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Comparison the Effectiveness of Capecitabine in Breast Cancer Vs Gall Bladder Cancer

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Conflicts of Interest: **Nil**
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ABSTRACT

Cancer is one of the most neglected diseases and is the leading cause of death worldwide. Breast cancer is the most common cancer and is the leading cause of death in women worldwide. In 2008, about 1.38 million new cases of breast cancer were diagnosed with symptoms of almost 50% of all breast cancer patients and about 60% of deaths occurring in developing countries. Breast cancer in women and prostate cancer in men are common worldwide. Worldwide; accounted for more than 27% of all cancers and approximately 15% of cancer deaths in women. Gallbladder cancer is one of the most common cancers in India with a high incidence in northern and central India. Gallbladder cancer is considered to be the fifth most common cancer and is one of the most aggressive cancers of the gastrointestinal tract. Most GBCs are epithelial adenocarcinomas. GBC has been reported to be three to five times more common in women than men. Worldwide; Clinical trials of targeted therapies and alternative therapies for breast and gallbladder cancer are ongoing and could offer significant new information on the treatment of this deadly disease, ultimately improving the effectiveness of treatment. For decades, there has been no worldwide neoadjuvant treatment or adjuvant treatment for used breast cancer and bile duct cancer. Therefore, adjuvant capecitabine was widely regarded as a standard adjuvant treatment. Adjuvant treatments including radiotherapy, chemotherapy and radiotherapy, as well as systemic chemotherapy can play a role in improving survival. This summarizes the current situation and future prospects for curative treatment for breast and gall bladder cancer. This article represents a comprehensive review of the literature on gallbladder and breast cancer literature examining epidemiology, pathology, diagnostic research and treatment with capecitabine and other drug combinations and also includes several therapies.

Keywords: breast cancer, gallbladder cancer, epidemiology, pathology, diagnosis and treatment, capecitabine.

Introduction

Cancer is one of the most neglected diseases and is the leading cause of death worldwide. More than a million Indians suffer from cancer and many of them die every year. The mechanisms underlying the growth of cancer or the mutation of oncogenic cells, their treatment and control have become one of the most important research fields in biology and medicine. Uncontrolled, abnormal and excessive cell division is called cancer (Crab = cancer). These abnormal, undifferentiated cells are called cancer cells. Cancer research is called oncology. In our body, cell growth and differentiation are highly regulated and controlled. In cancer cells, there is a breakdown in these controls. Normal cells exhibit a substance called contact inhibition, during which contact with other cells inhibits their uncontrolled growth. Cancer cells seem to have lost their properties. As a result, the

cancer cells continue to divide, producing a large number of cells called tissues (Anwar et al., 2019). Plants are classified according to the tissue of their origin. Most cancers fall into one of the following stages;

Carcinomas: Cancer of this type occurs in epithelial tissues such as the skin or epithelial membranes of internal organs or glands (about 85% of all cancers). For example; (a) brain cancer, (b) cancer of the mouth, (c) cancer of the stomach, (d) cancer of the intestines, (e) cancer of the lungs, (f) cancer of the cervix, (g) adenocarcinone (cancer of the prostate).

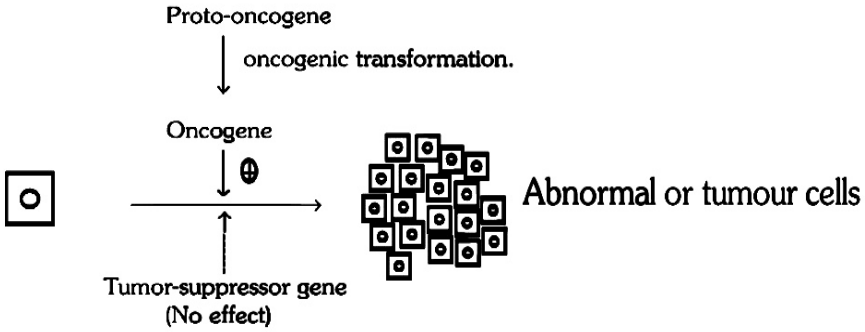

Figure 1: Gene transfer for causing cancer

Mechanism of Normal Body Growth:

Normal cell growth under the control of critical genes that control cell proliferation, differentiation, and survival. Modification of these genes leads to oncogenic mutations.

These genes can be divided into the following three categories:

(i) **Proto-oncogenes:** The genes that cause cell proliferation. For example; Genetic code gene growth, growth factor factors, transcription factor, etc. In addition, many genes are identified by normal cells called cell oncogenes or proto-oncogenes that, when activated under certain conditions, can lead to oncogenic mutations in cells.

(ii) **Tissue genes:** The genes that inhibit cell proliferation.

(iii) **Suicide genes:** The genes that control the planned cell death.

Carcinogenic DNA and RNA (viral viruses) have been shown to be associated with oncogenic mutations (Anwar et al., 2019).

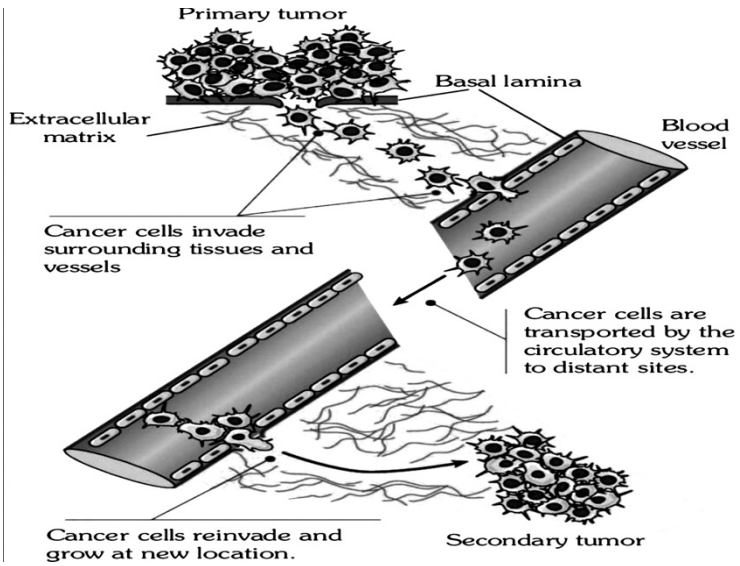

Figure 2: Occurence of cancer

BREAST CANCER:

Breast cancer is the most common cancer and is the leading cause of death in women worldwide. In 2008, about 1.38 million new cancer patients were diagnosed and about 50% of all breast cancer patients and about 60% of deaths occurred in developing countries (Coleman et al., 2008). Breast cancer in women and prostate cancer in smen are common worldwide. Worldwide; accounts for more than 27% of all cancers and about 15% of cancer deaths in women (World Cancer Report 2014, www.iarc.fr).

There are significant differences in breast cancer survival rates worldwide, with an estimated 5% survival rate in 80% of developed countries and less than 40% in developing countries (Coleman et al., 2008). Developing countries face resource and infrastructure challenges that challenge the goal of improving breast cancer outcomes through early detection, diagnosis and management (Anderson et al., 2008). In developed countries like the United States, approximately 232,340 women will be diagnosed in 2013 and 39,620 women will die of breast cancer. The risk of getting breast cancer in an American woman is 12.38% (Siegel et al., 2013). The dramatic decline in morbidity due to breast cancer in the United States from 1975 to 2000 was due to steady advances in the management of mammography and the practice of mammography (Berry et al., 2005).

According to the World Health Organization (WHO); Improving breast cancer prognosis and early detection remains the cornerstone of breast cancer legislation. Several modern drugs have been developed to treat breast cancer. Therapeutic breast cancer treatment with antiestrogens such as raloxifene or tamoxifen can prevent breast cancer in people who may develop it (Peng et al., 2005). Both breast surgeries are an additional way to prevent a higher risk of developing cancer in women. In patients diagnosed with breast cancer, a variety of treatment strategies include targeted therapies, hormone replacement therapy, radiation therapy, surgery, and chemotherapy. In people with distant metastases, treatment usually aims to improve quality of life and survival rate (Reeder et al., 2008). The negative effects of breast cancer treatment are one of the most motivating factors in seeking alternatives. The use of herbs to treat patients with breast cancer is considered to be a natural alternative because some plants may contain naturally occurring properties that have the potential to cure breast cancer (Abdull et al., 2013; Dwivedi et al., 2011; Mary et al., 2012; Mukherjee et al., 2006; Zhu et al., 2011).

Anatomy of breast:

Both men and women have breasts (Torre et al., 2016). The breast is formed from fat called adipose tissue (Aronson et al., 2000). Women's breasts often have more prostate tissue than men's (Stark et al., 1992). Female breasts consist of 12 to 20 lobes divided into smaller lobes (Tanis et al., 2001). These lobes and lobes are connected by milk ducts. Chest adipose tissue is excluded by a network of nerves, blood vessels, lymphatic arteries, lymph nodes and also contains muscle and muscle tissue (Thomsen et al., 1998). A woman's breast is designed to provide healthy baby food and to provide sex for the woman herself. Breasts are the most sensitive organs in hormonal changes in the body (Jagannathan et al., 2017). They embrace circulatory changes by adapting to the menstrual cycle. They are closely related to the female genital system. Nipple stimulation enhances prolactin secretion from the pituitary gland. This hormone also affects the uterus and can cause fractures. Lymph nodes that pull the breast tissue are also found in themarmpits. After a woman has had a baby and her milk has run out, the mother may have a noticeable swelling in her armpits due to the tightness of the breast tissue in that region. Breasts come in all shapes and sizes, such as nipples. Most women have slightly smaller breasts than others (Brayboy et al., 2017) The epidermis of the areola and nipple are large in color and somewhat wrinkled, and the skin of the nipple contains many apocrine and sweat glands and short hair. 15 to 25 milk ducts go to the bottom of the nipple where they extend to cover the milk breasts. These milk tubes act as

nipple carriers. A little below the surface of the nipple, these breasts end up with lumps shaped like a lump. The circular areola is located near the nipple and has a diameter of between 15 and 60 mm. Sebaceous glands, sweat glands and fluffy hairs are present on the skin, Montgomery glands, are large and altered glands with small ducts of milk entering the Morgagni tubercles in the epidermis of the areola. At the depth of the nipple and areola, several smooth muscle fibers are rounded and folded into the thick and distant bones of the milk ducts directly into the nipple. These muscle fibers cause the breasts to become empty, the nipples erect and the areola inserted. Most of the mammary parenchyma grow downwards from the second or third rib to the inframammary gland, lying almost where the sixth or seventh rib is located, and alternately from the edge of the chest to the inner axillary line. Breast tissue also grows abnormally into the armpit like a rare spinal cord. The posterior surface of the chest resides mainly on the pectoralis fascia, rectus abdominis muscles, the outer oblique of the abdomen and the anterior serratus (Hassiotou et al., 2013).

