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Spinal ependymal tumors

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Abstract

Spinal ependymomas are strictly to be subdivided into intramedullary lesions and extramedullary lesions as they are histologically and genetically distinct. Whereas the intramedullary lesions (SPE) are assigned to the WHO grade 2 and very rarely grade 3, the extramedullary lesions or myxopapilary tumors (MPE) are only as recently also assigned to WHO grade 2. The major difference is that in general, an intramedullary lesion of grade 2 remains confined to the local site of origin, even when rarely recurring after complete resection. In contrast, the MPEs have the capacity to spread throughout the cerebrospinal fluid compartment but can also be controlled by cautious complete resection.

We here review the clinical features of spinal ependymomas, contrasting the entities, and describe the treatment found best from the literature to manage these lesions including interdisciplinary approaches.

Key words

ependymoma | intramedullary | monitoring | spinal cord lesion | surgery

Ependymomas arise from the ependymal layer of the ventricles and in the spinal cord consequently from the remnants of that layer in the central canal or filum terminale. Recently tracking developmental gene expression patterns, spatiotemporal patterns were analyzed giving some insight into the signals regulating cell fates in the developing cord, but that has yet to be translated into clinical relevance.[1] The neuropathology of ependymomas has taken a major turn with the introduction of molecular genetics and methylation-based subclassification of ependymoma so that in general it has become rather an umbrella term for a sizeable group of molecularly defined entities as is reflected in the WHO 2021 classification[2] with further subgroup specification based on methylome analysis.[3–6] Currently there are 2 supratentorial subtypes distinguished by different gene fusions and age preference, 3 infratentorial subtypes which are without gene fusions but with different methylation patterns, and 2 spinal subtypes, the ependymoma of the spinal cord (SPE) which occurs intramedullary and the extramedullary myxopapillary ependymoma (MPE) of the filum terminale. Recently a MYC-amplified small subgroup of SPE with a worse prognosis has been added and this entity is not only very rare but in contrast to the non-MYC-amplified tumors also is extramedullary with infiltration of the cord but apparently no relation to the central canal.[7] Also for MPE there has been a further subdivision into MPE-A and MPE-B according to their methylation profile.[5] Apparently MPE-A occurs in a younger age group, lend themselves less to complete resection, and therefore have a worse prognosis.

In children and young adults, SPE may be associated with NF2 together with meningiomas which are also frequent in this syndrome.[8] For the purpose of this report, further consideration will only be given to the main groups of spinal ependymoma, SPE and MPE as far as clinical management is concerned.

In addition to ependymoma, there is also the subependymoma SE which does have a different cell layer of origin[9] and a separate neuropathology[2] but in the spinal cord is very rare[10] and when small has an almost identical growth pattern to SPE and can usually only be proven by histology or remains suspected when a lesion remains asymptomatic and inert and is followed for many years without histological verification.

Clinical Presentation

Typically the spinal ependymal tumors arise in adulthood, MPE somewhat later than SPE. In a population-based study of 1384 adult patients (>18 years) diagnosed with “ependymoma” in

