

**Original article:**

## **A review on retinoblastoma and ayurveda insight into the relevant management and advance care planning**

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### **ABSTRACT:**

**Background & Objectives:** In India, the current treatment modalities of systemic chemotherapy and focal treatment have contributed significantly to disability limitation and patient survival. There is also potential for developing targeted molecular therapies. However, side effects of retinoblastoma surgery, radiation therapy may include some complex conditions. We have subtle yet promising examples to manage all such complications effectively through Ayurveda. In this study, the *Ayurvedic* approach mainly concentrates on preventing the progression of the disease. The present protocol for the treatment is applicable at conservative tumor destructive therapy phase before enucleation and palliative therapy and/ or complementary therapy along with chemotherapy and radiation. The purpose of the study is to propose a non- surgical, non- invasive conservative approach for the management of the disease after thorough research work; need to be further analysed and clinically evaluated before recommendation.

**Methods:** Ophthalmology textbooks of recent edition, Ayurveda literature (Sanskrit, Hindi and English publication), Database, Keywords, Results, Filters, Relevant papers selected for review.

### **Results:**

1. A review is done on Retinoblastoma and relevance in *Ayurveda* classics
2. The cause of the disease in Ayurveda perspective discovered and noted.
3. A multi disciplinary management with an *Ayurveda* protocol is proposed.

### **Interpretation & Conclusion**

Therefore,

- Prognosis of eye cancer depends on early detection & awareness
- Ayurveda as healing reagent of the disease
- Childhood cancers = better improvements

**Keywords:** Retinoblastoma, multidisciplinary team approach, *bala roga*, *shalakya tantra*, *netra arbuda*, *nakulandhya*.

## INTRODUCTION:

Retinoblastoma<sup>1</sup> is a rare malignant tumor of the infant neurosensory retina which is the most common primary intra ocular malignancy of childhood and forms when both RB1 alleles mutate in a susceptible retinal cell, likely a cone photoreceptor precursor. It is a damaging disease that commonly affects children below 2 years of age. About 90% of patients affected by the disease are children; 20% - 25% cases of eye cancer worldwide in children are from India; 50% such cases in the world lose their life due to late detection & inadequate treatment<sup>2</sup>.

Truly said, "An eye complaint merits careful attention from all medical personnel" corresponds to importance of thorough eye examination<sup>3</sup>.

"*Tatwa gyana*" is said best example for *harshanam* by *Acharya Charaka*<sup>4</sup> which means if a person is able to perceive correct knowledge of an image, subject or happening, makes one happy [*tatwa avbodho harshanam*]. Also, *indriyajaya* is the best example of *nandanam* i.e. *samridhi karaka* (contentment). Thus, if a person with diminished sight is treated for improvement of vision; we as *shalakins* (netra- ophthalmologists) gift happiness. Therefore, for every cause of blindness it is our principle to discipline the action needed.

Taking all these points into consideration, this conceptual study was done.

## AIM OF THE STUDY:

A review on Retinoblastoma and *Ayurveda* insight into the relevant management and advance care planning

## OBJECTIVES OF THE STUDY:

1. A review on Retinoblastoma and relevance in *Ayurveda* classics
2. To discover the cause of the disease in *Ayurveda*.
3. To propose a multi disciplinary management, an *Ayurveda* protocol.
4. To study the effect of *Ayurveda* treatment in advance care planning

**STUDY DESIGN:** A Conceptual Study.

## MATERIALS & METHODS:

### SOURCE OF DATA:

- Central library and library of department of Shalaky Tantra, Shree Jagadguru Gavisiddheshwara Ayurvedic Medical College and hospital, Koppal, Karnataka.
- Library of Manthana Research Laboratory, Gurugram, Haryana.
- Online database search.