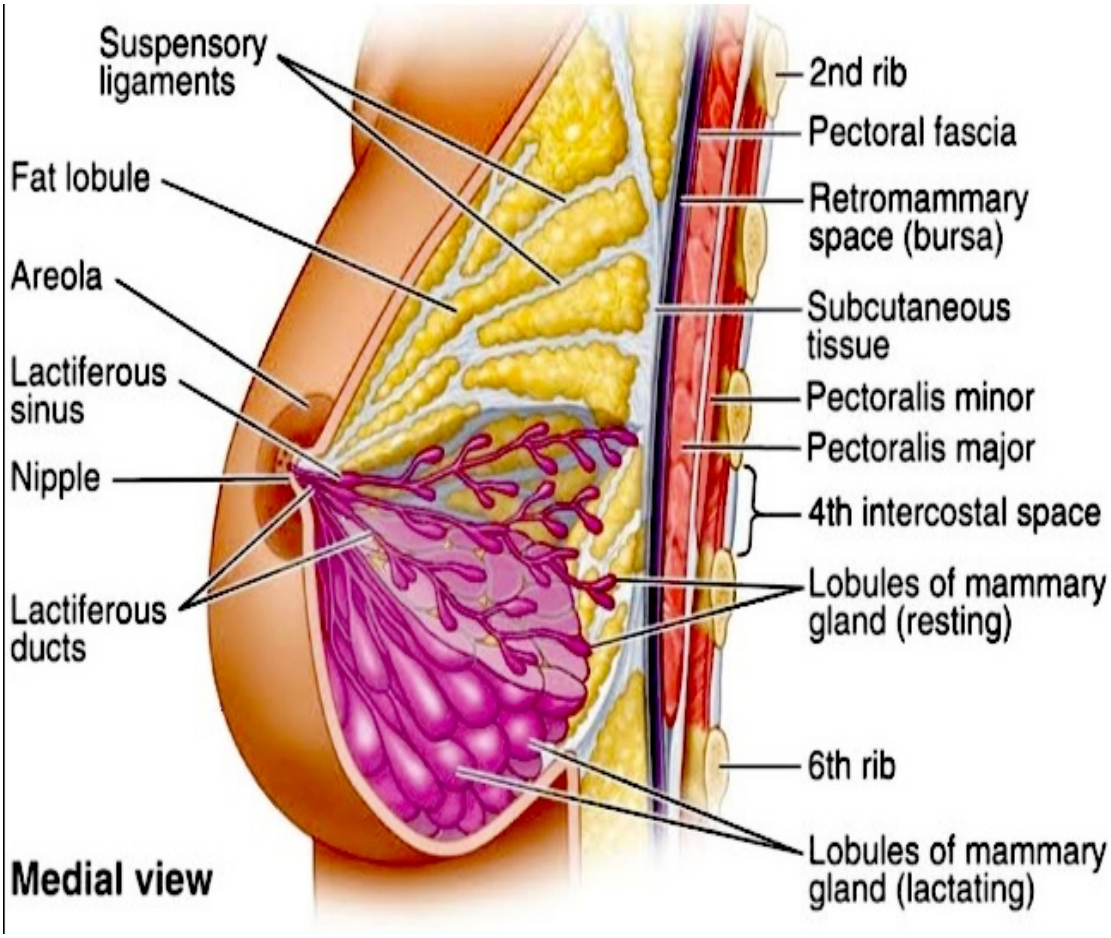

Figure 3: Anatomy of breast

Epidemiology:

Breast cancer is that the commonest sort of cancer and is that the second leading explanation for death. The disease is the leading cause of death among women aged 45 to 55 and is the second leading cause of death from cancer (Jemal et al., 2009). These days; one in twelve women between the ages of 1 and 85 in the UK develops breast cancer. With one million new cancer cases reported worldwide, breast cancer is more common in women, accounting for 18% of all cancer

cases in women. Breast cancer rates are expected to increase to 85 per 100,000 women by 2021 (Han et al., 2013). In 2012, there were 1.67 million new cases of breast cancer, accounting for 25 percent of all cancers in women. There are 883,000 cases in less developed countries and 794,000 in more developed countries (Ferley et al., 2015). According to data, 145.2 women in Belgium and 66.3 in Poland out of every 100,000 suffer from breast cancer (Agnieszka et al., 2014). The incidence of breast cancer in the United States is one in eight women, and one in 35 in,Asia suffers from breast cancer. In Iran, there are 10 cases per 100,000 people and 7,000 new cases are reported annually (Haghighat et al., 2012). The prevalence of breast cancer is on the rise in Pakistan (Bhurgri, 2004; Hanif et al., 2009; Khokher et al., 2012). Breast cancer is found mainly in densely populated areas in developing countries in South Asia (Badar et al., 2011; Moore et al., 2009). Male breast cancer has been diagnosed in northern Pakistan (Jamal et al., 2006). There are new cases of breast cancer in China: 168,013 in 2005 and 121,269 in 2000 (Yang et al., 2005).

Stages of breast cancer:

According to a cancer.org report, the stages of breast cancer depend on the size and type of tumor and how well the cancer cells penetrate the breast tissue (Heim et al., 1997). While category 0 describes a non invasive plant and category 4 describes the type of invasive plant. The descriptions of these stages of the plant are:

Stage 0: This is a non-invasive stage of the tumor that shows that both cancerous and non-cancerous cells are found inside the part of the breast where the tumor begins to grow and there are no signs of invasion surrounding their tissues. ., 1997).

Stage 1: This stage is defined as an incurable breast cancer and the least likely attack of this stage. It has two categories namely category 1A and 1B. Phase 1A describes a tumor up to 2 cm and no lymph nodes are involved while Phase 1B describes a small group of tumor cells larger than 0.2 mm located in the lymph node (Segal et al.,m2001).

Stage 2: Phase 2 and consists of two phases 2A and 2B. Section 2A states that the tumor is found in the lymph nodes or sentinel lymph nodes, but is not found in breast cancer. The plant may be smaller or larger than 2cm but not larger than 5cm. However, section 2B explains that the tumor can measure more than 5 cm but cannot reach axillary lymph nodes (Moran et al., 2014).

Stage 3: Divided into three sub-categories namely 3A, 3B and 3C. Among them, category 3A explains that no tumor is found in the chest, but can be found in the 4-9 axillary or sentinel lymph node, while section 3B explains that the tumor may be large but cause inflammation or ulcer on the skin. . and may have spread to 9 lymph nodes or sentine lymph nodes. Stage 3B can be considered an inflammatory breast cancer that includes red, warm swollen skin. However, section 3C describes tumor proliferation at 10 or more of the 10 axillary lymph nodes and affects the lymph nodes above and below the collarbone (Jacquillat et al., 1990).

Stage 4: This is a progressive and stable stage of cancer and this stage describes the spread of other body parts such as lungs, bones, liver, brain, etc. (Neuman et al., 2015).

Histological subtypes
Preinvasive
Ductal carcinoma in situ (DCIS)
• Spreads through ducts and distorts ductal architecture; can progress to invasive cancer; unilateral
Lobular carcinoma in situ (LCIS)
• Does not distort ductal architecture; can be bilateral
• Risk factor rather than precursor
Invasive
Ductal carcinoma no special type (NST)
• Develops from DCIS; fibrous response to produce a mass; metastasizes via lymphatics and blood
Lobular carcinoma (ILC)
• Isolated tumor cells (CDH1 mutations) minimal fibrous response; metastasizes preferentially via viscera
Adipose tissue
Fatty connective tissue
Rib
Muscle
Intercostal muscle
Lobule
Duct
Nipple
Collecting duct
Areola
Luminal epithelial cell
Lumen
Basal myoepithelial cell
Intrinsic subtypes (PAM50)
Basal-like
TP53 mutations; genetic instability; BRCA mutations; medullary-like histology poorly differentiatied
Claudin-low
Largely triple-negative; metaplastic
HER2-enriched
HER2 amplification; GRB7 amplification; PIK3CA mutations; TOPO2 and/or MYC amplification; NST, pleiomorphic lobular and micropapillary histology
Normal-like[b]
Luminal B
PI3KCA mutations (40%); ESR1 mutations (30–40%)[a]; ERBB2 and ERBB3 mutations; NST, micropapillary and atypical lobular histology
Luminal A
Activation of ER51, GATA3, FOXA1, XBP1; NST, tubular cribriform and classic lobular histology
Surrogate intrinsic subtypes
Triple-negative
ER–, PR–, HER2–; high grade; high Ki67 index; NST histology; special type histology (metaplastic, adenoid cystic, medullary-like and secretory); poor prognosis except for some special types
10–15%
HER2-enriched (non-luminal)
ER–, PR–, HER2+; high grade; high Ki67 index; NST histology; aggressive disease but responds to targeted therapies; intermediate prognosis
13–15%
Luminal B-like HER2+
ER+ but lower ER and PR expression than luminal A-like; HER2+; higher grade; high Ki67 index; NST and pleiomorphic; responds to targeted therapies; intermediate prognosis
Luminal B-like HER2–
ER+ but ER and PR expression lower than in luminal A-like; HER2–; higher grade; high Ki67 index; high-risk GES; NST, micropapillary and lobular pleiomorphic histology; intermediate prognosis
10–20%
Luminal A-like
Strongly ER+ and PR+; HER2–; low proliferation rates; typically low grade; low Ki67 index; low-risk GES; NST, tubular cribriform and classic lobular histology; good prognosis
60–70%
Proliferation
High grade
Basal-like genes
HER2 expression
ER expression
Low grade