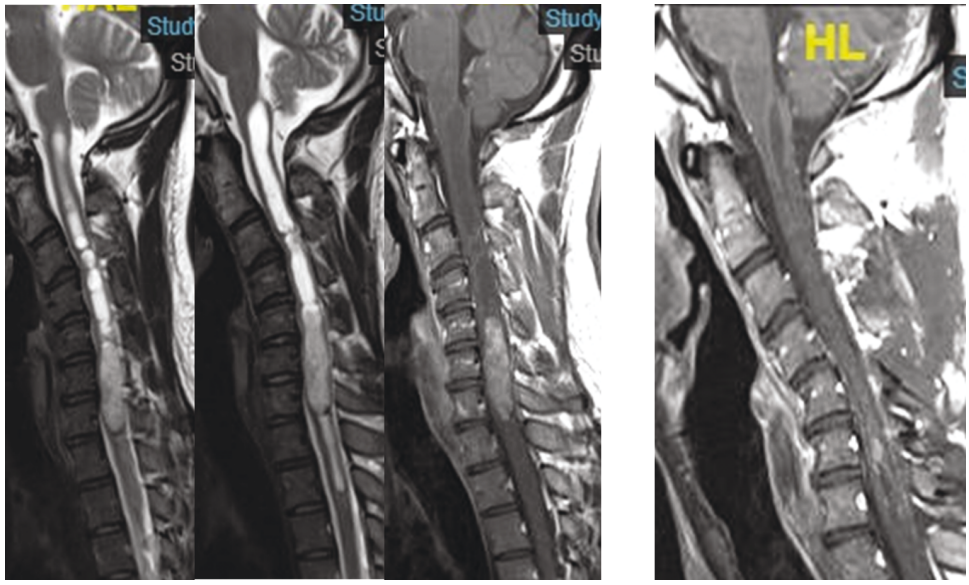

Figure 1. Paradigmatic example of a cystic intramedullary ependymoma with long-standing insidious symptoms which were in stark contrast to the impressive lesion spanning about 30% of the spinal cord from the medulla oblongata to Th 2. The T2 images on the left show the pseudo membranes which are still frequently wrongly considered to be septum's separating cysts but they are rather haustrations and there is always free communication in the polar cystic compartments. The tumor is seen in the contrast-enhanced T1 image and corresponds to the solid mass in the center of the syrinx of the T2 images. The postoperative images show the collapse of the cyst despite the removal of only the solid tumor nodule over a 3-level laminotomy, supporting the experience that even extended cysts are never compartmentalized.

the Netherlands,[11] spinal ependymoma (WHO grade 2) made up 56% and the anaplastic variant (WHO grade 3) 9%, myxopapillary ependymoma 20%, and subependymoma (although not originating from ependymal cells) 11%. There is an almost equal male/female distribution.[12] Overall it is the most common adult intrinsic spinal tumor but in absolute numbers still a rare tumor type with a share of about 1% of tumors of the central nervous system.[13] In children it is even less common and only a few series have been reported as recently reviewed.[14]

As intramedullary tumors, SPE becomes symptomatic with diffuse sensory symptoms, mostly dysesthesias, rarely pain, and occasionally paresis. It is common, as with all intramedullary tumors that there is a significant delay of months, sometimes years until the definitive diagnosis is made by imaging.[15] Upon imaging which is mandatory by contrast-enhanced MRI, the size of SPE lesions and their neuroradiological appearance are frequently in stark contrast to the mild symptoms leading to the imaging. SPE enhances upon contrast and tends to have polar cysts which can extend far beyond the proper tumor so that the cyst formation is reminiscent of syringomyelia (Figures 1–3). Hemosiderin deposits are common as these tumors tend towards microhemorrhages It is almost a rule, that the larger the lesion together with the typical polar cysts with contrast enhancing wall, the more likely it is that the lesion is an ependymoma and not an astrocytoma.[16] Incidental findings which are small and have no polar cysts may be mistaken for an inflammatory lesion but as tumor always causes a local distension in contrast to an inflammation that can be mostly differentiated on clinical symptomatology. Also, an inflammatory lesion usually has a short history of severe symptoms. SE is much rarer than SPE and in a large multicenter cohort it is described, that these lesions are rather excentric or even lateralised[17] which is easily explained by their origin somewhere in the subependymal glial cell layer which surrounds the obliterated central canal from which the SPE originate.

For a lesion suspected to be SPE, especially with proof of progressive symptoms and increasing size in imaging there is no question about the indication for treatment. In contrast, small lesions and those, which are found incidentally may be watched as they are very slowly growing and may even be stable for years or decades,—casting even doubt on the suspected diagnosis and may potentially be subependymoma. There is one report in which lesions which became symptomatic but for a variety of reasons were not treated remained stable and were observed for many years without progression or intervention[18] (Figure 4).

