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Integrated Approach for Diagnosis, Management and Prevention of Gall Bladder Carcinoma

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Review Article

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Abstract

Ayurveda, "The Science of Living", it has been in existence since the beginning of time and has been giving the health solutions for various named and unnamed diseases, to the humankind since ages. Cancer is indirectly described in Ayurveda texts in the form of various terms like 'arbud', 'gulma', 'granthi' which have been coined that could be related to cancer. Though an uncommon malignancy Gallbladder cancer is the commonest and fatal biliary malignancy as it is not easily diagnosed in early stages. The integrated approach for early diagnosis and prevention through Ayurveda could be helpful in the management of the biliary malignancy.

Aims and Objectives

- To review, evaluate, elaborate and discuss the gallbladder cancer as per Ayurveda and modern medicine.
- To evaluate, elaborate and discuss the current and ancient approach to the diagnosis, management and prevention of gallbladder cancer.

Materials and Methods: This Research Scientific Paper is based on Ayurvedic Clinical Experiences in Cancer & Gall Bladder Cancer, Research Article published on Cancer in Medical Journal. Ayurvedic and Modern Text have been reviewed to collect, analyze, evaluate, elaborate and discuss of concern subjects. A Medline, PubMed database search was performed to identify articles published using the keywords 'carcinoma of gallbladder', 'gallbladder cancer', 'gallbladder neoplasm', 'cholecystectomy', 'arbud', 'gulma'.

Conclusion: Gall Bladder Cancer can be diagnosed and managed by using diagnostic method recommended in Modern Medicine as well as by using basic principles and medicines described in Ayurveda. Gall Bladder Cancer can be prevented by reducing the risks factor of this disease through follow the wholesome diet and normal lifestyle described in Ayurveda.

Keywords: Cancer; Arbud; Gulma; Gallbladder Carcinoma; Ayurvedic Protocol

Abbreviations: GB: Gall Bladder; GBC: Gall Bladder Cancer; MRI: Magnetic Resonance Imaging; LLC: Lewis Lung Carcinoma; ROS: Reactive Oxygen Species; AJCC: American Joint Committee on Cancer; BMI: Body-Mass Index; LCHF: Low Carb/ High Fat; I3C: Indole-3-Carbinol; SK: Sudarshan Kriya.

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Introduction

An abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize [1]. Cancer of the gallbladder is cancer of the pear-shaped organ that lies on the under surface of the liver.

New global 2018 cancer data suggests that the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths, shows 2.25 million people living with the disease, 1157294 are new cancer patients registered while 784821 are cancer related deaths [2]. 5 years' prevalence is 2258208 [3].

Almost all types of gallbladder cancer are adenocarcinomas, papillary adenocarcinoma is a special subtype of adenocarcinoma while Other less common types of gallbladder cancers are adenosquamous carcinomas, squamous cell carcinomas, small cell carcinomas and sarcomas.

Ayurveda is ancient medical science which has been giving the health solutions to the human race since ancient times. In modern medicine surgery, chemotherapy and radiotherapy, these are the standard treatment for gallbladder cancer which then should be given. But these modern interventions have some complications and adverse effects. Though the term cancer is new for Ayurveda but abundant of medical literature has been found which have described malignant tumours in the various texts of Ayurveda like Arbuda, gulma, these are very nearer terms described for malignant tumours. While going through details of the text the clinical manifestations of gulma are likely to be similar to that carcinoma gallbladder.

Ayurveda is store of herbal, mineral and herbomineral medicines for various diseases including arbuda and gulma. The protocol for the diagnosis, the management and the prevention of gallbladder cancer may be prepared by using Ayurveda principles. This article is highlighted on integrated approach for diagnosis, management and prevention of gall bladder carcinoma.

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Etiology

Gallstones are present in 75-90% of gallbladder cancer cases, but an etiologic influence remains unproven.

Anatomy

The gallbladder is just below the liver. Bile is stored in the gallbladder and flows through the cystic duct and the common bile duct into the small intestine when food is being digested.

The wall of the gallbladder has 4 main layers of tissue: Mucosal layer, Muscle layer, Connective tissue layer and Serosal layer.

Primary gallbladder cancer starts in the mucosal layer and spreads through the outer layers as it grows.