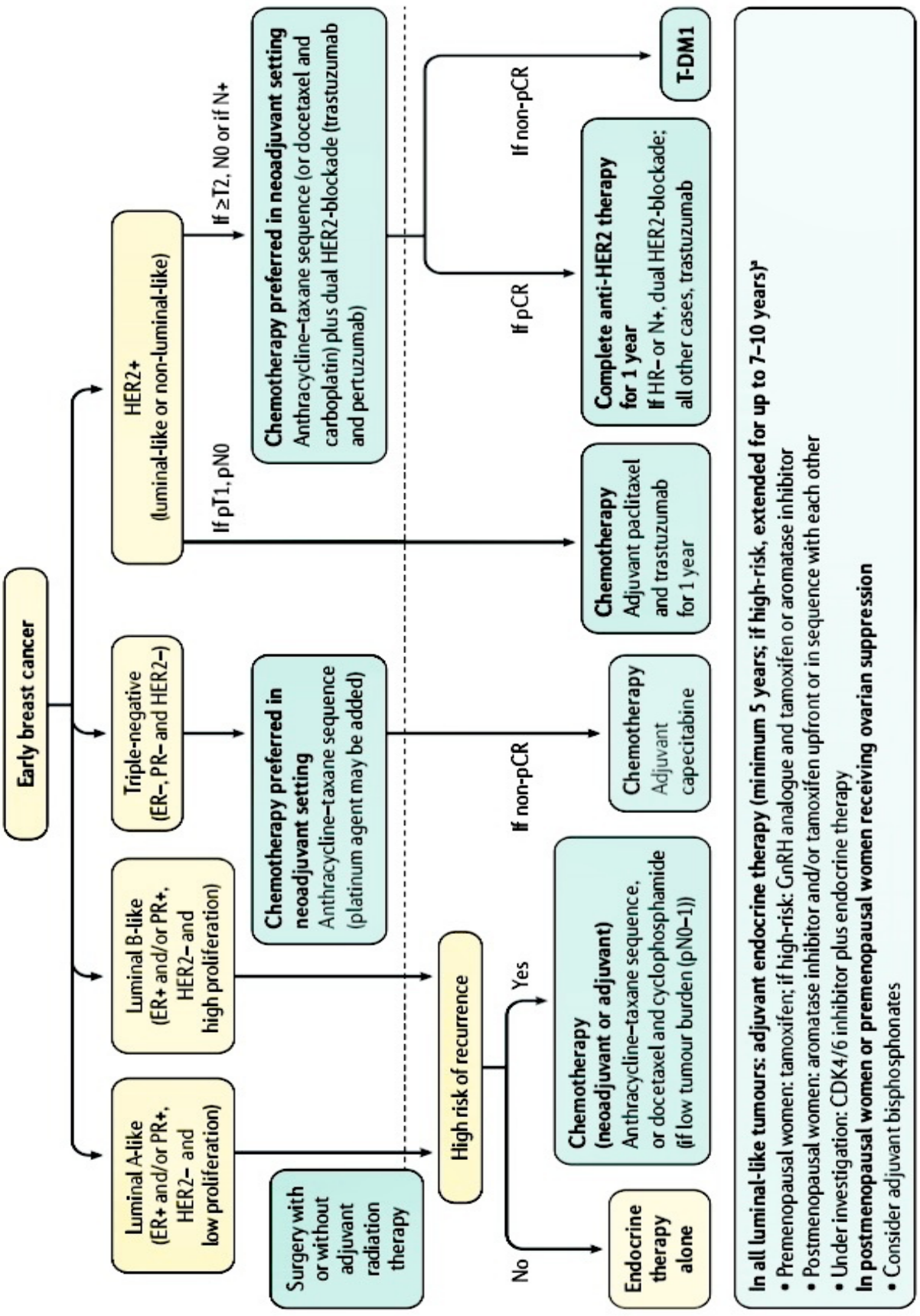

Figure 4: First stage breast cancer algorithm

Note: First line breast cancer treatment is based on the type of lump and load. All patients with estrogen receptor positive (ER) disease receive adjuvant endocrine therapy after surgery. If patients are at high risk of recurrence (for example, as a result of high-risk signature results of 0-3 symptoms involving lymph nodes, lymph4 lymph node involvement, or> 10% risk of dying from certain breast cancer in ten years) 130, and should chemotherapy is recommended. In human epidermal growth factor receptor 2 (HER2) the first three-fold malignant breast cancer, neoadjuvant subtype system treatment is common, followed by surgery. If a complete pathological response (pCR) is not available, systemic treatment can be intensified. Bisphosphonates are an additional complementary therapy for all postmenopausal and premenopausal patients experiencing ovarian depression; and they maintain bone density. If indicated, radiation therapy may be given after surgery. The management algorithm considers registered treatmentmoptions based on evidence. The discovery and refund of different diagnostic or therapeutic methods may vary by region and may need to be adjusted to the medical concepts described herein. , negative; +, good; GnRH, a hormone releasing gonadotropin; HR, hormone receptor; p, diseases; PR, progesterone receptor; N, node status; T, plant distance; T-DM1, ado-trastuzumab emtansine. One study showed benefit over 15 years of adjuvant endocrine therapy (Goss et al., 2016; Nadia et al., 2016).

The status of metastases of multiple organs in the chest is rare, accounting for only 0.5% to 0.6% (Shah et al., 2000). Breast metastases from the gallbladder are rare and only a few cases have been reported (Kallianpur et al., 2012; Beaver et al., 1986). The increase in the incidence of cancer in recent years and its impact on various physiological, psychological and,social structures in human health has made it one of the major problems of the century (Poorkiani et al., 2010). Outbreaks appear to be exacerbated in the developing world from 1 to 2%, with an annual increase of about 5% in developed countries (Aghabarari et al., 2005). It is estimated that more than 7 million people worldwide die from cancer. The number of new cancer cases is expected to increase from 10 million to 15 million by 2020 (Dehkordi et al., 2006; Saki et al., 2011). At present, breast cancer is the most common type of disease in women (Safaee et al., 2008) with more than a million new cases a year (McPherson et al., 2000). In Iran, breast cancer represents the most common type of cancer in women with 21.4 cases (Harirchi et al., 2004) or 32% (Hosseini et al., 2004). Breast cancer is the most common type of cancer in women in the United States with an incidence rate of 12.5%. The risk of dying from breast cancer is 1 in 35 (Lynch et al., 1990). Currently, the chance of surviving breast cancer is 12% (1 in 8) in the United States (Shishegar, 2011).

Table 1: Chances of a Woman Developing Breast Cancer by Age (Rodney et al., 2003)

By Age	Normal Risk	Genetic Risk*
45	1 in 93 (1%)	42%
55	1 in 33 (3%)	72%
65	1 in 17 (6%)	80%
75	1 in 11 (9%)	84%

Note: * Breast-related cancer antigen 1 and 2 (BRCA-1, BRCA-2). Data from American Cancer Society, Cancer Facts and Figures 2000.

Cancer affects patients' quality of life to varying degrees:

Major problems affecting the quality of life of patients are the psychological and emotional implications of the disease diagnostic and therapeutic approaches, depression, pain, depression and

the effects of the disease on family, marriage and social relationships, and the economic burden problems caused by, healthy eating. and treatment problems (Shakeri et al., 2009; Safaee et al., 2008). Determining the quality of life of cancer patients can provide medical professionals with a new solution to help them become more self-reliant in managing health problems in critical and non-critical situations (Zillich et al., 2002). Improving the quality of life of cancer patients is a major goal of medical care and treatment. Enhancing the skills and improving the working conditions and quality of patient health are important activities of the health care team (Mardani et al., 2009).

