10 Median age, 32 years. (range, 9–58)	78.9% GTR, with adjuvant RT in 20%. Of the 21.2% who underwent STR, 75% underwent postoperative RT	Tumor progression in 26.3%. Distant metastases were found in 57.9%, 36.4% of which were present at initial diagnosis. Following metastatic tumor diagnosis, 72.7% did not show progression or symptoms. OS 100% with excellent neurological outcome in 78.9% of cases	Median follow-up, 36 months. (range, 12–240)	For distant metastases of myxopapillary ependymoma without clinical manifestation, close clinical and MRI follow-up represents a sufficient strategy because most of the metastases remain asymptomatic and do not show progression over time. Additional resection or irradiation as salvage therapy would be recommended if metastases become symptomatic.

Sakai et al. [28] 2009	N = 20	GTR achieved in 14 Piecemeal GTR achieved in 3 STR achieved in 3	Neurologic deterioration after surgery was seen in 5 patients, all of which were unencapsulated tumors GTR in 2 patients STR in 3 patients Recovery of postoperative bladder dysfunction remained unchanged in 2 patients. There were no tumor recurrence and progression of the remaining tumors.	Follow-up period ranged from 2–12 years. (median, 72.9 months.)	In the unencapsulated ependymomas, tumor separation and manipulation of the surrounding neural tissue caused neurologic injury. The heterogeneously enhanced ependymoma not only should be evaluated and treated meticulously, but surgeons should also not stick to total removal in infiltrated and adhering tumors as subtotally resected tumors with postoperative radiotherapy have not always recurred.
Nakamura et al. [39] 2009	N = 25 Male = 5 Female = 3 Mean age, 33 years. (range, 14–58)	15 patients total resection + RT (6 en bloc, 9 piecemeal) 1 total resection without 4 STR + neuroaxis RT 6 partial resection after local radiation alone	In 1 case of total resection without RT, local recurrence occurred 2 years. after surgery 6 patients with partial resection after RT died of CSF dissemination 2 patients with STR + neuroaxis RT 2 developed recurrence	The mean postoperative follow-up period was 10.4 years.	Surgical margin obtained at the initial surgery and the extent and amount of postoperative radiation are crucial factors determining the prognosis. CSF dissemination can occur once tumor capsule is violated, before or during surgery. Therefore, early diagnosis is essential, and a therapeutic strategy including radiotherapy, on the assumption that this tumor is malignant, should be established.

(continued)

Table 15.2 (continued)

Authors Year Study Type Institutions (No.) Time Period	Patients (No. and age)	Treatment	Outcome	Follow Up	Findings
Balasubramaniam et al. [24] 2016	N = 44 M:35 F:9 Mean age, 30.95 ± 12.78	Total excision in 89%	In majority of patients at follow-up, back pain and motor weakness improved, Sphincter problems improved in only 25% Recurrence occurred in 2 patients	22.23 ± 11.32 months. Follow-up	Long term prognosis is excellent with respect to recurrence and functional outcome in cases with complete tumor excision.
Wang et al. [59] 2014	N = 19 Male = 11 Female = 8 Median age, 33 (range, 14–72)	9 patients had GTR 10 patients had STR. 5 patients with STR also received RT.	Higher tumor recurrence is associated with a lower LC rate and vice versa. All 9 GTR patients had no recurrence, with a 100% LC rate STR followed by RT group had a significantly higher LC rate than the STR alone group	142 months. Follow up	GTR of the tumor or STR followed by radiotherapy are more likely to avoid tumor recurrence than STR alone.

EGFR epidermal growth factor receptor, *GTR* gross total resection, *LC* local control, *MMP* matrix metalloproteinase, *OS* overall survival, *PDGFRα* platelet-derived growth factor receptor, *PFS* progression free survival, *RT* radiotherapy, *STR* subtotal resection

15.9 Recurrence

Recurrence in adults usually happens at the site of primary resection, whereas in the pediatric population, recurrence in the form of disseminated disease is more common [11]. Extent of resection and age are found to be major factors related to tumor recurrence [16]. Therefore, GTR is recommended whenever possible, unless neurological dysfunction following GTR is predicted. Younger patients demonstrate a shortened recurrence time [16]. Long history and infiltration of nerve roots are further independent factors for a tumor recurrence [36].