## METHODOLOGY:

**Method of textual reviews:** The narrative overview of the literature synthesizing findings retrieved from the search of computerized databases and authoritative texts. The study was limited to classical text books of *Ayurveda* and publications in English. The key words like Granthi, Arbuda, Nakulandhya, Timira chikitsa, Retinoblastoma, prevalence, chemotherapy, Radiation therapy, etc were used to search the computerized database. The search was not restricted to any particular study designs but studies related to exploring the anti cancer (ophthalmic and paediatrics) effects, mode of action of *Ayurvedic* formulations and causative factors for the disease were read to understand basic concepts related to the subject.

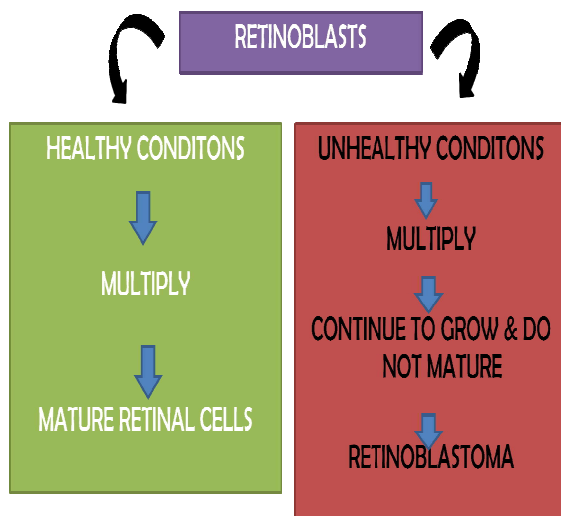
Database for research were PubMed, Ayush research portal, Digital Helpline for Ayurveda Research Article (DHARA), various other journals and medical news.

**Literary review:**

❖ **A review on retinoblastoma and relevance in *ayurveda* classics:**

Retinoblastoma is a rare malignant tumor of the infant neurosensory retina which is the most common primary intra ocular malignancy of childhood and forms when both RB1 alleles mutate in a susceptible retinal cell, likely a cone photoreceptor precursor. It is a damaging disease that commonly affects children below 2 years of age.

Overlook<sup>5</sup>:



Types<sup>6</sup>:

It can be broadly classified as:

1. Congenital [heritable]
  - 1 out of 3 children
  - **Germline mutation**
  - Gene change first occurs during early development in the womb
  - Bilateral/ multiple retinoblastoma
2. Sporadic [non heritable]
  - 2 out of 3 children
  - Abnormality develops in only one cell of the eye
  - One tumor in one eye

Clinical features<sup>7</sup>:

- Leukocoria [white pupillary reflex] = 60% (Visible in family photographs)
- Strabismus = 20%
- Painful red eye with secondary glaucoma

- Poor vision
- Inflammation / pseudo inflammation

#### Transmission electron microscopy<sup>8</sup>

- Revealed that RB tumor contains presence of structures that are characteristic of normal photoreceptor cells and the fetal retina.
- Such evidence indicates neuroretinal origin of retinoblastoma and also indicates that rosettes and fleurettes of retinoblastoma are an attempt to differentiate photoreceptor cells.

#### Management of retinoblastoma<sup>9</sup>:

##### Goal of management

- Save life
- Salvage of the organ (eye)
- Function (vision)

##### Management strategies depends on stage of the disease<sup>10</sup>

- Intra ocular retinoblastoma
- Retinoblastoma with high risk characteristic
- Orbital retinoblastoma
- Metastatic retinoblastoma

#### Treatment<sup>11</sup>:

##### **Multi disciplinary team approach needed.**

- Oncology
- Paediatrics
- Paediatric oncology
- Psychiatry
- Interventional radiology
- Pathology
- Neurodevelopmental medicine
- Ocular prosthetics (implants)
- Genetic counselling
- Etc

##### **Remission & chance of recurrence<sup>12</sup>**

Maybe temporary or permanent

**Review:** Careful review at frequent intervals is generally required following treatment, in order to detect recurrence or the development of a new tumor, particularly in heritable disease.