Pathophysiology of Gall Bladder Cancer

In a state of chronic inflammation, Gb cancer occurs. In the vast majority of patients (> 75 percent), cholesterol gallstones are the source of this chronic inflammation. The presence of gallstones raises the 4- to 5-fold risk of gallbladder cancer. Gallbladder cancer is also linked with other rarer causes of chronic inflammation. Primary sclerosing cholangitis, ulcerative colitis, liver fluke, chronic infections with Salmonella typhi and paratyphi, and Helicobacter infections are all causes. Chronic inflammation of the gallbladder, however, is possibly just part of the cause of the malignant transformation seen in gallbladder cancer. There were several other variables found. The risk of gallbladder cancer may be increased by consumption of certain drugs (e.g., oral contraceptives, INH, methyldopa). Similarly, certain exposures to chemicals (e.g. pesticides, rubber, vinyl chloride) and occupational exposures. Obesity may contribute to gallbladder cancer through its association

with gallstones, its association with increased endogenous estrogens, or through the ability of fat cells to secrete a large number of inflammatory mediators [4].

Hereditary syndromes, including the following, often have an increased incidence of gallbladder cancer: Gardner syndrome, Neurofibromatosis type I, Hereditary nonpolyposis colon cancer.

Based on morphological, genetic, and molecular data, (GBC) is the product of 2 or more distinct biological pathways. One of the pathological causes behind the development of gallbladder carcinoma is thought to be metaplasia. The definite association between metaplasia and dysplasia, however, is not yet clearly defined. The characteristic findings of gallbladder cancer are fibrosis and gallbladder thickening in gross pathology. The outer part is often better distinguished in microscopic histopathological examination than the deeper part, characteristic findings of gallbladder cancer [5].

Histological Classification of Tumors of the Gallbladder and Extrahepatic Bile Ducts [6]

The second edition of the classification of the WHO Histological Classification of Tumors of the Gallbladder and Extrahepatic Bile Ducts includes a greater variety of lesions as described in Table 1. Consonant with the World Health Organization series in general, the classification is based on routine light microscopic findings with recognition of the adjunctive value of immunohistochemistry and electron microscopy.

S.no				Tumor type
1				Epithelial tumors
	1.1			Benign
		1.1.1		Adenoma
			1.1.1.1	Tubular
			1.1.1.2	Papillary
			1.1.1.3	Tubulo papillary
		1.1.2		Cystadenoma
		1.1.3		Papillomatosis (adenomatosis)
	1.2			Dysplasia
	1.3			Malignant
		1.3.1		Carcinoma in situ
		1.3.2		Adenocarcinoma
		1.3.3		Papillary adenocarcinoma
		1.3.4		Adenocarcinoma, intestinal type
		1.3.5		Mucinous adenocarcinoma
		1.3.6		Clear cell adenocarcinoma
		1.3.7		Signet ring cell carcinoma
		1.3.8		Adeno squamous carcinoma
		1.3.9		Squamous cell carcinoma
		1.3.10		Small cell carcinoma (oat cell carcinoma)
		1.3.11		Undifferentiated carcinoma
2				Endocrine tumors
	2.1			Carcinoid tumor
	2.2			Mixed carcinoid-adenocarcinoma
	2.3			Para ganglioma

3				Non epithelial tumors
	3.1			Benign
		3.1.1		Granular cell tumor
		3.1.2		Ganglio neurofibromatosis
		3.1.3		Leiomyoma
		3.1.4		Lipoma
		3.1.5		Hemangioma
		3.1.6		Lymphangioma
		3.1.7		Neurofibroma
	3.2			Malignant
		3.2.1		Rhabdomyosarcoma
		3.2.2		Kaposi sarcoma
		3.2.3		Leiom yosarcoma
		3.2.4		Malignant fibrous histiocytoma
		3.2.5		Angiosarcoma
4				Miscellaneous tumors
	4.1			Carcinosarcoma
	4.2			Malignant melanoma
	4.3			Malignant lymphomas
5				Unclassified tumors
6				Secondary tumors
7				Tumor-like lesions
	7.1			Regenerative epithelial atypia
	7.2			Papillary hyperplasia
	7.3			Adenomyomatous hyperplasia
	7.4			Intestinal metaplasia
	7.5			Pyloric gland metaplasia
	7.6			Squamous metaplasia
	7.7			Heterotopias
	7.8			Xantho granulomatous cholecystitis
	7.9			Cholecystitis with lymphoid hyperplasia
	7.1			Inflammatory polyp
	7.11			Cholesterol polyp
	7.12			Malacoplakia
	7.13			Congenital cyst
	7.14			Amputation neuroma
	7.15			Primary sclerosing cholangitis

Table 1: WHO histological classification of tumors of GB and extrahepatic bile ducts.