A strong correlation between capsular violation and recurrence was found following removal of MPE [56]. One of the first series on MPEs reported a recurrence rate of 10% after complete resections, 34% after piecemeal removals, and 41% after partial removals [9]. The overall recurrence rates in series of 34 MPEs from Klekamp were 6.6%, 19.0%, and 37.0% after 1 year, 10 years, and 20 years, respectively [7]. For non-encapsulated MPEs, the corresponding rates were 15.6%, 32.5%, and 66.2% after 1 year, 10 years, and 20 years, respectively, with significantly lower rates of 9.1% after 10 and 20 years for encapsulated tumors [7].

The overall recurrence rate was shown to be 15.5% in patients treated by GTR and 32.6% in patients treated by STR, irrespective of whether they underwent adjuvant therapy ($p < 0.001$) and with higher rates in younger patients [60]. Another study, however, showed opposite results (i.e., that the use of radiotherapy as salvage therapy after initial recurrence significantly correlated with longer times to a second recurrence—9.6 years for those who received RT vs. 1.1 years for those who did not) [58].

Late recurrence can occur decades after the surgery with latest clinical recurrence described after 42 years [61]. In the event of recurrence, however, spinal MPEs continue to have a favorable prognosis [14]. Treatment of recurrent MPEs without evidence of seeding includes reoperation, whereas in cases of local or distant metastases or for refractory cases (i.e., second and third recurrence), surgical resection with postoperative radiotherapy and chemotherapy should be considered. It has been recommended to perform radiotherapy of the craniospinal axis following incomplete resection in order to prevent seeding and recurrence [39]. While some studies demonstrated no benefit in recurrence-free survival for patients treated with adjuvant radiotherapy after surgery [58], others found that adjuvant radiotherapy was associated with better outcomes for both patients who underwent GTR and those who underwent STR [3, 49, 62].

15.10 Primary (Metastatic) and Secondary (Post-Surgical) Seeding

“Seeding,” “metastasis,” and “tumor dissemination” are terms used interchangeably and present a known phenomenon that describes many tumors of the CNS [63]. Despite MPEs being classified as WHO I Grade tumors, recurrence after both partial and gross total resection is well documented.

Primary MPE seeding is well recognized in pediatric patients but under recognized in adults despite the fact that MPEs are far more common in the adult population [11, 64]. There are only few case reports of primary metastases into multiple cerebrospinal locations before resection of MPE [11, 65]. Two recent studies have shown that the proportion of patients presenting with metastases at initial diagnosis ranges between 36.4% in patient cohorts with dominantly adult patients, and 50% in pediatric cohorts [22, 66].

Secondary seeding (metastasis) of lumbosacral MPEs describe seeding after surgery and has been described in detail with reports as early as the 1950s [67–69]. Secondary seeding is not uncommon and occurs in patients undergoing subtotal resection. When MPE metastasizes, it tends to spread rostrally in the CNS [70], mostly affecting the thoracic and cervical spine, followed by intracranial seeding [22]. In cases of dissemination or metastasizing disease, histological characteristics of benignity are commonly preserved in MPEs [69]. The extent of the initial surgical resection was significantly associated with dissemination and patients with residual tumor were more likely to develop disseminated disease, whereas violation of the capsule during surgery may lead to CSF seeding and dissemination [71]. There are extremely rare cases of double MPEs that could not be directly considered as dissemination, since both tumors were in the site of classical origin of MPE [72].

In pediatric patients with primary seeding, GTR is followed by radiation, adjuvant chemotherapy, or both. Because these are subarachnoid metastases, focal radiation targets the lumbar theca and radiation is directed up to mid-thoracic levels or even applied to the entire craniospinal axis [60]. Chemotherapy is reserved for patients with tumors that are refractory to radiotherapy and is generally considered less effective [12]. In adults with primary seeding and after a GTR, however, the issue of adjuvant therapy is not established, probably because primary seeding of MPE is not a recognized phenomenon [11]. Only follow-up with craniospinal MRI studies after gross GTR—or “prophylactic” postoperative irradiation and chemotherapy after GTR or STR—may be considered [12].

Recent study showed that up to one-third of all patients with MPE have distant metastases at the time of diagnosis, whereas around 73% did not show progression or symptoms during the follow-up of 3 years [22]. For distant metastases of MPEs without clinical manifestation, some authors prefer close clinical examination; MRI follow-up represents a sufficient strategy because most metastases remain asymptomatic and do not show progression over time. Additional resection or irradiation as salvage therapy would be recommended if metastases become symptomatic [22].