The indication for treatment of progressive lesions has to be weighed against further deterioration and the fact, that surgical removal, which is the only option, may result in initial postoperative deterioration and mild but permanent sequelae which however are uniformly reported to be the more severe the more pronounced the more preoperative neurological deficits are.[19]

A spinal lesion is suspicious to be MPE as of the level of the conus and then downwards into the end of the dural sac in the sacrum. The lesions are mostly related to the filum terminale which harbors the epyndymal remnants of the embryonic neural tube. Depending on their location, they can irritate one or more nerve roots resulting in rather unspecific symptoms of dysesthesia or pain, paresis is highly unusual. By imaging, they are very difficult

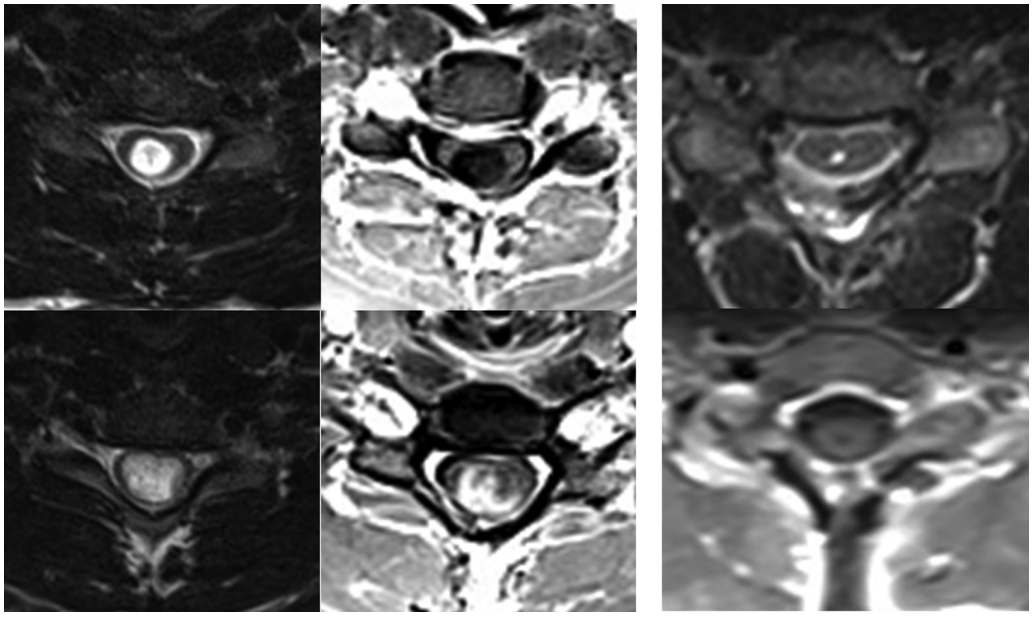

Figure 2. Axial views from the case presented in sagittal view in Figure 1. The 4 left panels show in the upper row the top part of the cyst which in T2 is sharply delineated, has no contrast enhancement in T1, and impresses like any syrinx. Below are 2 cuts through the tumor showing the heterogeneous contrast enhancement. To the right are 2 postoperative images, the T2 showing the near collapse of the cystic part and the contrast-enhanced T1 the complete removal and return to shape of the cord.