Sign and Symptoms

Gallbladder cancer signs and symptoms may include: Abdominal pain, particularly in the upper right portion of the abdomen, abdominal bloating, fever, losing weight, nausea, yellowing of the skin and whites of the eyes, there are no signs or symptoms in the early stages of gallbladder cancer, the symptoms of gallbladder cancer, when present, are like the symptoms of many other illnesses [7]. As per Acharya vaghbhatta lakshans (signs and symptoms) of gulma are as belching, constipation, loss of appetite, adhyamaan (flatulence), aatop (bloating), which resemble the clinical manifestations of gallbladder disease [8].

Similarity in Sign and Symptoms in Gall Bladder Cancer and Gulma

There are some similarities in the signs and symptoms

of gallbladder cancer described in modern texts and gulma described in ancient texts. The similarities are discussed in Table 2.

S.no	Symptom	GB cancer	Gulma
1	Abdominal pain	+	-
2	Abdominal bloating	+	+
3	Fever	+	-
4	Weight loss	+	-
5	Nausea	+	-
6	Yellowing of skin	+	-
7	Flatulence	+	+
8	Belching	-	+
9	Constipation	-	+
10	Loss of appetite	+	+

Table 2: Similarities in the signs and symptoms of gallbladder cancer.

Risk Factors

Risk factors for developing gallbladder cancer include advanced age, and the presence of a gallstone larger than 3 cm. Anomalous pancreato-biliary junction also may be a risk factor for the development of gallbladder cancer.

Bile acid composition, methyldopa, oral contraceptives, and occupational exposure to rubber, but these associations remain unproven. A 2008 study found evidence that excess body weight in women, specifically a 5 kg/m^2 increase in the body-mass index (BMI), is strongly associated with an increased risk of gallbladder cancer [9].

Diagnosis

Physical examination: General condition, Blood Pressure, Pulse, Temp, Built, Weight, Height, Respiratory Rate, Pallor, Icterus, Clubbing, Cyanosis, Lymph nodes

History: detailed history of patient with history of present illness, course of illness and family history. CECT scan, Ultrasound exam PTC (percutaneous trans hepatic cholangiography), ERCP (endoscopic retrograde cholangio pancreatography, MRI (magnetic resonance imaging) with gadolinium, Endoscopic ultrasound (EUS), Liver function tests : A higher than normal amount of a substance can be a sign of liver disease that may be caused by gallbladder cancer, Biopsy: The biopsy may be done after surgery to remove the tumor. If the tumor clearly cannot be removed by surgery, the biopsy may be done using a fine needle to remove cells from the tumor.

Diagnosis as per Ayurvedic

- **Trividh Pariksha** [10]

Trividhpariksha mentioned in Ayurveda have important role for examination of patients, when patient of gall bladder cancer comes to clinic the following questions must be asked by Prashanpariksha. If you have pain? then what is the nature of pain? site of pain? type of pain? radiation of pain? And frequency of pain? If you have abdominal bloating, then what is the severity? if bloating is related to the particular diet? If bloating occurs daily or occasionally? If patient have issues in bowel habits? Then what is the colour of the stools? consistency of the stool? frequency of stools? If patient have issues in urination? then what is the colour of the urine? consistency of the urine? frequency of urination? pain while micturition? Patient should be asked about loss of appetite, anorexia or any other digestive disturbances? If there is recent sudden weight loss? Then how much and in how much time?