Table 2: Various case reports of breast metastasis

Cases	Recurrence	Age (in yrs)	Survival post breast metastasis	Treatment offered	Duration- from primary diagnosis to metastasis	References
Solitary breast metastasis	Yes	35	Not reported	Wide local excision and exploratory laparotomy	24 months	Khangembam et al., 2013
Metastasis to skin, breast, lung	Yes	74	6–7 months	Surgery of the metastasis site and SBRT of lung nodules with 5FU and gemcitabine chemotherapy	6 months	Jeyaraj et al. 2013
Port site and breast metastasis	Yes	35	Alive and disease free at 3 months of follow up	Wide excision of breast followed by local RT and 5FU based chemotherapy	46 months	Kallianpur et al., 2012
Skin and B/L breast metastasis	No	42	3 weeks	Nil	3 weeks	Garg et al., 2013
Port site and breast metastasis	Yes	35	Not reported	Wide local excision of scar and breast lump	12 months	Shukla et al., 2014
Local recurrence with breast metastasis	Yes	50	5 months	Chemotherapy-gemcitabine and carboplatin	27 months	Malik et al., 2015
Breast with ovarian metastasis	Yes	45	Not reported [Alive on follow up]	Mastectomy with oopherectomy followed by Gemcitabine	5 months	Singh et al., 2010

GALL BLADDER CANCER (GBC):

The gallbladder may be a pear-shaped organ under the liver. It stores gall bladder, a fluid produced by the liver to digest fats. The gallbladder releases bile through a tube called the bile common bile duct during the digestion of food in stomach and intestine. The trench connects the gallbladder and liver to the tiny intestine. Symptoms include jaundice (yellowing of the skin and white of the eyes), abdominal pain, fever, nausea, vomiting, constipation and stomach cramps (Carriaga et al., 1995). The gallbladder may be a pear-shaped organ located below the liver within the upper abdomen. The gallbladder stores gallbladder, a fluid produced by the liver to digest fat. When food is digested in the stomach and intestines, the gallbladder is removed from the gut by a tube called bile bile duct, which connects the gallbladder to the liver and therefore the first a part of the tiny intestine. There are three main layers of

tissues are present in the wall of gall bladder like mucous layer (deep inside), muscle layer (middle, muscle) and serous layer (outer). Between these layers are the supporting supporting tissue. The primary cancer of the gallbladder begins in the inner layer and spreads to the outer layers as it grows. The negative prediction associated with GBC is believed to be related to an advanced diagnostic phase, due to both the location of gallbladder formation and the ambiguity and ambiguity of symptoms (Hamrick et al., 1982).

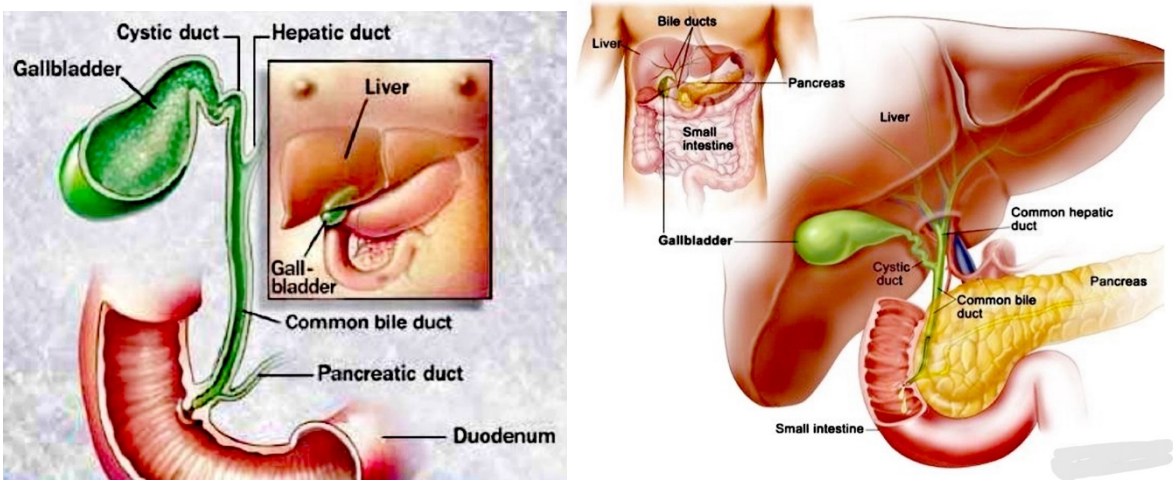

Figure 5: Association of Liver with Other organs

Epidemiology:

Gallbladder cancer is one of the most common cancers in India with a high incidence in northern and central India (Misra et al., 20003). Gallbladder carcinoma is considered to be the fifth most common tissue in the gastrointestinal tract and is one of the most aggressive (Siegel et al., 2015; Lazcano-Ponce et al., 2001). Most GBCs are epithelial adenocarcinomas. GBC has been reported to be three to five times more common in women than men. The pathogenesis of GBC is defined by two hypotheses, gallstone cholecystitis (related risk of 4.9) and abnormal bile ducts (Randi et al., 2006).

Worldwide; there are several local variations in the occurrence of GBC associated with an increase in cholelithiasis. A high level of GBC is observed in South American countries, particularly Chile, Bolivia and Ecuador, as well as in other parts of India, Pakistan, Japan and Korea (Hamrick et al., 1982). In Chile, GBC mortality rates are the very best within the world. All of these individuals share a high prevalence of gallbladder infections and / or salmonella infection, both of which are known risk factors for GBC (Yamaguchi et al., 1996).

Both the genetic and social and economic factors that delay or prevent the cholecystectomy of gallstones are thought to contribute (Strom et al., 1995). North America is considered a low-risk area. In the United States, GBC is the most common cancer in the biliary tract [5]. Estimates from the Surveillance, Epidemiology and End Results database reflect 1 to 2 cases per 100,000 people in the United State (Strom et al., 1995). Unlike most people, GBC is a very painful disease for both Southwest Native Americans and Mexican Americans (Lazcano-Ponce et al., 2004).

Gallbladder disease rates are high among people living near the Ganges and its tributaries, according to the largest study conducted by locals for six years in the region. Recent research shows a high level of bile in Bihar, near the Gandak River. An estimated 20,000 to 30,000 people suffer from gallbladder disease each year due to natural conditions in Uttar Pradesh and Bihar. In addition to geographical location, there are also age, race, and gender-related differences in GBC events. The women are more affected two to six times more than men as increase in

age (Wistuba et al., 2004), and GBC is more common in Caucasians than blacks (Miquel et al., 1998). At least some of the data suggest that the incidence is increasing in young people (Serra et al., 1996).

Worldwide; GBC is the sixth most common bowel cancer with an annual incidence rate of 2.2 per 100,000. But still; The effect of GBC varies widely across geographies, with more than 10 high mortality rates in Chile, where the disease is the second most common cause of cancer in women compared to the United States. In Bolivia, Peru, northern India, Bangladesh, Nepal, Japan, Korea, Slovakia and Czech Republic; the high risk of adenocarcinoma problems are repoted (Ferlay et al., 2012). The adenocarcinomas are nearly about (65% to 90%) of GBCs are followed by the squamous or adenosquamous cell carcinomas (5% to 10%) and undiagnosed carcinomas (5%).

A recent study analyzing data from the Netherlands Cancer Registry of 3,917 patients reported a 5-year survival rate of 12%, indicating the severity of the disease characterized by extensive local and lymph node attacks and long morning spreads. Patients who underwent surgery as part of their treatment had a 5-year survival rate of 19% to 26%, with a tendency to improve quality over the past two decades (Witjes et al., 1989). The most important predictive factors are the depth of the gall bladder attack and the presence of metastases in the lymph nodes or distant organs: a reviewed tumor, lymph node system and metastasis staging system have proven to be useful in assessing prognosis. diagnosis. In the treatment setting, R0 renewal is the most important predictor factor (Bettina et al., 2014). In one autopsy, about 92% of gallbladder cancers cause distant mastastase, the most common areas of the liver, lungs and brain (Sons et al., 1985). The most common site of metastasis is the liver and lymph nodes. Gallbladder cancer with breast metastases is less common (Kallianpur et al., 2012).

Risk factors for the development of gallbladder cancer are given listed as follows;

Demographic factors:

- Advanced age.
- Female gender.
- Obesity.
- Geography: South American, Indian, Pakistani, Japanese, and Korean,
- Ethnicity: Caucasians, Southwestern Native American, Mexican, and American.
- Genetic predisposition.

Gallbladder pathologies/abnormalities:

- Cholelithiasis.
- Porcelain gallbladder.
- Gall bladder polyps.
- Congenital biliary cysts.
- Pancreaticobiliary maljunction anomalies.

Exposures:

- Heavy metals.
- Medications: methyldopa, OCP, isoniazid and estrogen.
- Smoking.

Infections:

- Salmonella.
- Helicobacter (Kanthan et al., 2014).

Stages of gall bladder cancer: The following stages are used for gallbladder cancer;

- **Stage 0 (in Situ condition):** during this Stage, the abnormal cells are found in inner (mucous) a neighborhood of the gall bladder and it becomes somatic cell which spreads to nearby normal tissues.
- **Stage I:** During this stage, mucosal layer also affected by spreading cancer in the body.
- **Stage II:** During this stage, the lymph nodes also affected by cancer.
- **Stage IIIA:** During this stage, the cancer are getting to be spreading everywhere the tissues that covers the gall bladder or nearby organs.
- **Stage IIIB:** During this stage, the lymphatic system also affected by the cancer which spreads within the inner layer of gall bladder to a layer of tissue through the blood vessels or muscle layer; or beyond the lowest of the muscle to the muscles connected round the muscle; or by using thin layers of tissue covering the gallbladder and / or liver and / or nearby organ (such because the abdomen,

intestine , colon, pancreas, or bile ducts without the liver).

- **Stage IVA:** Within the IVA stage, the cancer has spread to an outsized vessel within the liver or 2 or more organs or nearby areas without the liver.
- **Stage IVB:** Lymph nodes along the foremost abdominal arteries and / or near the lower an area of the spine or organs or areas faraway from the gallbladder (Kiran et al., 2007).