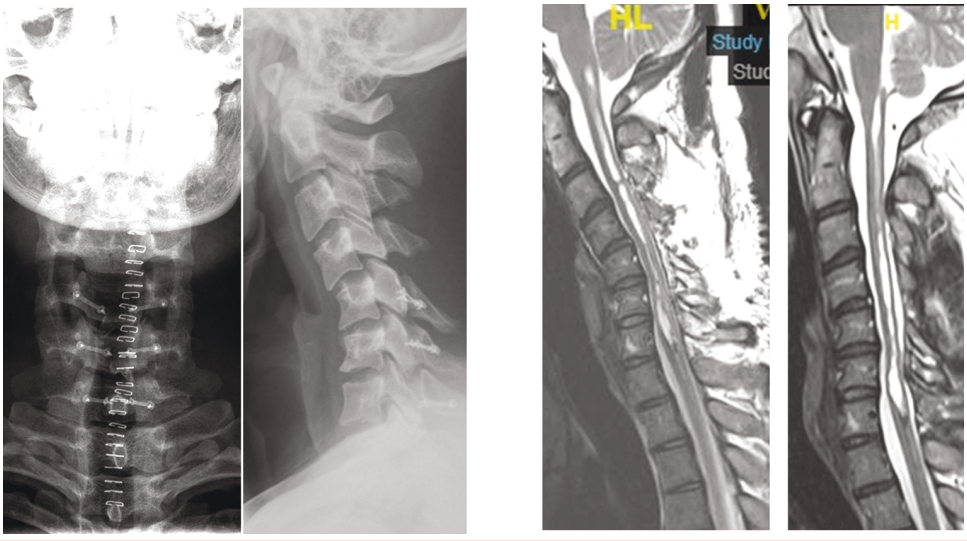

Figure 3. The same case as in Figure 1 showing on plain x-ray the limited 3-level laminotomy in 2 planes and the immediate sagittal spine deformity which was present already in the preoperative situation T2 images and is also seen somewhat accentuated postoperatively. After 1 year of follow-up, there is no indication in the sagittal T2 that the deformity which was suspicious of progressing toward a swan neck progressed but it rather showed that with adequate physiotherapy the region was stabilized and it also shows that the syrinx,- once the tumor is radically removed remains in its collapsed state.

to distinguish from a small neurofibroma or schwannoma of the cauda. MPE stays inside the canal and rarely goes undetected before contact with the bone. Schwannomas and neurofibromas when growing slowly over a long time can cavitate the vertebrae which never happens in myxopapillary ependymomas. Both types also show non-specific symptoms with very slow progression, usually pain, or dysesthesia.

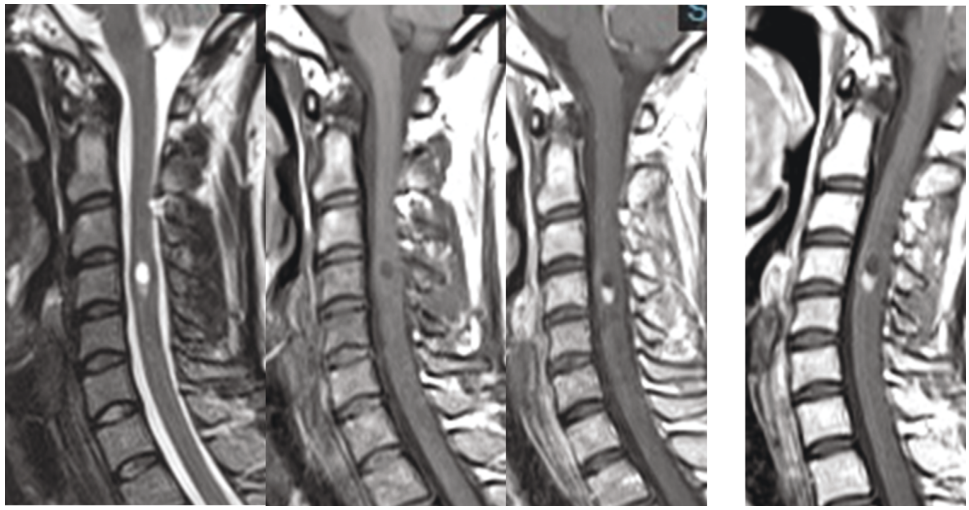

Figure 4. Small intramedullary lesion as an incidental finding after a blunt minor trauma. There is a polar cyst without extension into the central canal (left 3 panels) and over the course of 7 years, there was no change and also no emergence of symptoms so without histological proof this is thought to be an indolent subependymoma with no indication for any kind of intervention.

Therapy. Surgery SPE

The indication for treatment of intramedullary ependymomas results from the exhausted compliance of the fiber tracts in the cord at the time of symptomatic diagnosis. When patients report progressive symptoms, to prevent further deterioration, removal is indicated, even when a lesion is comparatively small (Figure 5), As complete removal results in long-term or permanent control, it is the primary option of choice as there is no first-line chemotherapy and no indication for radiotherapy. In patients with incidental diagnosis and no symptoms at all, a wait-and-see strategy may be adopted to wait for enlargement or onset of mild symptoms, both of which may not happen for a long time or at all (Figure 4).

There are many surgical series for intramedullary ependymoma and as many techniques as there are specialized centers.[13,19–26] There are, however, some common themes and cornerstones which emerge.