- **Darshan Pariksha** or inspection is an integral part of examination of diseased person which is helpful in diagnosis of disease. In patients of gallbladder cancer, the yellowish discoloration should be seen carefully on sclera (icterus), nail bed and skin of whole body which may be present in case of obstructive jaundice or metastatic involvement of liver.
- **Sparshan** or palpation in gallbladder cancer patient should be done by lying down the patient is supine position on examination table, folding the legs up to the knee. The abdomen should be palpated for any mass or tenderness or both on right hypochondriac region. Abdomen should be palpated to check the severity of bloating.
- **Tailabindu Pariksha** [11]

  It is the important ayurvedic diagnostic tool to see the vitiation and sadhya asadhyata (prognosis) disease by evaluating doshas.

Procedure

In tailabindu pariksha, after waking up in early morning, middle stream of the urine should be collected by patient of gall bladder cancer. Urine is taken in a glass vessel over which an oil drop should be dropped and behaviour of oil is noted down.

The snake like image, an umbrella shape image and pearl like image of oil drop in the urine of the patient indicates the predominance of vataja, pittaja and kaphajaroga. In case of sannipataja disease the mixed pattern may be found.

Sieve shape or human being pattern of the oil drop in urine sample of the patient will be indicating “kuladosha” (hereditary) and ‘bhutadosha’ (extrinsic factors) respectively.

If tailabinduspreads quickly on the surface of the urine, does not spread or directly goes inside and touches the bottom of vessel indicates the sadhya (curable or manageable), kashtasadhya (difficult to treat) and asadhya (incurable) respectively.

The direction of spreading should also be noted down. If the drop spreads in the purva(east) direction, in the south direction, in the northern direction or toward the west then there are chances the patient gets relief, recovers gradually, cured and becomes is happy and healthy respectively.

If oil spreads towards the ishanya (northeast), or into agneya (southeast) or nairutya (southwest) directions, or on to vayava (northwest) then the patient is bound to die.

Stages

The staging system most often used for gallbladder cancer is the American Joint Committee on Cancer (AJCC) **TNM** system [12], which is based on 3 key pieces of information which includes:

- The extent (size) of the tumor **(T)**, which explains how far has the cancer grown into the wall of the gallbladder or Has grown through the gallbladder wall into nearby organs such as the liver.
- The spread to nearby lymph nodes **(N),** which explains the spread of cancer to nearby number of lymph nodes.
- The metastasis to distant sites **(M),** which explains spread of cancer to distant organs such as the liver, the peritoneum, the lungs or any other organ of the body.

The Table 3, shows the staging of Gallbladder Cancer. Numbers or letters after T, N, and M provide more details about each of these factors. Higher numbers mean the cancer is more advanced.

AJCC Stage	Stage grouping	Stage description
0	Tis NO MO	Cancer is only in the epithelium (the inner layer of the gallbladder) and has not grown into deeper layers of the gallbladder (Tis). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
I	Tis NO MO	The tumor has grown into the lamina propria or the muscle layer (muscularis) (T1). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIA	T2a NO MO	The cancer has grown through the muscle layer into the fibrous tissue on the side of the peritoneum (the lining of the abdominal cavity) (T2a). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIB	T2b NO MO	The cancer has grown through the muscle layer into the fibrous tissue on the side of the liver, but has not invaded the liver (T2b). It has not spread to nearby lymph nodes (N0) or to distant sites (M0).
IIIA	T3 NO MO	The cancer has grown through the serosa (the outermost covering of the gallbladder) and/or it has grown directly into the liver and/or one nearby structure like the stomach, It has not spread to nearby lymph nodes (N0) or to distant sites (M0).duodenum (first part of the small intestine), colon, pancreas, or bile ducts outside the liver (T3).
IIIB	T1-3 NO MO	The cancer may or may not have grown outside of the gallbladder into the liver and/or one other nearby structure, but it has not grown into the main blood vessels leading It has not spread to distant sites (M0). into the liver (portal vein or hepatic artery) (T1 to T3). It has spread to no more than 3 nearby lymph nodes (N1).
IVA	T4 NO or N1 MO	The tumour has grown into one of the main blood vessels leading into the liver (portal vein or hepatic artery) or it has grown into 2 or more structures outside of the liver (T4). It has not spread to distant sites (M0). It may or may not have spread to no more than 3 nearby lymph nodes (N0 or N1).
IVB	Any T, N2 MO	The primary tumour may or may not have grown outside the gallbladder. The cancer has spread to 4 or more nearby lymph nodes (N2)

Table 3: Stage grouping and stage description of GB ca.

