

Review article

Intracranial epidermoid cyst: Characteristics, appearance, diagnosis, treatment and prognosis

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Abstract

Intracranial epidermoid cysts are uncommon congenital inclusion cysts. Cerebellopontine angle is the most common location that harbors the intracranial epidermoid cyst; however, they are also found in other parts of the brain. These have a characteristic hallmarking radiological feature and well defined hypoattenuated mass resembling cerebro-spinal fluid on computed tomography. T1weighted image shows the lesion as low signal, and T2 weighted image shows high signal, whereas diffusion weighted image shows restricted diffusion leading to hyperintensity of the lesion. We present a unique review compiling the data from the literature that includes the history, characteristics of benign and malignant epidermoid cyst, typical and atypical appearances, very near differential diagnosis, followed by treatment and prognosis at one place.

Key words: Diagnosis, hypoattenuated mass, intracranial epidermoid cyst, treatment and prognosis.

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Introduction

An intracranial epidermoid cyst is a rare congenital anomaly developed because of the dysembryoplasia during the third to fifth week of gestation. Epidermoid tumors are also called as inclusion tumors because they arise from remnants of epithelial tissue during the neural tube closure at the third and fifth week of developmental stages of a fetus. These account for 0.2% to 1.8% of all intracranial tumors [1]. These typical epidermoid cysts usually appear with signs and symptoms, but may also appear incidentally in the early stages of life with less signs and symptoms. Commonest location is cerebellopontine angle, but can also be seen in other parts of the brain. The classical and typical neuroimaging of epidermoid cysts are hypodense lesions resembling CSF that does not enhance on post contrast, low signal intensity on T1WI, high signal on T2WI sequences and on diffusion weighted images they show up with high intensity [2, 3].

Epidermoid cysts were first discovered by an artist in a French medical school in 1807 [4]. Cruveilhier described the epidermoids as “pearly tumors” and Dandy as “most beautiful tumors of the body”. Among epidermoids, the highest incidence of housing of these lesions was at cerebellopontine angle which were 51.8% followed by lateral ventricle with 4.9%, fourth ventricle with 3.2%, third ventricle with 0.7% and other sites includes 39.4% [5]. The epidermoid cysts of the brainstem are very rare, configuring of about almost six cases of precisely intrinsic epidermoid cyst of the brain stem in the literature [6, 7]. The procedure for initial diagnosis of

these tumors which benefit us with useful information mostly regarding the enhancement pattern is computed tomography [8].

The MRI stands separately and in the foremost position from other imaging modalities because of the fact that it allows us to differentiate the tumor from the CSF filled arachnoid cyst [9, 10] and cisterns containing CSF that are present adjacent to tumor [11, 12]. The high contrast enhancement of these cystic lesions is unusual and rarely reported [13]. The keratin rich content of the epidermoid cyst differentiates it from the thin walled cholesterol rich content Craniopharyngioma and mucoid colloidal filled fluid in Rathkes cleft cyst [14]. Epidermoid cyst should be considered as a differential diagnosis for tumors occurring at velum interpositum [15-17] such as pilocytic astrocytoma, atypical rhabdoid/teratoma, meningioma [18-20]. Misdiagnosis can sometimes occur clinically as the patients undergo remission of neurological symptoms and signs frequently. The hypothesis that explains the remissions of signs and symptoms are quite different; among which one explains that the decompression of cyst subsequently by spillage of cyst contents, and the other one goes this way that the slow growth rate and affinity to spread into the subarachnoid space causing no adjacent neural compression and thus allowing the flow of CSF in interstices normally [21, 22]. It has been concluded in the recently published studies that these epidermoids may present with localized, well encapsulated collections rather than being classic pearly white solid lesions that insinuates in the pathways of CSF [23]. Although being