##### ❖ **Ayurvedic relevance:**

1. Ayurveda mentions 12 and 27 disorders of drishtigata vyadhis by the acharya susruta<sup>13</sup> and vagbhata<sup>14</sup> respectively. **Nakulandhya**<sup>15</sup> (eyes looks like a cat under the flash light); the white pupillary reflex or red reflection from the retina (back of the eye) is suggestive of retinoblastoma of the eye or glioma of the retina.
2. The other clinical features of nakulandhyam include palinopsia (visual trailing) and/ or cerebral diplopia (“*chitram pashyati*”; “*chitrani rupani diva*”) and partial or total loss of vision (nyctalopia- *no nishi*).
3. There are 4 *patalas* in the *netra* and 2 are extra ocular. These are clinical division as layers of the eye. The 4 *patalas* are unique corresponding to the prognosis of eye disorder. The diseases that lie in 1<sup>st</sup> and 2<sup>nd</sup> ocular *patala* (*prathama patalagata*) are prognosed as *sadhya* (curable) *vyadhis*. The diseases in 3<sup>rd</sup> *patala* are *yapya* (management and follow up required regularly to maintain the health of the eyes). The 4<sup>th</sup> *patalagata* disorders are incurable (*asadhya*) ocular disorders. According to a commentary on susruta by srikantha acharya the disease is viewed under 4<sup>th</sup> *patalgata vyadhi*.
4. According to Ashtanaga Hridayam explanation the clinical features such as “*chitram pashyat*,” gradual loss of vision shadows, flashes of light, or wiggly lines in the vision, blurred vision etc are corresponding to the 3<sup>rd</sup> *patalagata vyadhi*<sup>16</sup>.

❖ **Cause of the disease:**

1. **The heart and 10 dhamani**<sup>17</sup>: According to acharya Bhela heart is called the meaning or substantial essence (of a person- being the most vital and vulnerable part of the body). Vital, because in it there are 10 *dhamanis*; 4 going upward and supplying *netra* and other organs, 4 going downwards and 2 going in *tiryaka* direction. Vulnerable, because it carries the *mula* (rasa) of what we eat. It is from these *dhamnis* that the *mula sira* get differentiated (not in one but) into many more *siras*. From here on existence of senses(*artha*), knowledge(*vigyana*), memory(*smriti*), mind(*manasa*) are formulated(*yogam*).

Though this statement is not acceptable by modern medicine readers, but the interpretation of this saying is well correlated today. The rightful meaning of this metaphorical sentence is that the *dhamani*, bifurcated into the *siras* travel and carry life (sense= *artha*), accompanied with oxygen rich blood, nutrition (*rasa*) and everything needed to keep up the working of each cell of body. Henceforth, wakefulness and knowledge, memory, orderly functioning and response of mind are formulated, actually propagated through these vital channels. Acharya Bhela also mentions *manastu chintyamatha*, which means, “Mind is what thinks.” Thus, Aurvedists like Bhela regarded the capability of thinking and making images and decisions being seated in the head; brain.

**Modern view**<sup>18</sup>:

Anatomical hierarchy1: Cardiovascular system > Arteries > Aorta > Aortic arch > Common carotid artery > Internal carotid artery > cerebral part > Anterior cerebral artery

Anatomical hierarchy2: CVS > Arteries > Aorta > Aortic arch> Common carotid artery > Internal carotid artery > Cerebral part > Ophthalmic artery > Central Retinal artery.

Anatomical children: Central retinal artery (Intraocular part and Extraocular part)

2. **Rasavaha srotasa**<sup>19</sup>: Considering the fundamental concepts of fetal origin of childhood disease, *srotodushti* should be kept in mind. Disobeying the principles of *dinacharya*, *ritucharya* and *garbhincharya* by the mother

may vitiate doshas and cause srotodushti, especially rasavaha srotasa because it ensures the nutritional supply in the fetus. Again, the moolam of the rasavaha srotasa (one of the 14 major gross channels = srotasa) is **heart and 10 dhamnis.**

Acharya Chakrapani<sup>20</sup> has described “*moolamiti prabhava sthana,*” which means the mula of a srotasa is the anatomical seat of the respective srotasa, the main seat of pathology of that channel, the principal seat of manifestation of that disease.