Management According to Modern Medicine

Treatment will depend on the stage of cancer. The initial goal of treatment is to remove the gallbladder cancer, but when that isn't possible, other therapies shown in Table 4, may help control the spread of the disease and keep the patient as comfortable as possible.

Stage grouping	Management description [13]
Tis	simple cholecystectomy
T1	Patients may require cholecystectomy with wedge resections involving segment IVb and V of the liver as well as portal lymphadenectomy
T2	T2 lesions invade peri muscular connective tissue with no extension beyond the serosa or into the liver. This often requires a more formal resection of segments IVb and V
T3	The tumor burden may extend to the serosa, liver, and/or adjacent organs/structures. Under these circumstances, resection becomes more radical, including an extended right hepatectomy with possible caudate lobectomy, regional lymphadenectomy, and extirpation of other affected structures. Some centers further advocate pancreaticoduodenectomy to improve outcomes
T4	Disease is widely disseminated through vascular invasion and/or metastasis Surgery can't cure gallbladder cancer that has metastized to other areas of the body. Instead, should use treatments that may relieve signs and symptoms of cancer and make patient as comfortable as possible.
	Options may include Chemotherapy which is a drug treatment that uses chemicals to kill cancer cells. Radiation therapy which uses high-powered beams of energy, such as X-rays and protons, to kill cancer cells

Table 4: Stage groping and management description of the GB ca**.**

Management According to Ayurveda

The word gallbladder carcinoma is not mentioned in Ayurveda but the pathogenesis and clinical manifestations are likely similar to pitta Pradhan sannipataja gulma. Gallbladder carcinoma could be managed by using anticancerous, herbal, mineral and herbo-mineral compound along wit, rejuvenation therapy and symptomatic management. The anti-cancerous drugs that could be used for management GB ca are given in Table 5. Some of the single herbal drugs that have been proved anti-cancer ous are given in sub table 5.1.

Table 5: Anti-Cancerous Drugs.

S. no	Name of Anticancer drug	Dose	Frequency	Anupana
1	Haridra	Churna-3gm	Thrice a day	Milk
2	Tulsi	Churna-1-3gm,swarasa-5-10ml	Thrice a day	Water
3	Shigru	Moolatwak swarasa-10-20ml,Beejachoorna-1-3gm	Thrice a day	Water
4	Sadabahar	Patra swaras- 20 ml, kalka-10gm	twice a day	Water

Table 5.1: Herbal.

Some of the anticancer preparations with the combination of herbal and mineral drugs are given in table 5.2.

S.no	Name of Anticancer drug	Dose	Frequency	Anupana
1	Loknatha ras [14]	125 mg	twice a day	Draksha- avleha
2	Shankh drava [15]	125 mg	twice a day	Draksha- avleha
3	Tapayadi loha [16]	125 mg	twice a day	Draksha- avleha
4	Kalanal ras [17]	125 mg	twice a day	Draksha- avleha
5	Gulmakuthar ras [18]	125 mg	twice a day	Draksha- avleha

Table 5.2: Herbomineral.

Some of the minerals that have been proved beneficial in the anticancerous properties are given in table 5.3

S.no	Name of Anticancer drug	Dose	Frequency	Anupana
1	Swarnabhasma	32 mg	twice a day	Honey
2	Yashadabhasma	32 mg	twice a day	Honey
3	Hirakbhasma	32 mg	twice a day	Honey

Table 5.3: Mineral.

Other than the single herbal drug, there are poly-herbal drugs with combinations of various single drugs that individually have been proved anti-cancerous are given in table 5.4.

S.no:	Name of the drug	Dose	Frequency	Anupana
1	Arbudharkshaya	10 gm	twice a day	-
2	Yakrutpliha har kwath	10 gm	twice a day	-

Table 5.4: Polyherbal.

Along with the anticancerous drugs there is also a need to pacify the symptoms that are presented in the GB ca. For various symptoms that are present in this disease, the symptomatic drugs are given in table 6.

S.no:	Name of the drug	Dose	Frequency	Anupana
1	Mahashankhvati [19]	250 mg	twice a day	Butter milk
2	SarjiKshar [20]	1 gm	twice a day	Butter milk
3	Lavanbhaskar churan [21]	5 gm	twice a day	Butter milk

Table 6: Symptomatic.