Gallbladder cancer is one of the family bile duct cancers, including intrahepatic, extrahepatic and hilar cholangiocarcinomas. It is a rare and aggressive cancer with a survival rate of 5% of 5% (Gourgiotis et al., 2008). Although surgical resuscitation is the only treatment, the number of patients who can undergo surgery for treatment is small and relapse is common (Bridgewater et al., 2016). The goal of GBCA re-surgery depends on the depth of the tumor attack (phase T of the eighth AJCC program). Simple cholecystectomy is sufficient for T1a tissue trapped in the lamina propria, as the chances of finding remaining infections in these tissues are almost negligible (Fuksjean et al., 2011; Lee et al., 2014). In T1b or T2 tissues, cholecystectomy with bloc resection of the parenchyma adjacent to hepatoduodenal lymphadenectomy is highly recommended. However, the precise surgical strategy of T1b cancer that attacks the muscle layer is still being debated and the role of strong regeneration of such tissue remains in doubt (Lee et al., 2014; Abramson et al., 2009; Kim et al., 2018). Although there is still debate about T2a stage cancer treatment, the current standard is to perform major resection with limited hepatectomy or, in some advanced cases, extended hepatectomy and GBCA regional lymphadenectomy across T2 that attacks the connective tissue (Lee et al. Al., 2014; Kim et al., 2013).

Adjuvant therapy in gall bladder: Adjuvant therapy plays an important role in improving survival. The major role of adjuvant therapy is to reduce the rate of relapse by eliminating micrometastatic disease that is not found in the image. The toxicity profil should agree to allow for effective management (Shroff et al., 2019). Simple cholecystectomy can be used to treat gallbladder cancer and it survives for a long time if the tumor is found inside lamina propria (Hueman et al., 2009; North et al., 1998). However, in the first stage with tumors invading the mucosal, the five-year survival rate dropped rapidly to 62.5% (Lee et al., 2018). Therefore; Adjuvant treatment is recommended for each stage of cancer according to the guidelines of the National Network of Cancer Centers (NCCN Clinical Guidelines in Oncology).

Table 3: Major genes implicated in gall bladder carcinogenesis as available in the published literature (2000–present).

Gene		Expression in GBC	Tissues of comparison	Additional information	Reference(s)
Oncogene	KRAS	Higher (10–67%)	Adenoma (0%)	Marker of GBC in PBM.No correlation with stage, histology, and survival.	Maurya et al., 2012; Goldin et al., 2009; Kuroki et al., 2005
	EGFR	Higher (63.4%)	Dysplasia (71.4%) Hyperplasia (15.4%) Normal (0%)	Nil	Maurya et al., 2012
	HER-2/neu (ERBB2	Higher (16–64%)	Carcinoma in situ (0%) Gallstones (0%)	Marker of metastatic disease (70%)Marker of poor prognosis (10x mortality).	Maurya et al., 2012; Li et al., 2014; Kumari et al., 2012
	TP53	Higher (58.3–100%)	Adenoma (10–20%)	Unknown relation to	Maurya et al., 2012; Wang et

Tumor suppressor			Normal (0%)	prognosis More prominent with poor differentiation	al., 2006
	P16	Lower (48.8%)	Adenoma (100%) Chronic cholecystitis (100%)	Related to poorer prognosis Negative correlation with cyclin D1.	Ma et al., 2005
	Fragile histidine triad (FHIT)	Lower	Normal	Early change in carcinogenesis	Goldin et al., 2009
	Retinoblastoma	Lower (58.5%)	Adenoma (100%) Cholecystitis (100%)	Causes cell proliferation, apoptosis, and developmental defects	Ma et al., 2005
	VHL	Lower (48.1%)	Peritumoral tissue (80.4%)Polyps (80%) Chronic cholecystitis (88.6%)	Marker progression, biological behavior, and prognosis	Yang et al., 2014
Adhesion molecules and mucins	Cadherins	Higher (N-cadherin 55%; P-cadherin 53%)	None	Associated with large tumor size, invasion, and node metastases	Yi et al., 2014
	MUC1	Higher (78%)	Normal tissue (absent)	Higher expression in more advanced tumours; poor survival	Ghosh et al., 2005
	Erythrocyte complement receptor 1 (CR1)	Lower	Chronic cholecystitis Cholelithiasis Normal	Role under investigation	Maurya et al., 2012
Angiogenesis	Thrombospondin-1	Higher (74.5%)	Normal (0%) T1 cancer (0%)	Associated with venous involvement.Predictor of vascular involvement and nodal metastases	Maurya et al., 2012
	Cyclooxygenase-2	Higher (59.2–71.9%)	Normal (0–25%) Dysplasia (70.3%)	Associated with poor prognosis, mean survival, and tumor progression	Maurya et al., 2012; Goldin et al., 2009
	VEGF-A	Higher (81%)	Chronic cholecystitis (5.1%)	Expression related to histologic grade, TNM stage, and prognosis	Letelier et al., 2014
Cell cycle regulators	Cyclin E	Higher (33%)	Adenoma (12.5%)	Marker of lymphatic/venous involvement and lymph node metastases	Maurya et al., 2012
	Cyclin D1	Higher (41–68.3%)	Adenoma (57.1–67%) Chronic cholecystitis (7.1%) Normal (0%)		Maurya et al., 2012; Yang et al., 2014

	P27Kip1	Lower (43–65%)	None		Maurya et al., 2012
Apoptosis	Caspases	Higher (95%; caspase 3; 77%; caspases 6 and 8)	None	Higher extent apoptosis in grade II/III GBC compared with grade I/dysplasia	Maurya et al., 2012
	Bcl-2	Higher (34.7%)	None		Maurya et al., 2012

CAPECITABINE

Capecitabine (5-deoxy-5-fluoro-N [(pentyloxy) carbonyl] citidine) (XELODA) is an orally administered prodrug of systemic 5-FU absorbed as a stable molecule of the intestinal tract (Ishikawa et al., 1998; Schuller et al. , 2000; Miwa et al., 1998; Saeki et al., 1999). It is combined with carboxylesterase and cytidine deaminase in 5-deoxy-5-fluorocytidine which is converted to 5-FU by the angiogenic factor thymidine phosphorylase (dThdPase) (Miwa et al., 1998). Since dThdPase is more concentrated in tumor cells than surrounding tissues, treatment with capecitabine resulted in a 5-FU concentration in tumor samples that had reached 127 times rather than a corresponding concentration in plasma model samples (Endo et al., 1999) and 5-FU in the human colorectal colorectal body samples was 20 times more likely than the corresponding concentration in plasma samples (Schuller et al., 2002).

Capecitabine in Breast Carcinoma:

Capecitabine (XELODA) has been tested in breast cancer testing in combination with docetaxel and monotherapy. Table 4 summarizes the data from one of the most important combination studies as well as important monotherapy.

Capecitabine in Combination with Docetaxel: The dose of XELODA used in combination with docetaxel in a phase III clinical study was based on the results of the phase I am studying, where a dose of docetaxel was given in combination every three weeks. XELODA version has been tested. The combined dosage of choice was selected according to the tolerance profile of 75 mg / m2 every three weeks of docetaxel in combination with 1250 mg / m2 twice daily for 14 days XELODA performed daily every three weeks. The recommended dose of docetaxel 100 mg / m2 given every 3 weeks was in the control group in a phase III study.

As shown in Table 4, XELODA in combination with docetaxel led to improved statistical timing for disease progression, overall survival and the rate of intentional response compared to docetaxel monotherapy. Health-related quality of life (HRQoL) was assessed using the EORTC QLQ-C30 (version 2) and the EORTC breast cancer module (BR23). HRQL was similar to the two treatment groups. Approximately 11% of patients in the combined group and 10% in the monotherapy group did not complete the quality of life questionnaires at least once at the beginning or during the treatment.

Table 4: Clinical Studies in Breast Carcinoma (Capecitabine Monograph, 2021)

Design and Diagnosis	Drug/Dosage	No. Women Enrolled	Results
PIVOTAL STUD44Q- MONOTHERAPY			
Open label□Females with advanced or metastatic breast cancer refractory to previous paclitaxel therapy: (77% resistant, 23% failed paclitaxel; 41% resistant, 26% failed anthracycline therapy; 82% prior 5-FU exposure).	Capecitabine 2510 mg/m2/day for 2 weeks with a 1 week rest period (given as 3 week cycles)	162 (135 measurable disease)	Overall response rate (ORR) intentto-treat (n=135): 20% (95% CI:13.6-27.8); 3 complete responses - ORR (standard population, n=117): 23% (min. 6 weeks therapy) - Median duration of response: 241 days - Median time to progression: 93 days - Median survival: 384 days - Clinical benefit response: positive 29 pts.

			(20%); stable 45 pts. (31%). In 51 pts. with baseline pain ≥20 mm (visual analogue scale), 24 pts. (47%) positive response in pain intensity (≥50% decrease)
SUPPORTIVE STUDIES - MONOTHERAPY			
Open label, randomized, Parallel group Females ≥55 with advanced or metastatic breast cancer without previous chemotherapy (other than adjuvant treatment)	Capecitabine 2510 mg/m2/day for 2 weeks with a 1 week rest period (given as 3 week cycles) Cytoxan, methotrexate, 5FU (CMF) 600/40/600 mg/m2 iv q3 weeks.	95	- Capecitabine response rate: 25% (95%CI: 14%-37%) - CMF response rate: 16% (95% CI: 5%-33%) - Median time to disease progression: capecitabine-132 days; CMF-94 days
Open-label, randomized parallel group Females with disease progression within 12 months of previous anthracycline treatmen	Capecitabine 1331 mg/m2/day (continuous) for 6 weeks Capecitabine 2510 mg/m2/day for 2 weeks with a 1 week rest period (given as 3 week cycles) (intermittent) Paclitaxel 175 mg/m2/q 3weeks	44	- Capecitabine response rate (intermittent arm): 36% (95%CI: 17-59%); 3 complete responses - Paclitaxel response rate: 21% (95% CI: 6-46%). - Median time to disease progression: capecitabine 92 days; paclitaxel 95 days.
PIVOTAL STUDY – COMBINATION THERAPY			
Open label, randomized, parallel group Females with advanced and/or metastatic breast cancer resistant to or recurring during or after anthracycline-containing therapy or relapsing during or recurring within 2 years of completing anthracycline containing adjuvant therapy	Capecitabine 2500 mg/m2/day for 2weeks with a 1 week rest period in combination with docetaxel 75 mg/m2 every 3 weeks Docetaxel 100 mg/m2every 3 weeks	255 256	- Response Rate Combination therapy: 41.6% Docetaxel monotherapy: 29.7% (p=0.0058) - Time to Disease Progression Combination therapy: 186 days Docetaxel monotherapy: 128 days (p=0.0001) Hazard Ratio: 0.643 - Overall Survival Combination therapy: 442 days Docetaxel monotherapy: 352 days (p= 0.0126) Hazard Ratio: 0.775