relatively avascular tumors, these cause hemorrhages due to the neovascularisation caused by outpouring of the cystic contents and furtherly causing granulation into surrounding that lead to neovascularisation and thereby causing hemorrhage. Hemorrhage as a typical epidermoid cyst is also correlated with the presence of cholesterol crystals and granulation. It has also been stated that the growth rate of these epidermoid cysts which is known to be slow, causes the slow displacement of adjacent structures that do not lead to hydrocephalus in some of the cases [24]. The squamous cell carcinoma of central nervous system usually arises as a result of direct spread of tumor from head/neck or metastasis from the tumor located primarily in other parts of the body [25]. Intracranial squamous cell carcinoma primarily occurring in the brain is rare and if done, is usually from the intracranial epidermoid or intracranial dermoid cyst transforming into malignant from benign variety [26]. Fourth to fifth decade is the usual timing of epidermoid to occur [27]. This usual timing helps with the appearance of epidermoid mostly at the commonest locations such as cerebellopontine angles. Sequestration taking place in the third week of embryogenesis is believed to be the cause for occurrence of epidermoid cyst at intracerebral/superficial cerebral, or intraventricular, whereas if the same sequestration procedure taking place during the fifth week of embryogenesis is thought to be the reason for the occurrence of epidermoid cyst at orbit middle ear and cerebellopontine angle [28]. Spinal canal, diploe of cranium, middle cranial fossa, intraparenchymal cerebrum, brain stem and supratentorial are the rarest sites of epidermoid cyst to occur [29]. Epidermoid cyst occurring entirely intraparenchymally are rare and may be less than 1%, but still there are few case reports of frontal lobe intraparenchymal epidermoid cyst [30]. The differential diagnosis includes the dermoid cyst, cystic neoplasm like ganglioma, arachnoid cyst, neuroepithelial cyst, hydatid cyst and even brain abscess. Dermoid cysts are usually fat resembling not cerebro-spinal fluid, but epidermoid resembles cerebro-spinal fluid. Abscess often enhances with presence of surrounding edema and do not resemble cerebro-spinal fluid completely. The hallmark indicators for hydatid cyst are circular, on-enhanced, thin walled, singular, CSF-like lesion in the parietal regions of brain without perilesional edema while neuroepithelial cysts resemble CSF, which are sharp and regularly border lined.

Typical appearance

The classical and typical appearance of epidermoid cyst on MRI shows low signal intensity on T1WI and high signal intensity on T2WI [2, 3]. Diffusion weighted image is hyperintense and has a high value on apparent diffusion coefficient [31]. Capsular enhancement of the cyst is not often seen; the high contrast enhancement of epidermoid capsule is rare [13].

Atypical appearance

Epidermoid cyst undergoing hemorrhage may show different signal intensities on MRI depending on the duration of bleeding [32]. A case of epidermoid cyst with repetitive hemorrhage in the supracallosal region had atypical findings radiologically that included hyperdense multinodular appearance on CT, heterogeneous hyperintensity on T1WI and homogenous hypointensity on T2WI and was diagnosed as cavernous malformation but histological examination revealed as stratified squamous epithelium without hair follicles suggestive of epidermoid cyst, hence it comes to a conclusion that epidermoid cyst must be taken into consideration as a differential diagnosis if cavernous malformation at any location is suspicious [33]. The atypical features like hyperintensity on both T1WI and T2WI may be due to the increase in protein concentration and semi liquid content [34]. They also even showed hyperintensity on T1WI and hypointensity on T2WI due to the combo of increased viscosity and protein content [35]. The unusual muddy fluid like contents in the cystic lesions has been reported in a particular case report [23]. The other rare variety known as "white epidermoid" may appear hyperattenuated on CT scan due to the increased protein content. The cystic contents can sometimes be very clear mimicking the arachnoid cyst [36]. Lipid and cholesterol components of cyst attribute to the hypodensity on CT [37]. The saponification of these lipids within the capsule is also one of the attributions to hyperdensity of epidermoid cyst on CT [38]. It is to be noted that not all epidermoid cyst contains cholesterol [39-41]. Occasionally the appearance of epidermoid cyst on CT is hyperdense [42, 44, 45], that can be difficult for interpretation [46, 47, 48]. The hyperdensity may be due to keratinized debris calcification [38], and increased polymorphonuclear leukocytes [49]. The correlation between protein concentration of fluid and CT has been reported [50]. Spontaneous intracystic micro-bleeding or trauma