The immunity of the patient due to the disease have already been compromised that is why it is necessary to add immunomodulatory drugs given in table 7; for the enhancement of the immunity.

S.no	Name of the drug	Dose	Frequency	Anupana
1	Amalak rasayan [22]	6 gm	Twice a day	-
2	Draksha avleha [23]	6 gm	Twice a day	-

Table 7: Immunomodulators/rasayana.

Along with the management of GB ca, there are possibilities of the metastasis and liver involvement, thus the liver protective drugs given in table 8 are necessary to help in the improvement of liver functions. Hepatoprotective drugs as follows can be given.

S. no	Name of the drug	Dose	Frequency	Anupana
1	Bhumyamalakighanavati	500mg	Twice a day	Water
2	Bhumyamalakiswaras	10 ml	Twice a day	-
3	Sharpunkhachurna	5 mg	Twice a day	Water
4	Arogyavardinivati	250 mg	Twice a day	Warm Water
5	Kutakichurna	5 mg	Twice a day	Warm water
6	Syrup M-liv	10 ml	Thrice a day	-
7	Syrup liv 52	10 ml	Thrice a day	-

Table 8: Liver metastasis.

Prevention

Avoiding use of tobacco, eating a healthy diet, fruits and vegetables, drink alcohol, only in moderation, Limit processed meats, maintain a healthy weight and be physically active.

Diet

During cancer treatment, dietary interventions in cancer patients can be effective in alleviating adverse outcomes and may improve overall survival. Cancer metabolic pathways are complex and highly regulated, and there is growing evidence that dietary modulation can be beneficial in cancer treatment, i.e. a diet rich in fat and protein or restricted in calories. According to the Warburg's observations, many tumors depend heavily on glucose for their metabolic demands and ferment into lactate-even under sufficient oxygen, also tumor cells often lack ability to use fatty acids or ketone bodies as an energy source and could even be harmed by them. Thus calorie restricted low carb/ High fat (LCHF) diets should be consumed [24].

Example for the daily diet is shown in table 9 [25]:

Meal Time	Food Group	Raw	Recipe	Servings Amounts
Breakfast	Cow's Milk	100 ml	Haridra Milk	1 Cup
	Cereals	70 g	Wheat dalia	1/2 Cup
Lunch	Cereals	120 g	Chapatti	3 no.
			Brown Rice	1 cup
	Pulses	20 g	Green gram dal	½ cup
	Vegetables	150 g	Mix Veg. curry	¾ cup
	Vegetables	50 g	Salad	¼ cup
	Buttermilk	100ml	Buttermilk with sarjikshar	½ cup
Snacks	Fruits	100g	Seasonal fruit	1cup
Dinner	Cereals	120g	Brown rice	2cups
			Chapatti	2 no.
	Pulses	20g	Green gram dal	½ cup
	Vegetables	150g	Seasonal vegetables	¾ cup

Table 9: Basic Daily diet for the Patient.

Hyperthermia

Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues [26]. By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors. Several methods of hyperthermia are currently under study, including local, regional, and whole-body hyperthermia. In local hyperthermia, heat is applied to a small area, such as a tumor, using various techniques that deliver energy to heat the tumor. Different types of energy may be used to apply heat. In Ayurveda, application of aamihaldi, with heated mahavishgarbh oil is done for local hyperthermia followed by patrapotlisweda twice a day.

Alkalization

Acidity is a well-known factor associated with cancer. Lower pH levels in the extracellular space promote the invasive and metastatic potential of cancer cells. Extracellular acidity is mostly generated by tumor cells due to upregulated proton [H+] and lactic acid production. This phenomenon is distinct from 'acidity' caused by a net-acid diet. A net-acid diet or acidogenic diet is determined by the balance between acid and base-forming dietary constituents. Most fruits and vegetables are net-base producing foods There is scientific evidence supporting the concept that appropriate alkali supplementation in the form of fruits and vegetables serves aptly to neutralize excess [H+] produced from protein metabolism [27]. Since the acidosis is more critical for the survival of tumor cells, it would not be a surprise to see a dramatic effect on tumor apoptosis by simply modulating the

pH of the tumor micro environment with sodium bicarbonate [28]. In Ayurveda, kshar which are used in the treatment contains sodium bicarbonate as a content so, they can be used in diet and medicine for maintaining alkaline levels in body.