15.11 Adjuvant Treatment

Radiotherapy of the brain and whole spine may be recommended when a piecemeal resection is performed due to the rupture of the tumor capsule during surgery in order to prevent the local recurrence and CSF dissemination [39]. Usually, adjuvant high-dose radiotherapy (≥ 50.4 Gy) will be administered to patients undergoing subtotal resection or biopsy [13].

In 2006, Akyurek et al. [3] observed a significant decrease in the rate of tumor progression with adjuvant radiotherapy regardless of the extent of resection. Further studies showed that 5-year PFS was improved in patients receiving surgery plus radiotherapy (74.8%) compared with PFS in patients who received surgery alone (50.4%) [49]. Radiotherapy increases 10-year PFS from <40–70% in patients who received radiotherapy [13]. Radiotherapy dose-response relationship with PFS was also demonstrated in research that focused on pediatric MPE patients [54], which suggested that stereotactic radiosurgery with adjuvant radiotherapy provided an improved prognosis in disease control than with GTR alone [73] with significant improvement in the 5-year local control rate in patients who were treated with radiation doses higher than 50 Gy than those who received lesser doses [62].

However, the role of adjuvant radiotherapy remains controversial. One meta-analysis found that radiotherapy did not result in significant improvements in treatment with GTR alone compared with GTR plus radiotherapy, or in treatment with stereotactic radiotherapy alone compared with stereotactic radiotherapy or radiotherapy [60].

Chemotherapy has been suggested as a potential treatment to prevent recurrence, but its efficacy has not been established in MPEs. There are single case reports that describe the benefit of use of temozolomide concomitant with radiotherapy following multiple surgeries of recurrent MPEs with disseminated metastases [74]. Imatinib as second-line chemotherapy and the multi-kinase inhibitor sorafenib as third-line chemotherapy for metastatic MPEs have been reported [75].

15.12 Outcomes

We differentiate between the surgical (neurological) outcome and survival of patients with MPEs. In one recent analysis, the Surveillance, Epidemiology, and End Results (SEER) database, which includes over 700 cases of MPEs, identified surgical resection, radiotherapy (adverse prognostic factor of overall survival, likely due to selection bias), age < 30 years, and Caucasian race (decreased OS on multivariate analysis) as significant prognostic factors [4]. Despite their delicate location and often enormous size, surgical morbidity in experienced hands is low with good chances for postoperative clinical improvements and very low recurrence rates after GTR for encapsulated tumors [7]. Long-term outcome depends on the amount of resection and the presence of a tumor capsule [7], whereas larger tumors are found to perforate the capsule due to delayed diagnosis [39]. Preoperative functional status and the extent of removal were the significant prognostic factors influencing postoperative outcome [46]. Outcome is better for patients presenting predominantly with pain rather than neurological deficits [6]. Presence of urinary difficulties at the time of diagnosis is a relatively poor prognostic sign [76]. Permanent surgical morbidity is seen in 8–15% of patients [7, 23].

The estimated 10-years overall survival has been reported to be 92.4% [13] with 10-year PFS of 61.2% [13]. Age (<36 vs. ≥36 years), treatment modality (surgery alone vs. surgery and radiotherapy), and extent of surgery are prognostic factors for

local control and PFS [13]. However, treatment failure—including local failure, distant spinal relapse, and brain failure—has been reported to occur in up to one-third of patients [13]. The observed pattern of failure is mainly local, but up to one-fifth of patients presents with a concomitant spinal or brain component [49].

Risk of treatment failure decreases with GTR [9, 13]. According to most studies, GTR is strongly associated with PFS, while other studies suggest that GTR must be combined with high-dose radiotherapy in order to increase PFS [49]. Factors having a positive influence on the prognosis (risk of recurrence) are clinical history >1 year, confinement of tumor to the filum terminale, and total tumor removal [10]. Postoperative radiotherapy tends to prolong the recurrence-free interval for patients with unencapsulated tumors [7].

15.13 Follow-Up

If a complete resection of MPE is performed, the patient should be followed conservatively; however, if the capsule was violated or there was a STR, craniospinal irradiation may be performed to prevent CSF dissemination [39]. Neurosurgeons should be aware of the possibility of primary seeding and drop metastasis of an MPE, and they should also consider complete craniospinal imaging as part of both the preoperative work-up and postoperative follow-up and surveillance [11]. Diagnostic lumbar puncture at the time of diagnosis and before resection—or at a time of recurrence—to assess dissemination should be considered [11]. Long term or even lifelong MRI follow-up for these patients could be considered [11].

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