also fits in the causative factors of hyperdensity, and the yellow color fluid (xanthochromic fluid) collection in the cyst is also attributed by microbleeding [37, 43, 51]. The reason for hyperdensity of epidermoid cyst at cerebellopontine angle may be due to increased concentration of protein [34]. Even though the pathophysiology still remains unclear, some of the factors have been contributed suggesting to it. Pearly showing up with waxy material is seen in hypodense epidermoids considering the hyperdense epidermoids that contain fluids of different colors and is cystic in nature. The increased protein concentration may be due to generative and exudative reaction to minor leaks occurring recurrently because of the lipid material in the capsule. The signals of MRI confide on the configuration of keratin and cholesterol contents of cyst relatively. Typically epidermoids appear hypointense on T1WI due to solidity of cholesterol [10]. Short T1 values have increased lipid content and show non-enhancing mass on CT, whereas long T1 values have decreased lipid content and show water density mass on CT [52]. White epidermoid, the another variant has the atypical appearance of hyperdensity on CT, hyperintense on T1WI and variable signal intensity on T2WI; the breakdown products of hemoglobin cause the paramagnetic effect that results in hyperintensity on both T1WI and T2WI [2]. Neuroenteric cyst can be similar to a rare white epidermoid cyst in which both of them have the hyperintensity on T1WI but are difficult to differentiate it from epidermoid cyst if present in the midline [53, 54]. The variable signal intensities on T2WI are fundamentally dependant on the proportion of free water and protein content. According to Ahmadi et al. [55], the increase in signal intensity of intracystic fluid on T1WI is because of the protein level of more than 100 ml or 9.0g. There is a gradual increase and decrease in T1WI signal intensities as the protein concentration of lysozomal solution increases [55], whereas the signal intensity on T2WI decreases with increasing protein concentration [56]. The other feature that differentiates the arachnoid cyst and epidermoid cyst is that the former displaces the adjacent structures, whereas the latter insinuates between them. The presence of lipids and cholesterol within the capsule is the cause for low density on CT. The decreased apparent diffusion co-efficient is due to the interference of oily contents of the cyst with the Brownian motion of water molecules within it that leads to restriction of the molecules and causes hyperintensity on DWI which is also a differentiation factor for arachnoid cyst that shows absence of

restriction on DWI and shows hypointense on DWI [57]. MRI of arachnoid cyst shows a smoothly margined mass that is isointense to cerebro-spinal fluid on all imaging sequences.

Differential diagnosis

1. Arachnoid cyst most commonly appears as hypointense on both FLAIR and DWI located mostly at middle cranial fossa, whereas epidermoid appears as hyperintense due to the restricted Brownian motion of the molecules within the cyst.

2. Dermoid cyst can be differentiated from epidermoid cyst in terms of location as it has the tendency to occur in the mid line 5-9 times fold than epidermoid cyst. Dermoid cysts usually contain dermal appendages like hair follicles, teeth, lipids. In terms of appearance, it is hypodense on CT, hyperintense on T1WI and iso-hyperintense on T2WI and in terms of onset dermoid cyst appears in 2nd to 3rd decade of life whereas epidermoids appears in later decades of life and grows slowly, but the dermoids grow fast and rapid leading to the occurrence of clinical features. Lining of dermoid cyst is simple stratified squamous epithelium supported by collagen.

3. Colloid cyst occurs most commonly at the foramen of Monroe (third ventricle) which is very helpful in the differential diagnosis, whereas the epidermoids are very rarely seen in the third ventricle.

4. Rathkes cleft cyst arises from remnants of Rathkes pouch at 3-4 weeks of embryogenesis. It shows low signal intensity to isointensity on T1WI, iso to high signal intensity on T2WI, non-enhancing, usually containing mucoid colloid fluid in the cyst. Lining of Rathkes cleft cyst is single cuboidal or columnar epithelium, with ciliated, goblet cells.

5. Craniopharyngioma is a true neoplasm that appears to be iso to hypointense to brain parenchyma on T1WI, variable/mixed intensities on T2WI, vivid enhancement, cyst is usually thin walled containing cholesterol.

6. Hydatid cyst in the brain is mostly located in the interhemispheric parenchyma especially in the perfusion area of middle cerebral artery. These cysts are single, large, spherical masses and can be differentiated by the presence of their daughter cysts and have signal intensity similar to CSF on CT and MRI.

7. Neurocysticercosis unlike epidermoid cyst shows different images finding at different stages of cyst development, especially the cyst with a particular

Table 1 The cases of remnant epidermoid cyst transforming into malignancy after the initial excision.