Antioxidants

Apigenin from parsley, Curcumin from turmeric, Crocetin from saffron, Cyanidins from grapes, Indole-3-carbinol (I3C) is found in Brassica vegetables, such as broccoli, cauliflower, collard greens, Epigallocatechin gallate from green tea, Fisetin from strawberries, apples, Genistein from soybean, Gingerol from gingers, Kaempferol from tea, broccoli, grapefruit, Resveratrol from grapes, Rosmarinic acid from rosemary, Sulforaphane from cruciferous vegetables. The above are the examples of dietary antioxidants. In several in vitro and animal studies the hypothesis has been testedthat antioxidants benefit patients receiving chemotherapy [29]. Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Betacarotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. The vitamin A and Beta-carotene have actions by quenching both single oxygen and other free radicals generated by photochemical reactions [30]. Although further studies are needed, the predominance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of chemotherapy in the treatment of a wide variety of cancers.

Oxygenation

In yogic philosophy, prāna is the vital force in all living beings in the universe. Prana represents the interface between energy and consciousness. Yogic philosophy also appreciates that mind is more powerful than prana and hence can direct the pranic flow [31]. The practice of yoga includes physical postures, breathing practices, and meditations. It is known to alter immune and endocrine functions at the cellular level through influencing cell cycle, aging, oxidative stress, cell death, and several pathways of stress signaling. Yogic postures (asanas) and breathing techniques (pranayama) focus on airflow in the lungs, thus increasing their capacity, endurance, and efficiency. Back-bending postures open the chest, improving both lung and heart functions. A study assessed blood oxygen saturation before, during, and after two yoga breathing techniques and a significant increase in oxygen saturation was observed in the high-frequency yoga breathing. Another study measured the impact of asanas and pranayama on blood oxygen saturation level. Yoga practices have also been shown to improve ROS levels and oxidation status. Sudarshan Kriya (SK), which is a type of pranayama in which breathing is in three different rhythms, has been shown to lower blood lactate levels and provides better antioxidant defense [32].

Discussion

Gallbladder cancer is 5th most common cancer involving the gastrointestinal tract, but it is the most malignant biliary tract cancer. This tumor is traditionally regarded as a highly lethal disease with an overall 5-year survival rate less than 5%.

Though modern medicine has options which usually focus on the curative resection, which can be compromised by the extent of the tumor invasion. If the invasion is limited to the mucosa or submucosa the 5-year survival rate is over 95%.

And when lesions are unresectable, palliation, alternative medicine or integrated approach is more appropriate sitting.

Though the term cancer is new for Ayurveda but abundant of medical literature has been found which have described malignant tumours in the various texts of Ayurveda like Arbuda, gulma, these are very nearer terms described for malignant tumours. As Acharya charaka has considered gulma as one type of shotha [33]. Also, from the five adhishthans (places) acharya charaka has described parshav (lateral parts of body) as one of the gulma adhishthan [34], which can be taken as the place for gallbladder. And Acharya chakarpanidutt in his commentary has described the details of the five adhishthans whereby it is said that the pittashaya (gallbladder) is one of the gulma sthana [35].

As per Acharya sushruta any granthi which lies in between hruday (heart) and basti Pradesh (bladder) has been named as gulma [36]. Also, the various symptoms of gulma are likely to resemble the clinical manifestations of gallbladder cancer [37].

And as per Madhav Nidaan while describing gulma has mentioned any granthi(organ/gland) insidekoshta(abdomen) is called as gulma [38].

The abundant drugs and therapies in Ayurveda have also been proved fruitful in the management of Gallbladder cancer.

Haridra have been proved to have anti-cancerous effects. Curcumin has cancer chemoprotective properties in a variety animal models chemical carcinogenesis [39,40]. The evidence suggests that it can suppress tumorigenesis, tumour promotion, and metastasis and, therefore, has

enormous potential as an anticancer agent [41].

Similarly, Vinblastine is the official specific name for the Sadabahar alkaloid and known as vincaleukoblastine. The sulphate derivative of Vinblastine compound is used in the clinic. It is an anti-cancer drug which is widely used medicines for the treatment of different kinds of cancers disease. Catharanthus (sadabahar) plant has reached the bedside in modern medicine. There are many other anticancer drugs of plant origin have yielded success stories, e.g. Taxol, combretastatin, camptothecin [42].