**Modern view:**

Firstly, the retina is a thin multilayer of mainly neuronal cells derived from ectoderm<sup>21</sup>. The epiblast<sup>22</sup> can first be identified as a tissue at the late blastocyst stage. The epiblast is known to generate extraembryonic mesoderm and all fetal cell lineages, including germ line. This pluripotency is its most distinctive.

Secondly, retina is one of the most metabolically active tissues<sup>23</sup>, and it relies on d-glucose for its metabolic activity. The tight junctions composed of endothelial and epithelial cells restrict paracellular diffusion of glucose to the retina from the systemic circulation. To compensate the glucose demand of the retina, glucose transporters (GLUT) present on the outer and inner BRB facilitate glucose passage to the retina. In humans, expression of GLUT1<sup>24</sup> is reported in both the retinal capillary endothelial cells and the pigment epithelium. Additionally, GLUT1 is also expressed on the ganglion cell layer, photoreceptor and Muller cells of the human retina. Researchers have also studied changes in the expression of glucose transporters in response to various factors associated with retinopathies in certain pathological conditions. Also, there have been studies in another metabolically active ingredient of Retinal cells and also the retinoblastoma cells i.e. Glucose transporter.

In a study<sup>25</sup>, the effect of proliferation modulators on the levels of the expressed transporter in the RPE cell line of Retinoblastoma cells was found via cultured pig RPE cells and two human RPE cell lines, D407 and ARPE-19, as well as the human retinoblastoma cell line Y79 were used. Glutamate transporter expression was evaluated with Western blot analysis and immunocytochemistry. The study revealed unexpected expression of neuronal glutamate transporter/chloride channel EAAT4 in these three cell lines (human RPE cell lines and retinoblastoma cell line). Thus gene expression and functioning also depends on the metabolic variance.

First and second theories may help us conclude that germ line expression of the disease may or may not depend on metabolic efficiency of embryonic retinal development via nutrition sufficiency from the mother.

Thirdly, the Warburg effect<sup>26</sup> might help understand metabolic pathways within the cells and between cells in the retina and the correspondence with retinoblastoma cell growth pattern.

**3. Medo-dhatu dushti<sup>27</sup>:** Meda dhatu is a balance between purva (previous) and uttarotara (following) dhatus. It is barrier in a way if medo dhatu dushti is there it shall block the nutritional flow in the following channel making them weak and aposhaka. Also, it will keep on building itself in the deranged manner. Thirdly, it shall lead to accumulation of itself and the viated dosha in the previous channels causing rasa, rakta, mamsa dushti altogether. Medo dhatu in the deranged form may cause cancer (arbuda).

**4. Oj<sup>28</sup>:** “*Preenita sarvadehina,*” by this acharya Charaka proclaimed the nucleus of all the cells that would help in functioning of all cells, the mitochondria of the cells that empower the cell nutrition and strength and the immune system of body is oja. It is also said, “*garbha rasada,*” which means the oja is present in a *kalala* state

in the *garbha* as *sara bhaga* of *rasa* i.e. the core nutrition (maybe the amniotic fluid content surrounding the fetus).

Also, said this, acharya charaka explained the **importance of heart and 10 dhamanis** as ojevaha since oja as an essential component (dhatu) is carried everywhere in the body, “*vidhamyante samantatah sharira asmin.*”

5. **Swabhava adi 6 dhatu**<sup>29</sup>: prithvi, jala, teja, vayu, akasha, integrated with **atma** are responsible for all chemico-physiological actions taking place in the body i.e. addition (joining) and division (separation); “*...samyogam cha viyogama cha teshama karmev karanam.*” Thus there stability in the body is essential as well. Their deranged action, especially agni vitiating the pita dosha and predominating kapha dosha factors in particular may cause eruption or overactivity of *samyogam* and blocking the vayu useful in stopping the overaction (viyoga).

This has been explained aptly by *Acharya Charaka* in *yuktima* in *chaturvidha pariksha*; he said “*shada dhatu samyogata garbhana sambhavastatha,*” is an example of *yukti*.

“*samudyat garbhajanma*” is “*kartri karana samyogata kriya*” in *yukti* application.