Capecitabine along with Oxaliplatin in Gall Bladder Cancer:

Capecitabine is an oral fluoropyrimidine prodrug with a selective 5-FU modification of body tissues over normal by exploiting the internal expression of thymidine phosphorylase (Schuller et al., 2000) and is now widely used in the treatment of colon cancer. (Cassidy et al., 2008; Cassidy et al., 1998; Comella et al., 2005; Diaz-Rubio et al., 2002; Ducreux et al., 2010; Haller et al., 2011; Mackean et al., 1998), breast cancer (Blum et al., 2001 Oshaughnessy et al., 2001) and stomach cancer (Okines et al., 2009). Oxaliplatin is a third-generation analogue of cisplatin, with different activity and toxicity profiles than other platinum derivatives, including carboplatin and cisplatin (Mathe et al., 1989) and by clinical practice, alone or in combination with 5-FU , in the development of colorectal cancer (Cassidy et al., 2008; Comella et al., 2005; Diaz-Rubio et al., 2002; Ducreux et al., 2010; Haller et al., 2011; Diaz-Rubio et al. , 2007).

When the combination of capecitabine and oxaliplatin was tested in the phase I was

studying, a patient with gallbladder cancer who had developed treatment with a combination of 5-FU and leucovorin had an incomplete response when treated with XELOX. This, combined with the activity of 5-FU as a single agent and 5-FU in combination with cisplatin in bile duct cancer, led us to explore the combination function of capecitabine and oxaliplatin as a first-line treatment. Phase II study on gallbladder tissue tissue (Diaz-Rubio et al., 2002).

Treatment Administration:

Capecitabine was given periodically (14-day treatment; 7-day rest period) at a dose of 1000 mg / m2 twice daily orally over a 21-day treatment cycle. Two daily doses of capecitabine were given 12 ± 2 hours outside, within 30 minutes after a meal with approximately 200 ml of water. The daily dose was "collected at the top" and given in equal doses divided twice a day. Patients received a learning diary card to record drug administration.

Oxaliplatin was administered on day 1 at a dose of 130 mg / m2 as a 2-hour infusion, following a morning dose of capecitabine, in a 21-day treatment regimen. When patients develop laryngopharyngeal dysesthesia, subsequent doses of oxaliplatin are administered as a 6-hour infusion.

Treatment was repeated every 21 days for six cycles, but was stopped early if there was evidence of an increase in disease, intolerable toxicity despite dose adjustment, patient refusal, or investigator's decision to stop. treatment. Patients received antihmetic antihmetic drugs before injecting oxaliplatin with intravenous dexamethasone and granisetron followed by oral dexamethasone and domperidone for 3 and 5 days respectively (Graham et al., 2016).

Capecitabine along with Gemcitabine in Gall Bladder Cancer:

A study of gemcitabine with capecitabine shows similar levels of response (RR) to gemcitabine with cisplatin (Sandanti et al., 2012; Cho et al., 2005; Knox et al., 2005; Reichemann et al., 2007). Eg; In a combination of phase II, the gemcitabine and high-dose capecitabine Study provided a 33% PR (8/24) PR, 75% DCR (18/24), median TTP at 6 (95% CI%, 3.8- 8.1) and a 16-month intermediate OS (95% CI, 13.8-18.3) (Cho et al., 2005). In Riechelmann's phase II study of gemcitabine and capecitabine in patients with undiagnosed gallbladder cancer, 1/227 patients had complete responses (4%), 9/27 with PR (33%), DCR was 64% (15/27), median PFS and median OS were 4.4 months (95% CI, 0.1-9.4 months) and 7.7 months (95% CI, 4.6 months, unattended) (Reichemann et al. , 2007).

Table 5: Gallbladder cancer: prior therapy, concurrent chemotherapy, and treatment duration (Javle et al.m 2015)

Sites of disease	Prior therapy	HER2/neu test	HER2/neu therapy	Concurrent therapy	Duration of the therapy (weeks)	Overall survival (weeks)	Best response
Liver	Gemcitabine + cisplatin, capecitabine, FOLFOX	ERBB2 NGS amplification	Trastuzumab	Gemcitabine + irinotecan	40	62	PR
Sternum, pleura, lung	Gemcitabine, capecitabine	AMPLIFIED (FISH)	Trastuzumab	Nil	168	178	PR
Retroperitoneal LN, supraclavicular LN	Gemcitabine + capecitabine, gemcitabine + cisplatin, pazopanib, dovitinib	ERBB2 NGS amplification	Trastuzumab + pertuzumab	Nil	8+	8+	SD
Liver, LN	Gemcitabine + cisplatin	ERBB2 NGS amplification	Trastuzumab	FOLFOX capecitabine	92	92	PR

Note: HER2-positive tumors IHC 3+, FISH HER2/centromere 17 ratio ≥2.0 or both SD - stable disease, MR - mixed response, PR - partial response, LN - Lymph node

CONCLUSION

Breast cancer and gallbladder cancer are only treated if they are diagnosed before they spread, when they can be surgically removed. Once cancer has spread, diminished treatment can improve a patient's quality of life by controlling the symptoms and severity of the disease. The disease affects several physiological, psychological and social aspects of a woman's health. Second; factors such as social and family support during illness can reduce its negative effects. Today; the various clinical strategies are being developed and the development of targeted drugs is growing rapidly, making it even more difficult to provide more agents to identify these markers in vivo animal diversity research and clinical trials. Increased knowledge about the pathophysiological processes of breast cancer has led to a dramatic increase in the number of biomolecular markers. Various approaches are involved which including the effective management of breast and gallon cancer. With the development and implementation of surgical techniques; the future studies are needed to focus on specific secondary sites of biliary tract. As agents and new chemotherapy techniques, including targeted therapies and immunotherapy, they have shown promising effectiveness. What else; the development of capecitabine has been found to be safe in patients with breast cancer and gall bladder cancer.

FUTURE PERSPECTIVES: Further research in this area should be directed to finding the best cytotoxic agent to include capecitabine or to modify the dose or course of treatment for gallbladder cancer and advanced breast cancer. Future research is needed to incorporate these new therapies into the ongoing treatment of bile cancer viruses.

REFERENCES

Analysis of Tree Models.Ofogh-e-Danesh. Journal of Gonabad University of Medical Sciences. 2011; 17(2):60-9.

Aghabarari M, Ahamadi F, Mohammadi E, Hajizadeh E, Farahania V. Physical, emotional and social dimension of quality of life among breast cancer women under chemotherapy. Iranian Journal of Nursing Research. 2005; 3:55-65.

Abramson, M.A.; Pandharipande, P.; Ruan, D.; Gold, J.S.; Whang, E.E. Radical resection for T1b gallbladder cancer: A decision analysis. HPB 2009, 11, 656–663.

Anderson B, Yip C, Smith R, Shyyan R, Sener S, Eniu A, et al. Guideline implementation for breast healthcare in low-income and middleincome countries: overview of the breast health global initiative global summit 2007. Cancer. 2008;113:2221–43.

Abdull R, Noor N. Cruciferous vegetables: dietary phytochemicals for cancer prevention. Asian Pac J Cancer Prev. 2013;14:1565–70.

Agnieszka M, Magdalena K, Grazyna J, Iwanowicz P. Assessment of midwifery student preparation for erforming the role of breast cancer educator. Asian Pac J Cancer Prev. 2014;15:5633–8.

Aronson K, Miller A, Woolcott C, Sterns E, McCready D, Lickley L, et al. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Prev Biomarkers. 2000;9:55–63.

Bhurgri Y. Karachi cancer registry data implications for the national cancer control program of Pakistan. Asian Pac J Cancer Prev. 2004;5:77–82.

Badar F, Faruqui Z, Uddin N. Management of breast lesions by breast physicians in a heavily populated south Asian developing country. Asian Pac J Cancer Prev. 2011;12:827–32.

Blum JL, et al. Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients. Cancer. 2001;92(7):1759–68.

Brayboy L, Oulhen N, Long S, Voigt N, Raker C, Wessel G. Multidrug resistance transporter-1 and breast cancer resistance protein protect against ovarian toxicity, and are essential in ovarian physiology. Rep Toxicol. 2017;69:121–31.

Cassidy J, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol. 2008;26(12):2006–12.

Cassidy J, et al. A Phase I study of capecitabine in combination with oral leucovorin in patients with intractable solid tumors. Clin Cancer Res. 1998;4(11):2755–61.

Comella P, et al. Capecitabine plus oxaliplatin for the first-line treatment of elderly patients with metastatic colorectal carcinoma: final results of the Southern Italy Cooperative Oncology Group Trial 0108. Cancer. 2005;104(2):282–9.

Diaz-Rubio E, et al. Capecitabine (Xeloda) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. Ann Oncol. 2002;13(4):558–65.

Ducreux M, et al. Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first-line treatment for metastatic colorectal cancer. Int J Cancer. 2010;128(3):682–90.

Haller DG, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011;29(11):1465–71.

Mackean M, et al. Phase I and pharmacologic study of intermittent twicedaily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol. 1998;16(9):2977–85.