First, the enhancement along the walls of polar cysts, in some cases covering more than half of the total extension is not to be mistaken for tumor but rather represents reactive gliosis which is relevant for surgical planning. To avoid instability or deformation, only the solid tumor parts are to be exposed but generously so both poles can be detached from the gliosis leading into the cysts or central canal (Figures 1 and 2). To be able to open the cord wide, the roof of the spinal canal is taken off usually by laminotomy as that gives optimal exposure for a centrally located intramedullary lesion allowing it to reach the whole circumference of the tumor at its equator with equal bilateral exposure through a midline approach. Laminectomy has become inappropriate because of frequently observed deformities, especially in the cervical spine and in young patients causing a paradigm shift since the 1990s.[19] The risk for deformity is reduced for smaller exposures[27] and even further with laminoplasty[28,29] but it is still a risk which cannot be completely avoided and should be part of the consent (Figure 3). Laminoplasty is also of advantage should recurrence or progression necessitate another exposure.

After dural exposure, transdural ultrasound helps to determine the correct extent of exposure. After the midline opening of the dura and the arachnoid, a subdural electrode for the D-wave is inserted, proceeding by opening of the spinal cord in the midline sulcus to expose the tumor. The techniques to resect the lesions used from that point on are as individual as neurosurgeons are individual ranging from debulking with CUSA, piecemeal removal, sharp dissection, or laser dissection with the tumor bulk left intact as much as possible[30] to apply traction to open the dissection plane to the fiber tracts, a technique preferred by the authors.[31] Apart from the most used midline approach, a less used alternative is a dorsolateral approach just medial to the dorsal root entry zone.[32]

A special consideration has to be given to electrophysiological monitoring. Monitoring in itself is a complex methodology in itself, far from having uniformly acknowledged standards which still seem to be elaborated.[33–36] On the other hand, when removing a tumor, a considerable amount of manipulation cannot be avoided so it is not uncommon that with the resection, the evoked potentials diminish, with the D-wave being the most stable parameter. With the technical possibilities to obtain more and more refined measurements, there is on the other hand much discussion on the mandatory consequences of the findings during monitoring. It has been observed that stopping surgery and letting the patient recover ended in a situation where there were no deficits and the tumor had to be removed in a subsequent second setting so that monitoring was related to incomplete removal.[35] Thus, deliberately not using monitoring and concentrating on total removal has been discussed and demonstrated to be safe

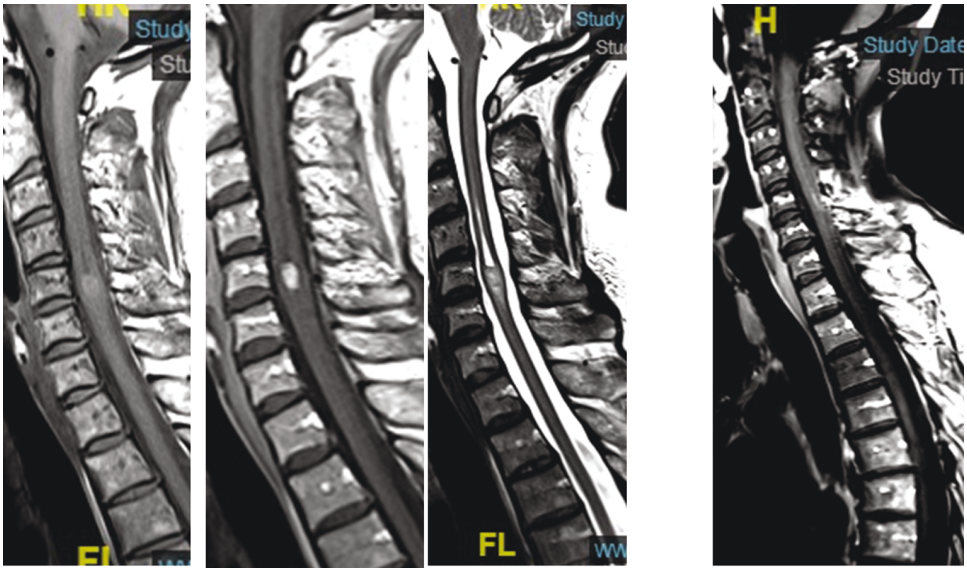

Figure 5. Small intramedullary ependymoma with the initial typical signs of a nodular contrast enhancement central to the spinal cord and emergence of a diagnostic polar cyst in the position of the normally obliterated central canal which seems to be widened until way above the nodulus. The postoperative image shows, that with a very limited single-level laminotomy the tumor can be completely removed without compromising the alignment of the spine.