#### 6. Other factors:

1. **Adi bala pravritta**<sup>30</sup>: Acharya Sushruta said, “*shukra shonita doshanvyah*” i.e. beeja dushti (genetic mutation) as one of the main genesis of netra rogas. The causative factors for genesis of netra rogas due to beeja dushti includes:
  - (1) **Atma** karma (action of atma)
  - (2) **Ashaya** (the stagnancy of deranged doshas in the netra; drishti region here)
  - (3) Kala (represents, sudden climatic alterations; unnatural variations)
  - (4) Ahara viahara (the diet and living pattern hampering the genetic pattern; ratri jagarana is said to alter DNA pattern according to a study)
2. **Janma bala pravritta**: “*maturapcharaata*” i.e. vitiating/altering factors during pregnancy includes:
  - (1) **Rasa krita**: nutritional deficiency.
  - (2) **Dauhrida apchara kritascha**: not fulfilling desires of pregnant lady.

#### Modern view:

**Some studies have suggested some parental factors that might be linked to an increased risk of retinoblastoma, such as:**

- Diets low in fruits and vegetables among mothers during pregnancy
- Exposure to chemicals in gasoline or diesel exhaust during pregnancy
- Exposure of fathers to radiation
- Older age among fathers

**The possible link between these factors and retinoblastoma is still being studied.**

#### ❖ Method of development of treatment protocol:

- Reduce the risk of the tumor spreading
- To maintain health & vision.

- Advanced cancer care planning
- **Contribution by Ayurveda**<sup>31</sup>
  - ❖ Basics
  - ❖ Retinoblastoma (disease)
  - ❖ Side effects following RT
  - ❖ Remission & recurrence
  - ❖ Scopes & hopes

### Basics

- ❖ *Vata-pita-kapha* = **the three triads**: the disease is *kapha vata prahana vyadhi* presented as *netra arbuda* with dominant vitiated doshas in *tritya*(3<sup>rd</sup> *patala*) *patala* of the netra.
- ❖ *Nakulandhyam* is said to be *yapya* (**relievable**, may be managed to a certain extent; not curable completely) according to *Acharya Vagbhatta*
- ❖ *Nakulandhyam* is proclaimed as incurable (*asadhyam*) according to the *Acharya Susruta* ( 4<sup>th</sup> *patalagata vyadhi*)
- ❖ The clinical features of the disease relate to 3<sup>rd</sup> *patalagata vyadhi* according to *Ashtanaga Hridayam*
- ❖ Acharya Vagbhatta has advised **Timira chikitsa** for *Nakulandhyam*
- ❖ Therefore, a protocol is established on the basis of *timira chikitsa* according to the dosha predominance specific to the disease interpretation and variance in disease manifestation and progression (presenting features, reoccurrence and side effects following chemotherapy, radiation therapy and enucleation.)

### Retinoblastoma management

#### STEPWISE:

- ❖ Use of basti
- ❖ Sirodhara
- ❖ Nasya
- ❖ Seka चरणपाना चरणपाना
- ❖ Oral medications
- ❖ Disease specific & dealing with complications
- ❖ Subsiding prominent signs & symptoms

#### NIRUHA BASTI:

- Eliminate the impurities in an order viz, Pita, Kapha, Vayu.
- Establish laghavam of the body

#### TARPANA

- “अथ तर्पणकं वच्मि नेत्रतृप्तिकरं परम्।” Sha. S. Ut. K.13/ 37 ½.

It is said to be the best vision empowering therapy and most preferable modality in *timira chikitsa*.