Oshaughnessy JA, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol. 2001;12(9):1247–54.

Okines AF, et al. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol. 2009;20(9):1529–34.

Mathe G, et al. Oxalato-platinum or 1-OHP, a third-generation platinum complex: an experimental and clinical appraisal and preliminary com-parison with cis-platinum and carboplatinum. Biomed Pharmacother.1989;43(4):237–50.

Diaz-Rubio E, et al. Phase III study of capecitabine plus oxaliplatin compared with continuous-infusion fluorouracil plus oxaliplatin as first-line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the Treatment of Digestive Tumors Trial. J Clin Oncol. 2007;25(27):4224–30.

Shah RJ, Koehler A, Long JD. Bile peritonitis secondary to breast cancer metastatic to the gallbladder. Am J Gastroenterol 2000;95:1379–81.

Beaver BL, Denning DA, Minton JP. Metastatic breast carcinoma of the gallbladder. J Surg Oncol 1986;31:240–2.

Goodman K, Wagman R, Ho AY. Cancer of the Liver, Bile Duct, and Gall Bladder. In: Hoppe RT, Phillips TL, Roach M, editors. Leibel and Phillips Textbook of Radiation Oncology. Philadelphia: Elsevier Saunders; 2010. p. 820–41.

Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. Lancet Oncol 2003;4:167–76.

Sons HU, Borchard F, Joel BS. Carcinoma of the gallbladder: autopsy findings in 287 cases and review of the literature. J Surg Oncol 1985;28:199–206.

Kallianpur AA, Shukla NK, Deo SV, Singh M, Subi TS, Kapali A. A rare case of gallbladder carcinoma metastases to the breast treated with curative intent. Trop Gastroenterol 2012;33:155–8.

Schuller J, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol. 2000;45(4):291–7.

Singh S, Gupta P, Khanna R, Khanna AK. Simultaneous breast and ovarian metastasis from gallbladder carcinoma. Hepatob Pancreat Dis Int 2010;9:553–4.

Khangembam BC, Sharma P, Naswa N, Sahoo MK, Kumar R. Solitary breast metastasis from recurrent gallbladder carcinoma simulating a second primary on 18F-FDG PET/CT. Clin Nucl Med 2013;38:e433–4.

Jeyaraj P, Sio TT, Iott MJ. An unusual case of isolated, serial metastases of gallbladder carcinoma involving the chest wall, axilla, breast and lung parenchyma. Rare Tumors 2013;11:e7.

Garg PK, Khurana N, Hadke NS. Subcutaneous and breast metastasis from asymptomatic gallbladder carcinoma. Hepatob Pancreat Dis Int 2009;8:209–11.

Shukla P, Roy S, Tiwari V, Mohanti BK. Unusual presentation of metastatic gall bladder cancer. J Cancer Res Ther 2014;10:397–8.

Malik AA, Wani ML, Wani SN, Malik RA, Malik TR. Breast metastasis from carcinoma of gall bladder. Int J Health Allied Sci 2013;2:35–6.

M. Siraj Anwar, Shveta Uppal, Arun Chitkara, Bibash Kumar Das, Shashi Chadha, Mukesh Gaur. BIOLOGY TEXTBOOK FOR CLASS XII. National Council of Educational Research and Training (NCERT). First Edition December 2006. Reprinted August 2019. Page no. 156-159.

Siegel RL, Miller KD, Jamal A. Cancer statistics 2015. CA Cancer J Clin 2015;65:5–29.

Lazcano-Ponce EC, Miquel JF, Mun˜oz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51:349–64.

Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006;118:1591–602.

J. S. Graham1, K. Boyd1*, F. Y. Coxon2, L. R. Wall3, M. M. Eatock4, T. S. Maughan5, M. Highley6, E. Soulis1, S. Harden1, P. Bützberger-Zimmerli1 and T. R. J. Evans1,7. RESEARCH ARTICLE - A phase II study of capecitabine and oxaliplatin combination chemotherapy in patients with inoperable adenocarcinoma of the gall bladder or biliary tract. BMC Res Notes (2016) 9:161. DOI 10.1186/s13104-015-1778-4.

World Cancer Report 2014, www.iarc.fr.

Wagstaff AJ, Ibbotson T, Goa KL: Capecitabine: a review of its pharmacology and therapeutic efficacy in the management of advanced breast cancer. Drugs 2003;63:217–236.

Si W, Zhu YY, Li Y, Gao P, Han C, You JH, Linghu RX, Jiao SC, Yang JL: Capecitabine maintenance therapy in patients with recurrent or metastatic breast cancer. Braz J Med Biol Res 2013;25:1074–1081.

Blum JL, Jones SE, Budzar AU, LoRusso PM, Kuter I, Vogel C, Osterwalder B, Burger HU, Brown CS, Griffin T: Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 1999;17:485–493.

Fumoleau P, Largillier R, Clippe C, Dièras V, Orfeuvre H, Lesimple T, Culine S, Audhuy B, Serin D, Curé H, Vuillemin E, Morère JF, Montestruc F, Mouri Z, Namer M: Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 2004;40:536–542.

Stockler M, Sourjina T, Grimison P, Gebski V, Byrne M, Harvey V, Francis P, Nowak AK, Van Hazel G, Forbes J: A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). J Clin Oncol 2007;25(suppl 18S):1031.

O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G, Fumoleau P, Jones S, Lui WY, Mauriac L,

Twelves C, Van Hazel G, Verma S, Leonard R: Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial, results. J Clin Oncol 2002; 20:2812–2823.

Rani Kanthan,1 Jenna-Lynn Senger,2 Shahid Ahmed,3 and Selliah Chandra Kanthan4. Review Article Gallbladder Cancer in the 21st Century. Journal of Oncology. Hindawi Publishing Corporation. Volume 2015, Article ID 967472, 26 pages.

S. K. Maurya, M. Tewari, R. R. Mishra, and H. S. Shukla, "Genetic aberrations in gallbladder cancer," Surgical Oncology, vol. 21, no. 1, pp. 37–43, 2012.

R. D. Goldin and J. C. Roa, "Gallbladder cancer: a morphological and molecular update," Histopathology, vol. 55, no. 2, pp.218–229, 2009.

T. Kuroki, Y. Tajima, K. Matsuo, and T. Kanematsu, "Genetic alterations in gallbladder carcinoma," Surgery Today, vol. 35, no.2, pp. 101–105, 2005.

M. Li, Z. Zhang, X. Li et al., "Whole-exome and targeted gene sequencing of gallbladder carcinoma identifies recurrent mutations in the ErbB pathway," Nature Genetics, vol. 46, no. 8, pp. 872–876, 2014.

N. Kumari, V. K. Kapoor, N. Krishnani, K. Kumar, and D.K. Baitha, "Role of c-erbB2 expression in gallbladder cancer, "Indian Journal of Pathology and Microbiology, vol. 55, no. 1, pp. 75–79, 2012.

S.-N. Wang, S.-C. Chung, K.-B. Tsai et al., "Aberrant p53 expression and the development of gallbladder carcinoma and adenoma," Kaohsiung Journal of Medical Sciences, vol. 22, no. 2, pp. 53–59, 2006.

H.-B. Ma, H.-T. Hu, Z.-L. Di et al., "Association of cyclin D1, p16 and retinoblastoma protein expressions with prognosis and metastasis of gallbladder carcinoma," World Journal of Gastroenterology, vol. 11, no. 5, pp. 744–747, 2005.

Z. Yang, Z. Yang, L. Xiong et al., "Expression of VHL and HIF-1α and their clinicopathologic significance in benign and malignant lesions of the gallbladder," Applied Immunohistochemistry and Molecular Morphology, vol. 19, no. 6, pp. 534–539, 2011.

S. Yi, Z.-L. Yang, X. Miao et al., "N-cadherin and P-cadherin are biomarkers for invasion, metastasis, and poor prognosis of gallbladder carcinomas," Pathology Research and Practice, vol. 210, no. 6, pp. 363–368, 2014.

M. Ghosh, H. Kamma, T. Kawamoto et al., "MUC1 core protein as a marker of gallbladder malignancy," European Journal of Surgical Oncology, vol. 31, no. 8, pp. 891–896, 2005.

P. Letelier, P. Garcia, P. Leal et al., "Immunohistochemical expression of vascular endothelial growth factor a in advanced gallbladder carcinoma," Applied Immunohistochemistry and Molecular Morphology, vol. 22, no. 7, pp. 530–536, 2014.

Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11. Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr. Accessed on December 29, 2013.

Bettina G. Mu¨ller, MD, Xabier De Aretxabala, MD, FACS, and Manuel Gonza´lez Domingo, MD. A Review of Recent Data in the Treatment of Gallbladder Cancer: What We Know, What We Do, and What Should Be Done. MANAGEMENT OF GALLBLADDER CANCER. Article in American Society of Clinical Oncology - Educational Book · May 2014.

Witjes CD, van den Akker SA, Visser O, et al. Gallbladder cancer in the Netherlands: incidence, treatment and survival patterns since 1989. Dig Surg. 2012;29:92-98.

Poorkiani M, Hazrati M, Abbaszadeh A, Jafari P, Sadeghi M, Dejbakhsh T, Mohammadian Panah M. Does arehabilitation program

improve quality of life in breast cancer patients. Payesh. 2010; 9(1):61-8.

Hasanpoor Dehkordi A, Azari S. Quality of life and related factor in cancer patients. Behbood. 2006; 10(2):110-19.

Saki A, Hajizadeh E, Tehranian N. Evaluating the Risk Factors of Breast Cancer Using the Safaee A, Zeighami B, Tabatabaee HR, Moghimi Dehkordi B. Quality of life and Related Factors in Breast Cancer Patients under Chemotherapy. Iranian Journal ofEpidemiology. 2008; 3(4):61-6.