and effective.[30] The general opinion is, however, that monitoring should be used but that only when a surgical maneuver leads to directly correlated findings, surgery should be stopped and time given to see recovery. Also, technical issues like dislocation of the electrodes need to be checked.

Another controversy surrounds the use of high-dose steroids in spinal cord surgery. The controversy originates from the simple fact, that all studies supporting the efficacy of high-dose methyl-prednisolone (MPS) were generated in highly standardized experimental trauma models mostly in rats and all studies to evaluate the clinical benefit are done in heterogeneous cohorts of patients with acute nonstandardized trauma. There are no randomized controlled studies on the use and efficacy of MPS in spinal cord surgery. However, elective surgery for an intramedullary tumor is more closely related to experimental trauma than random accident-induced injury (see Westphal for discussion[15]). Therefore it can be recommended to use a high-dose MPS scheme as of dural opening and maintain it for 24 h in analogy to the NASCIS II scheme.[37] Interestingly, none of the reports which go into great technical detail about intramedullary tumor resection mentions the use of steroids.[38–40]

Therapy. Surgery MPE

The treatment indication for myxopapillary ependymoma is somewhat different. When the lesion is symptomatic, treatment is warranted. But even in an asymptomatic lesion, when there is the suspicion that it could be that entity, early treatment diminishes the likelihood of spontaneous dissemination. Also here, the lesions need to be exposed so that both poles can be reached but a unilateral partial or complete hemilaminectomy, spinal keyhole.[41] with undermining of the spinous process is sufficient for most lesions to get access to the whole canal and content of the dural sac. The lesions are to be carefully dissected off the roots and when the filum with the typical blood vessels is exposed, it is coagulated and cut at the cranial pole and then caudally and the lesion pulled out in toto as any debulking or piecemeal resection can cause dissemination. Should the lesion be too large for a keyhole, laminectomy is preferable to piecemeal removal to ensure en-bloc resection and avoid dissemination. MPE is known to disseminate within the CSF space, spontaneously or after resection so that revision surgeries may be advised for symptomatic lesions while others may remain stable for a very long time[42,43](Figures 6 and 7.

Electrophysiological monitoring is commonly used for forensic reasons but is not very helpful in cases in which there is no encasement of nerve roots which is rare. In those cases comprehensive monitoring may indicate undesired stress to nerve roots, depending on how many roots will be monitored. Undue stress to an adherent root may result in "trains" as seen with facial nerve monitoring in the CP angle.

Adjuvant Treatments

The vast majority of SCEs are WHO grade 2 and can be durably controlled by gross total resection. Control rates and overall survival in a series meta-analysis with 906 cases of "low-grade ependymoma" a ten-year survival of 96% in reports after 1990 is reported so,—considering nonspecific