Case	Age	Sex	Site	Time to form SqCC	Treatment	Postoperative prognosis	Reported year	References
1	52	Male	Cerebellopontine angle	6 months	S + R therapy	Good follow-up for 3 months	2011	Lakhdar et al. [85]
2	74	Female	Cerebellopontine angle	20 yrs	S + R therapy	Alive for 17 months	2010	Nakao et al. [79]
3	50	Male	Temporal	6 yrs	S	Not described	2009	Ge et al. [86]
4	56	Female	Cerebellopontine angle	8 yrs	S + Gamma knife	Alive for 13 months	2006	Tamura et al. [26]
5	45	Female	Temporal lobe	11 yrs	S + R therapy	Alive for 12 months	2004	Guan et al. [87]
6	54	Female	Temporal lobe	3 months	Ch	Death after 13 months	2003	Hamlat et al. [88]
7	46	Female	Temporal	-	S	Not described	2001	Nawashiro et al. [82]
8	55	Female	Cerebellopontine angle	13 yrs	S	Death after 3 months	2001	Asahi et al. [89]
9	50	Female	Cerebellopontine angle	10 yrs	S + Ch +R therapy	Alive for 60 months	1999	Murase et al. [90]
10	67	Female	Frontotemporal	31 yrs	S	Death after 1 month	1991	Tognetti et al. [91]
11	36	Male	Cerebellopontine angle	2 yrs	S	Not described	1989	Abramson et al. [77]
12	59	Female	Intraventricular	33 yrs	S + R therapy	Alive for 36 months	1987	Goldman and gandy [92]
13	43	Male	Temporal Lobe	7 yrs	S	Death after 1 month	1965	Fox and south [93]
14	54	Male	Base of brain	1 yr	S	Death after 6 weeks	1965	Togliola et al. [94]

S = surgery, R = radiation, Ch = chemotherapy; All patients have one operative history except case no. 13 and 14 who have 3 and 2 operative history, respectively.

“dot” like appearance in the cyst which represents the scolex, a particular feature of vesicular stage

8. Neuroenteric cyst almost appears same as the epidermoid with the very near imaging features like iso to mild hypo to hyperintense on T1WI and indeed definitive bright hyperintense on T2WI, but the point which is the best diagnostic evidence of neuroenteric cyst is the location in which it appears that is in front of the brainstem/pontomedullary junction with its lobulated or mass lesion.

Signs and symptoms

The symptoms produced by epidermoid are due to the mass effect of the tumor locally on the brain parenchyma, vascular elements, and cranial nerves present alongside. The symptom of epidermoid tumor is difficulty in hearing that account for 37.6%, trigeminal neuralgia 29.7%, facial palsy 19.4%, headache 17.9% and diplopia 6.7% [58]. Other uncommon symptoms include seizures, changes in mental status [59], glossopharyngeal neuralgia [60] and neuralgiform attacks of headache lasting for a short span of time [61]. Tumors causing trigeminal neuralgia arise mostly from the posterior fossa like epidermoid cyst, acoustic neuromas, and some even from central forces such as schwannomas, meningiomas and adenomas of the pituitary gland [62]. Among them epidermoid cyst contributes to 1.0-1.4% of cases [58, 62]. The posterior fossa epidermoid tumor presents with initial signs of bilateral gaze nystagmus that may be due to the follicular compression by enlarged CPA cyst [63, 64]. Nonetheless, these can also sometimes cause abrupt neurologic deficits, such as pituitary apoplexy if tumor present at intrasellar as reported by Hakan et al. [65] leading to clinical features such as nausea, ophthalmoplegia, acute onset of headache, vomiting, visual acuity loss, meningismus and endocrine dysfu-