#### PUTAPAKA

- Three types:
  - Ropana Drishti Bala, Pita- Rakta Netra Rogas [300]
  - Lekhana Snigdha Netra [100 Vaka Matra]
  - Snehana Atiruksha Netra (Dry Eye) [200]
- Lekhana Kshara Tikshana Amla Dravyas
- Ropana Kshaya Tikta Rasa Sneha Dravyas
- Snehana Madhura & Sneha Dravyas

#### IMPORTANCE OF DRUGS USED:

- Vata = Eranda
- Rakta = Triphala, Lohdra, Yashtimadhu, Sarkara, Bhadra Musta
- Kapha = Shigru Patra
- Pita = Dhatri, Maha Nimba Phala, Triphala

#### RASA PREPARATIONS:

[b.r. Baalroga 163-163 ½]

Kumara kalyana rasa: baal rog, agni vikruti

Anupana: milk, honey, sita

- Vati kalpana:
  1. Chandraprabha vati: arbuda, tridoshaja rogas, netra rogas
  2. Sanjeevani vati: ½ - 1 gunja dosage all year long with ardaraka swarasa anupana
- Anupana:
  - V= snigdha, ushna
  - K= madhura, sheetala
  - P= ruksha, ushna
  - R= ksira, ikshurasa

**Visha**= asava of arka, selu & sira

#### Side effects following RT:

Following may help in relieving of side effects such as loss of madarosis, keratitis, conjunctivitis, radiation retinopathy, vision impairment, fatigue, skin problems, hair loss, nausea and vomiting, myelotoxicity, increased risk of infections and low platelet counts

- **Sukhoshna** seka
- Parisheka in **shushka** akshipaka
- Powder from sabaram in **abhighata** netra rogas
- Kalka prepared with laksha, madhuka, lodhra & pundarika is macerated with cold water & filtered to use in **rakta vikara**.

**Remission & recurrence:**

**Nidra , murcha, bhrama and tandra.**

- **Netra kandu & shotha:** pindi of shunthi, nimbadala & little saindhava lavana
- **Netra ruja:** bidalaka prepared with paste from equal quantity of yashtimadhu, gairika, saindhava lavana, daruharidra& swarna makshika triturated with water. [all types of netra rogas]
- **Pathya:**
  - **V=** snigdha, ushna
  - **K=** madhura, sheetala
  - **P=** ruksha, ushna
  - **R=** ksira, ikshurasa
  - **Visha=** asava of arka, selu & sira
- Kalyanika rasa kriya

**DISCUSSION:**

1. Ayurveda mentions 12 and 27 disorders of drishtigata vyadhis by the acharya susruta and vagbhata respectively. Nakulandhya, the white pupillary reflex or red reflection from the retina (back of the eye) is suggestive of an important clinical feature of retinoblastoma of the eye (retina).
2. Retinoblastoma may be compared to drishtigata tridoshaja vyadhi – nakulandhyam; order of dominant dosha being kapha-vata- pita
3. According to Ashtanaga Hridayam explanation the clinical features such as “*chitram pashyat,*” gradual loss of vision shadows, flashes of light, or wiggly lines in the vision, blurred vision etc are corresponding to the 3<sup>rd</sup> **patalagata vyadhi** and is **yapya** (relievable condition)
4. Long-term follow-up is important because there is a chance that cancer can recur. Late side effects from treatment can also develop. To prevent such conditions few of the said Ayurveda techniques may be incorporated and continued for over long duration without harm.
5. Retinoblastoma is treated by more than one specialist with more than one type of treatment known as multi disciplinary team approach, Ayurveda could be a part.

**CONCLUSION:**

It can be concluded that the *Ayurvedic* approach of the disease would mainly concentrates on preventing the progression of the disease successfully.

Also, it could be beneficial in order to have a satisfying result with respect to improvement in vision and correcting the overall debilitating effects of the disease, surgery, chemotherapy and radiation in the following ways:

- ❖ Collaborative approach
- ❖ Treatment is highly individualized.
- ❖ Considering alternative or complementary methods

Clearly, a great deal rests on establishing the precise status of the study: that is on clarifying the details of its application and correct usage.

#### **FUTURE SCOPE AND LIMITATIONS:**

- Multi centric trial may be carried out with large sample size.
- In future *Ayurvedic* approach may be used as an alternative option to avoid enucleation and complications following chemotherapy and radiations.
- Histopathology study to prove the mechanism of healing of Retinoblastoma tumor with “Ayurveda multidisciplinary protocol” may be done.

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