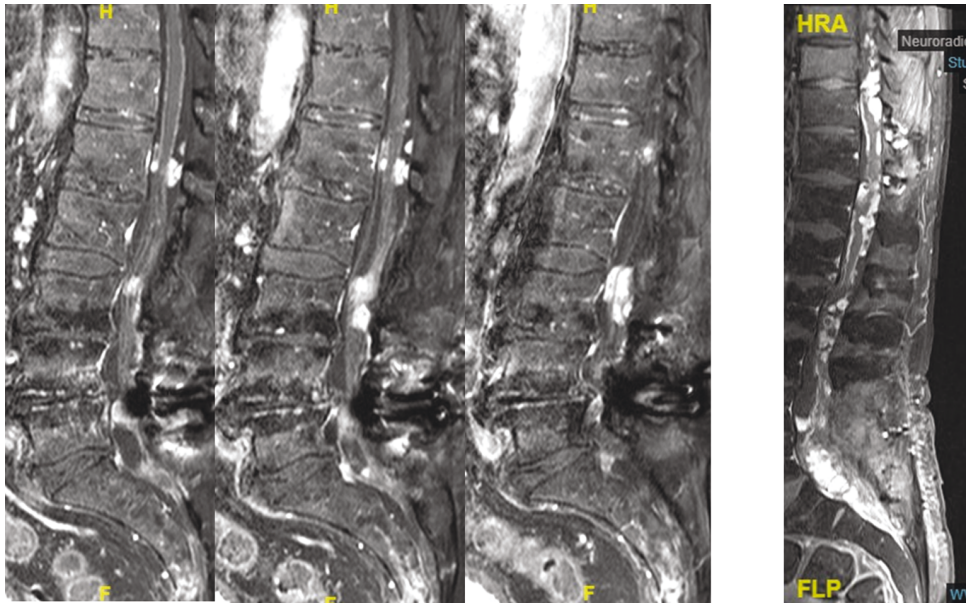

Figure 6. Two cases of extensive dissemination of a myxopapillary ependymoma. The tumor shown in the left 3 panels was initially treated 20 years prior to this situation but could not be removed in toto so several revision surgeries for debulking of symptomatic lesions took place. The encasement of the nerve roots in the cauda equina is clearly visible. Another case with massive dissemination involving the whole spinal canal is seen on the right.

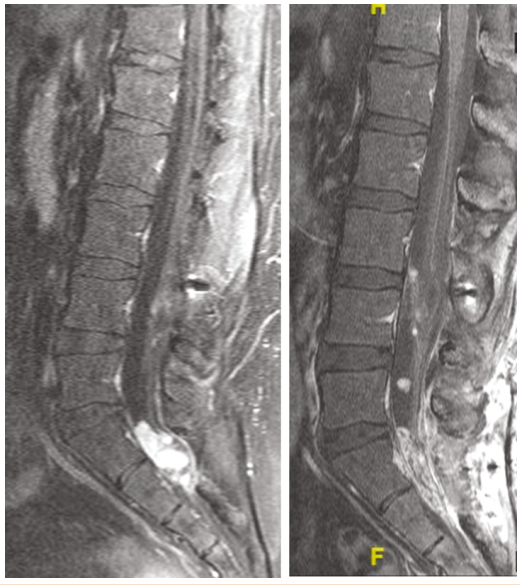

Figure 7. Another case where salvage surgery was done for a local, mildly symptomatic recurrence 10 years after removal of a lumbosacral MPE was performed. Further 12 years later, several disseminated nodules already present then have only minimally enlarged.

"all-cause-mortality" as an additional factor, the prognosis is excellent and should for grade 2 lesions be normal as for life-expenctency.[13] Even recurrent lesions should first be removed as they are usually detected during routine follow-up which is done initially in yearly, later in longer intervals. Recurrent tumors are then small and unproblematic to remove with the fiber tracts of the cord "protected" by an interface of gliosis towards the tumor. Also, most recurrences are anyway slowly growing residuals of incompletely removed primaries and stay with the original grading.

Adjuvant treatments therefore are considered rather in the context of anaplastic lesions.[44] Anaplastic ependymomas (AE) are rare and still a major challenge with unchanged poor prognosis. It is reported that despite their aggressive biology, AEs have a dissection plane identical to the grade II lesions, and therefore gross total resection should be attempted before adjuvant therapy.[45]

Radiation

Radiation is the most commonly used adjuvant therapy. In a recent review, the recommendation emerges, that for AEs local radiation with 45–60 Gy with 2 cm margins proximal and distal to the lesion delays progression.[45] In the retrospective analysis of a national cohort, the same impression was generated although the numbers are too small to obtain statistically solid data.[26] For grade II ependymomas, there is no proven role for radiation even for cases with subtotal resection[26] and few reports on positive effects make the role of adjuvant radiation for incompletely resected SPE grade II at best controversial. Looking at guidelines, there is no compelling evidence, that incompletely resected SPE WHO grade 2 should receive adjuvant radiation (evidence level III) whereas the indication for anaplastic lesions is undisputed.[46]