nction. Epidermoid cystic rupture can sometimes lead to chemical meningitis, persistent headaches. It has also been stated that the growth rate of these epidermoid cysts is known to be slow, hence causing the slower displacement of adjacent structures which do not lead to abrupt hydrocephalus [24]. Mutism has also been reported in the literature as a clinical presentation of epidermoid cyst in the quadrigeminal cistern by Kawal et al. [66]. Epidermoid cyst manifesting in the pineal region presents with diverse syndromes such as Sylvian aqueduct syndrome causing paralysis of downward gaze with palsy of horizontal gaze; Parinaud's syndrome resulting due to compression of superior colliculi causing convergence, paralysis of upward gaze, pupillary dissociation with near light; Colliers syndrome which results due to compression of dorsal brainstem leading to ptosis and retraction of eyelid [67]. Sometimes the vascular compression at the cerebellopontine angle by the tumor can result in hemifacial spasm [68]. Hyperprolactinemia was reported in a case of intrasellar epidermoid by Hakan et al. [65], the reason for hyperprolactinemia was thus explained as the pituitary stalk compression resulted in the disruption of transport of prolactin inhibiting factor [69] 15% of all intracranial epidermoid tumors manifest in quadrigeminal cistern [70, 72, 73]. Median location of epidermoid tumor occurs with separation of neuroectoderm from the cutaneous counterpart. Epidermoid cyst at other intracranial locations has the unusual findings of hydrocephalus [73, 74]. Epidermoids in the pineal region also contrarily appear with raised intracranial pressure and hydrocephalus very early rather than the usual; this may be due to the presence and obstruction of cerebral aqueduct Sylvius and the posterior part of third ventricle adjacently [70, 71, 75]. Epidermoid cysts have been reported to be

Table 2 The malignant transformation of benign epidermoid cyst without any initial excision reported from the literature.

Case	Age	Sex	Site	Treatment	Postoperative prognosis	Reported year	References
1	52	Male	Cerebellopontine angle	-	Autopsy	1912	Ernst
2	46	Male	Frontal lobe	S	Alive	1960	Davidson and small [95]
3	73	Male	Frontopolar	-	Autopsy	1960	Landers and Danielski [96]
4	53	Male	4th ventricle	S + R therapy	Death after 2 month	1981	Dubois et al. [97]
5	53	Female	parasellar	S	Death after several weeks	1983	Lewis et al. [98]
6	62	Male	parasellar	S	Death after 1 week	1993	Acciari et al. [99]
7	58	Male	Cerebellopontine angle	S + R therapy	Alive 2.5 yrs	1995	Nishio et al. [100]
8	45	Male	Prepontine	S + R therapy	Death after 12 months	2005	Michael et al. [101]
9	65	Female	Pineal region	S	Vegetative state	2007	Pagni et al. [102]
10	67	Male	Cerebellopontine angle	R therapy	Death after 11 months	2007	Kodam et al. [103]
11	45	Male	Posterior fossa	S	No follow up	2007	Agarwal et al. [104]
12	72	Female	Cerebellopontine angle	S + R therapy	Alive 12 months	2008	Kim et al. [105]
13	63	Female	Pre pontine	S	Death after 36 days	2008	Shuyu et al. [106]

S = surgery, R = radiation; All patients have no operative history and time taken to form SqCC was 6 years only for case no. 13.

present at velum interpositum due to the epithelial tissue displacement within the velum interpositum [76]. It can be here argued that they can even arise in quadrigeminal cistern present posteriorly, and migrate to cavum velum interpositum, in such cases Desai et al. reported a series of epidermoid tumors in quadrigeminal cisterns that even though being large in size the cyst has displaced the third ventricle, but did not enter the velum interpositum or the ventricles [70]. MRI here is useful in portraying the precise anatomy of the velum interpositum region by clearly demonstrating the displaced neurovascular structures [20, 71]. Displacement of the internal cerebral veins ventrally, corpus callosum and posterior peri callosal arteries dorsally assure the presence of a mass in the velum interpositum [71], whereas the third ventricular tumors displaces the internal cerebral veins dorsally [16].

Malignant changes

The transformation of the benign condition of cyst into malignant is not common, and if occurs is more aggressive. The precise mechanism of benign epidermoid cyst transforming to malignancy is still yet unclear, but causes like subtotal excision of the cystic wall, and recurrent cystic rupture leading to severe inflammatory response may lead to malignant transformation [77-79] or the inflammation due to foreign body reaction or with carcinoma in situ Symptoms and signs that have the sudden onset and develop speedily is the significant indication clinically, of epidermoid cyst transforming into malignancy [80], the typical imaging pattern includes the features such as growth of the focally enhanced mass rapidly, on MRI and CT imaging [81] The appearance of malignant part of epidermoid cyst on DWI is hypointense [82], whereas the classical

epidermoid cyst on DWI appears as hyperintense that can be useful in diagnosing and follow up post operatively [83]. Immunohistochemistry of the malignant epidermoid cyst reported in the literature showed the positivity of tumor cells with P53 protein. The abnormal or the rampant growth illustrates malignant transformation rather than the linear growth [84]. The cases of remnant epidermoid cyst after initial excision transforming into malignancy are remarkably rare and are reported here till the recent (Table 1).