There are various in-vitro studies on Tulsi (O. sanctum) which showed that ethanolic extract is cytotoxic to mouse Lewis lung carcinoma (LLC) cells and it also reduced the number of tumor nodule formation in LLC-injected mice [43].

Also, the different parts of the Shigru (M. oleifera) plant have antioxidant, anti-inflammatory, anticancer, chemo preventive, and even radioprotective activities. Most of the research has focused on moringa leaf extracts, and the published results suggest that the extract is cytotoxic to a wide variety of different cancerous cells [44].

The herbo-mineral drugs like Loknathras, Shankhdrava, Tapayadiloha, Gulmakutharras and Kalanalras in various ayurvedic tests have been used since ages as the treatment for gulma. Due to the presence of various minerals like Swarna (gold), Tamra (copper), Rajat(silver), Parad(mercury), Gandhak(sulphur), Loha(iron), they not only manage gulma but also have proved anti-cancerous properties.

Talking about the various minerals, "*Swarna*" meaning gold, "*Bhasma*" meaning ash is an ancient Indian Ayurvedic medicine used for rejuvenation and revitalization during old age.

There are studies which suggest that Gold-silica nano shell has been used in Nano Shell-Assisted Photo-T thermal therapy (NAPT) to kill tumor cells by near Infra-Red (IR) light. Gold-EGFR conjugates have been used to detect the cancer cells by exploiting the light scattering properties of gold nano conjugates. *Swarna Bhasma* showed fare results in several solid tumors [45]. Swarna Bhasma can be a potential drug for anticancer therapy.

Also, Yashada Bhasma (Zinc) induce cell growth arrest. This may open up new possibilities for cancer control [46].

Heerak Bhasma (Diamond), mainly used in the treatment of internal abscess, tumor, cancer, angina pectoris and tuberculosis [47].

The polyherbal drugs Abudharkshaya and yakrutpliha har kwath are self-prepared drugs by National Institute of Ayurveda Jaipur, Rajasthan- India, which contains proved anticancerous drugs and has been giving good results in management of cancer patients in Cancer consultation and treatment unit of National Institute of Ayurveda Jaipur, Rajasthan- India.

Also, symptomatic management is necessary, due to involvement of gallbladder the metabolism is disturbed which there by can be improved by improving the agni (digestive fire) by the agnivardhak drugs like Mahashankhvati, Sarjikshar ,lavanbhaskarchurna. As liver in later stages liver is also affected thus, some hepato- protective drugs like bhumyamalkai, sharpunkha, kutaki are necessary to protect liver.

Despite all these managements there is still one factor which plays an important role that is immunity of the patient. To improve the patient's immunity, the immunomodulators in ayurvedic texts like amalakrasayan and drakshadiavleha are given. The main ingredients of these are amalaka [48] (Emblicaoffinalis) and draksha [49] (Vitis vinifera) respectively which have proved immunomodulatory effects.

'Prevention is better than cure' is not any unknown saying, but both prevention and cure is equally important in cancer patients. Avoiding use of tobacco in any form reduces the risk of cancers. Diet having antioxidants and alkaline nature may ultimately provide a medium which is not suitable for survival or growth of the tumor cells. Aamihaldi application as the local hypothermia technique followed by patrapotli swedana karma may helpful in reducing or stopping the further growth of the tumor. Practicing pranayama may allow better systemic and immune functions by reducing the free radicles and oxidative stress.

Conclusion

Gall Bladder Cancer can be diagnosed and managed by using diagnostic method recommended in Modern Medicine as well as by using basic principles and medicines described in Ayurveda. Characterized by the lack of symptoms at the initial stage leading to the difficulty in the treatment, survival is critically dependent on early diagnosis. Hence it should be prevented by reducing the risks factor of this disease through follow the wholesome diet and normal lifestyle described in Ayurveda. Thus Ayurveda may play an important role in both treatment and prevention of Gallbladder cancer through its holistic approach. Depending upon the severity of the disease the medicines from the various groups mentioned above could be chose which can be prescribed to the patients for prevention as well as management of the disease.

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