There is widespread agreement that upon dissemination of MPE, radiation should be recommended[42] and there is also some evidence that adding local radiation to incompletely resected tumors may improve local control[46]—although still controversial,[47] while a combination of salvage surgery and salvage radiation, however, showed significant efficacy.[47]

Chemotherapy

Chemotherapy on the other hand is even less frequently used than radiation as that would be indicated only for AEs and should not even be considered for grade II tumors. The reports are few and the regimens are mixed with temozolomide, CCNU, carboplatin being used in small institutional series.[48] A recently completed phase 2 trial with dose-dense temozolomide and lapatinib for all patients with histologically verified ependymoma showed also activity for the subgroups of SPE, AE, and MPE with improvement of symptoms and a shorter response duration for anaplastic tumors.[49]

Chemotherapy for myxopapillary ependymoma is reported on even less but more often considered because of the tendency for leptomeningeal spread and widely disseminated disease.

Treatment Sequelae

Postoperatively, patients may experience a variety of aggravated or new symptoms. The most frequently used approach for the removal of an SPE is through the midline. That may compromise the fiber tracts of the dorsal columns, so impaired proprioception is a frequent complaint of the patients which usually improves within the first weeks but may not recover completely. Interestingly, even severe loss of proprioception allows patients to walk on the first postoperative day as visual control of leg movement is a powerful compensatory mechanism for the immediate postoperative period. Likewise, some patients experience an irritation to their pain sensory system in the cord resulting in persistent, neuropathic pain which has been reported in up to 30%.[19,48] In some patients, a pain syndrome may develop secondarily after some months or even years and in that case, this may be due to arachnoidal adhesions of the myelotomy which then result in tethering and continuous microtrauma.[50] Tethering which has been reported to occur in up to 37% of cases may be reduced by closing the pia and when present the arachnoid.[19]

The postoperative sequelae described above may well be seen as subclinical causes of impairment of the quality of life (QoL), especially as SPE is basically a benign disease with an excellent prognosis for life expectancy. It is most likely attributable to the small cohorts in individual institutions, that no systematic evaluation of QoL is assessed and reports are rare and only recently emerging.[51] Without explicitly evaluating the small group of SPE in that series, it emerges, that the impairment from subclinical pain and dysesthesias has a larger impact than superficially appreciated because most patients willreturn to work and can do exercises but retire earlier and are easier exhausted. It also emerges that the tools to assess QoL for patients with intramedullary lesions in general are to be refined revealing an important gap in all the series mainly concerned with the extent of resection or progression-free survival based on imaging.

As for other sequelae, postoperative spinal deformity may have severe reconstructive consequences. This is not an issue for MPE as these are usually approached by a keyhole[41] without impairment of spine biomechanics. For SPE however, the most important aspect is the limitation of the exposure to the solid tumor compartment to keep the length of the laminotomy as short as possible. Even when three levels are removed, this can lead to limited local kyphosis but these patients have to be alerted to the need for sustained physiotherapy which can stabilize the situation and avoid surgical stabilization (Figure 2). Spinal deformity is more of a problem in pediatric cases who also seem to have longer tumors, needing longer exposures in a spine still growing so that in a long-term cohort of 55 pediatric patients, the new-onset deformity after intramedullary spinal cord tumor surgery was reported as high as 16%, with a necessity of stabilization in 55%.[52]

In summary, spinal ependymomas remain a challenging group of tumors, both, SPE and MPE. Larger homogenous series are close to impossible to generate because the incidence is low and recommendations or standards are often developed from meta-analyses of institutional series collected over decades with constant adaptation to technological or medical progress. Nevertheless, some standards have emerged and for these entities safe surgical complete removal is still the gold standard which can lead to a complete cure with acceptable sequelae as long as the lesions are not anaplastic. It is to be hoped that specific molecular targets for effective therapy will eventually emerge from the ongoing efforts of thorough molecular analysis so that surgery can be complemented with other therapies in the future.

Conflict of interest statement

None declared.

Authorship statement

M.W. performed all surgeries and both authors contributed equally to developing the concept, assembling data and literature research and approving the final version.

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