In the above mentioned cases (Table 2), all the patients at least had one operative history before the recurrence or malignant transformation, which can be one of the causes of transformation into malignancy. Among all the above cases, case no: 1, 2, 4, 5, 9, 12, who have been treated with radiotherapy after the excision of malignant epidermoid cyst have shown better prognosis, which states that postoperative radiotherapy leads to a better prognosis of patients and is highly recommended. There are even some cases (Table 2) that showed malignant epidermoid tumor without any previous operative history.

Treatments

The treatment is generally carrying very good prognosis for epidermoid cyst is total surgical resection grossly [79]. Whereas the decompression of cyst can just be a temporary relief [107-109], while subtotal resection can result in recurrence of tumor which is estimated to appear at the time of an interval equal to age of patient with the addition of nine months to the initial presentation of symptom [110]. A routinely suggested approach for suprasellar epidermoid cyst is transcranial, peculiarly if the epidermoid is adhered to the adjacently present vessels and nerves. The adjuvant therapy coupled up with subtotal/total resection depending upon the

adherence is promising management strategy if the malignant transformation has occurred. The benefits of the radiosurgery have been well documented for the control of malignant epidermoid tumors [90, 111]. Postoperatively stereotactic radiation therapy has been effective, that showed the control of local tumor growth for two and half years, and with disease free survival rate for more than five to eight years in some reported cases [78, 112]. In case of adjuvant therapy, gamma knife radiosurgery has been reported as a useful treatment [26]. The epidermoid tumors, in which the complete removal of them is difficult, have to be followed up for the recognition of their malignant transformation. The immediate surgical procedure should be carried out for epidermoid cyst located in the sellar region as in the delayed cases may cause a sudden neurological deficit due to the proximity of abundant neurovascular structures.

Surgical complications

The main post-operative complications are dysfunction of cranial nerves and aseptic meningitis [113, 114]. The cautious imaging study preoperatively especially regarding to the region of the internal cerebral veins (velum interpositum); will forbid the damage to these structures intraoperatively while undergoing for masses in these areas. Aseptic meningitis stands between 2-50% incidences occurring postoperatively according to literature data; patients mostly whose cystic capsule has been excised incompletely are prone to these complications [115, 116]. Chemical meningitis results in the rupture of the cyst. Removal of epidermoid cyst leads to complications such as hydrocephalus, which may be obstructive or communicating [117]. The surgical resection of epidermoid in the posterior fossa may sometimes lead to hypertrophic olivary degeneration. The clinical picture of this includes palatal myoclonus, which is an involuntary movement of oropharynx, uvula and soft palate, ocular myoclonus and dentatorubral tremor [118].

Prognosis

As the growth rate of these epidermoid tumors resembles the same as the human skin any cell retained can lead to risk of recurrence or regeneration. According to the recently published studies, subtotal excision of posterior fossa epidermoid cyst has the recurrence rate between 0-54% [120-122]. Children after initial resection of epidermoid cysts in the pineal region should have a close follow up, as a potential to develop a

metachronous neoplasm (germinoma) is possible [123]. Whereas even the subtotal removal of the fourth ventricular epidermoid cyst carries a good prognosis [124], even if the tumor is subtotally resected long term survival can be expected in atypical epidermoid cystic patients. Even if the tumor is excised subtotally in neurologically preserved patients the prognosis remains quite good which is confirmed by the experience [125, 126]. The location of the tumor and the time taken from onset to diagnosis are the important factors for the prognosis than the size of tumor.

Conclusions

It is also considered necessary to revive that these epidermoids may be provincial, well enveloped with collections on behalf of the classical solid pearly white tumor insinuating between the adjacent structures as described usually. One of the major tools for diagnosing and post-operative follow-up is diffusion weighted Mirth subtotal or partial resection of the tumor can cause the regeneration of the tumor from the remnants leading to recurrence or malignancy as the leftover cells of the cystic wall/tumor are nothing but the epidermal cells that has the regenerating capacity as such of epidermis of skin. The adjuvant treatment with radiotherapy after surgical resection is important and has good results.

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