McPherson K, Steel CM, Dixon JM.ABC of breast diseases. Breast cancerepidemiology, risk factors, and genetics. BJM. 2000; 321(7261):624-8.

Harirchi I, Karbakhsh M, Kashefi A, Momtahen A. Breast cancer in Iran: results of a multi-center study. Asian Pacific J Cancer Prev. 2004; 5(1):24-7.

Hosseini M, Hassannejad R, Khademolghorani SH, Tabatabaeian M, Mokarian F. Identification of Patterns of Breast Cancer Metastasis among Women Referred to Isfahan SeyedoshohadaCenter, Iran, between 1999 and 2009 byAssociation Rules and Ordinal LogisticRegression. Scientific Research Journal of Health System Research (HSR). 2012;7(6):746-62.

Lynch HT, Watson P, Conway TA.Clinical/ genetic features in hereditary breast cancer. Breast Cancer Res Treat. 1990; 15:63-71.

Shishegar A. New breast cancer screening. Journal of Army University of Medical Sciences of TheI. R. Iran. 2011; 9(1):58-66.

Tabari F, Zakeri Moghadam M, Bahrani N, Monjamed Z. Evaluation of the Quality of Life in newly Recognized Cancer Patients. HAYAT. 2007; 13(2):5-12.

Shakeri J, Abdoli N, Paianda M, Chareh-Ga G. The frequency distribution of depression among patients with breast cancer in Kermaneshah u.m.s chemotherapy centers in 2007. Journal of Medical Council of Islamic Republic of Iran. 2009; 27(3):324-8.

Safaee A, Moghimi-Dehkordi B, Zeighami B, Tabatabaee HR,Pourhoseingholi MA. Predictors of quality of life in breast cancer patients under chemotherapy. Indian Journal of Cancer. 2008; 45(3):107-11.

Zillich AJ, Blumenschein K, Johannesson M, Freeman P. Assessment of the relationship between measures of disease severity, quality of life, and willingness to pay in asthma. Pharmacoeconomics. 2002; 20(4):257-65.

Mardani Hamule M, Shahraky Vahed A. The Assessment of Relationship between Mental Health and Quality of Life in Cancer Patients. Scientific Journal of Hamadan University of Medical Sciences. 2009; 16(2):33-8.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59:225-49.

Heravi Karimovi M, Pourdehqan M, Jadid Milani M, Foroutan SK, Aieen F. Study of the effects of group counseling on quality of sexual life of patients with breast cancer under chemotherapy at Imam Khomeini Hospital. J Mazandaran Univ Med Sci. 2006, 16(54):43-51.

Sariego J. Breast cancer in the young patient. Am Surg. 2010; 76(12):1397-1400.

Steiner E, Klubert D. Assessing Breast Cancer Risk in Women. Am Fam Physician. 2008; 78(12):1361-1366.

Yager JD, Davidson NE. Estrogencarcinogenesis in breast cancer. N Engl JMed. 2006; 354(3):270-282.

Venturi S. Is there a role for iodine in breastdiseases?. Breast. 2001; 10(5):379-382.

Aceves C, Anguiano B, Delgado G. Is iodinea gatekeeper of the integrity of the mammary gland?. J Mammary Gland Biol Neoplasia. 2005; 10(2):189-196.

Stoddard FR 2nd, Brooks AD, Eskin BA, Johannes GJ. Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. Int J Med Sci. 2008; 5(4):189-196.

Labrecque LG, Barnes DM, Fentiman IS, Griffin BE. Epstein-Barr virus in epithelial

cell tumors: a breast cancer study. Cancer Res. 1995; 55(1):39-45.

Glaser SL, Hsu JL, Gulley ML. EpsteinBarr virus and breast cancer: state of the evidence for viral carcinogenesis. Cancer Epidemiol Biomarkers Prev. 2004; 13(5):688-697.

Gourgiotis S, Kocher HM, Solaini L, et al. Gallbladder cancer. Am J Surg 2008;196:252-64.

Bridgewater JA, Goodman KA, Kalyan A, et al. Biliary Tract Cancer: Epidemiology, Radiotherapy, and Molecular Profiling. Am Soc Clin Oncol Educ Book 2016;35:e194-203.

Shroff RT, Kennedy EB, Bachini M, et al. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. J Clin Oncol 2019;37:1015-27.

Hueman MT, Vollmer CM Jr, Pawlik TM. Evolving treatment strategies for gallbladder cancer. Ann Surg Oncol 2009;16:2101-15.

North JH Jr, Pack MS, Hong C, et al. Prognostic factors for adenocarcinoma of the gallbladder: an analysis of 162 cases. Am Surg 1998;64:437-40.

Lee AJ, Chiang YJ, Lee JE, et al. Validation of American Joint Committee on Cancer eighth staging system for gallbladder cancer and its lymphadenectomy guidelines. J Surg Res 2018;230:148-54.

NCCN Clinical Practice Guidelines in Oncology. Available online: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.

FuksJean, D.; Regimbeau, J.M.; Le Treut, Y.-P.; Bachellier, P.; Raventos, A.; Pruvot, F.-R.; Chiche, L.; Farges, O. Incidental Gallbladder Cancer by the AFC-GBC-2009 Study Group. World J. Surg. 2011, 35, 1887–1897.

Lee, S.E.; Korean Pancreas Surgery Club; Jang, J.-Y.; Kim, S.-W.; Han, H.-S.; Kim, H.-J.; Yun, S.-S.; Cho, B.-H.; Yu, H.C.; Lee, W.J.; et al. Surgical Strategy for T1 Gallbladder Cancer: A Nationwide Multicenter Survey in South Korea. Ann. Surg. Oncol. 2014, 21, 3654–3660.

Lee, H.; Choi, D.W.; Park, J.Y.; Youn, S.; Kwon, W.; Heo, J.S.; Choi, S.H.; Jang, K.-T. Surgical Strategy for T2 Gallbladder Cancer According to Tumor Location. Ann. Surg. Oncol. 2014, 22, 2779–2786.

Kim, H.S.; Park, J.W.; Kim, H.; Han, Y.; Kwon, W.; Kim, S.-W.; Hwang, Y.J.; Kim, S.G.; Kwon, H.J.; Vinuela, E.; et al. Optimal surgical treatment in patients with T1b gallbladder cancer: An international multicenter study. J. Hepato Biliary Pancreat. Sci. 2018, 25, 533–543.

Kim, N.H.; Kim, S.H.; Choi, G.H.; Kang, C.M.; Kim, K.S.; Choi, J.S.; Lee, W.J. Role of Cholecystectomy and Lymph Node Dissection in Patients with T2 Gallbladder Cancer. World J. Surg. 2013, 37, 2635–2640.

D'Angelica, M.; Dalal, K.M.; DeMatteo, R.P.; Fong, Y.; Blumgart, L.H.; Jarnagin, W.R. Analysis of the Extent of Resection for Adenocarcinoma of the Gallbladder. Ann. Surg. Oncol. 2008, 16, 806–816.

Santini D, Virzi V, Vasile E, et al. A phase II trial of fixeddose rate gemcitabine plus capecitabine in metastatic/advanced biliary tract cancer patients. Oncology 2012;82:75-82.

Cho JY, Nam JS, Park MS, et al. A Phase II Study of Capecitabine Combined with Gemcitabine in Patients with Advanced Gallbladder Carcinoma. Yonsei Med J 2005;46:526-31.

Knox JJ, Hedley D, Oza A, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 2005;23:2332-8.

Riechelmann RP, Townsley CA, Chin SN, et al. Expanded phase II trial of gemcitabine and capecitabine for advanced biliary cancer. Cancer 2007;110:1307-12.

Kiran RP, Pokala N, Dudrick SJ. Incidence pattern and survival for gallbladder cancer over three decades--an analysis of 10301 patients. Ann Surg Oncol 2007; 14:827.

Ishikawa T, Utoh M, Sawada N, et al. Tumor selective delivery of 5-fluorouracil by capecitabine, a new oral fluoropyrimidine carbamate, in human cancer xenografts.

Biochem Pharmacol. 1998;55:1091–1097.
Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol. 2000;45:291–297.
Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. Eur J Cancer. 1998; 34:1274 –1281.
Saeki T, Takashima S. [Mechanism and possible biochemical modulation of capecitabine (Xeloda), a newly generated oral fluoropyrimidine]. Gan To Kagaku Ryoho. 1999;26:447– 455.
Endo M, Shinbori N, Fukase Y, et al. Induction of thymidine phosphorylase expression and enhancement of efficacy of capecitabine or 5-deoxy-5-fluoroudine by cyclophosphamide in mammary tumor models. Int J Cancer. 1999;83:127– 134.
Twelves C, Gynne-Jones R, Cassidy J, et al. Effect of hepatic dysfunction due to liver metastases on the pharmacokinetics of capecitabine and its metabolites. Clin Cancer Res. 1999;5:1696 –1702.
Hoff PM, Ansari R, Batist G, et al. Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized Phase III study. J Clin Oncol. 2001;19:2282–2292.

Borner MM, Dietrich D, Stupp R, et al. Phase II study of capecitabine and oxaliplatin in first- and second-line treatment of advanced or metastatic colorectal cancer. J Clin Oncol. 2002;20:1759 –1766.
Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H. Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. Clin Cancer Res. 1998;4: 1013–1019.
Bajetta E, DiBartolomeo M, Mariani L, et al. Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first line treatment in metastatic colorectal carcinoma. Cancer. 2004;100:279 – 287.
Patt YZ, Hassan MM, Lozano RD, et al. Phase II trial of systemic continuous fluorouracil and subcutaneous recombinant interferon alfa-2b for treatment of hepatocellular carcinoma. J ClinOncol. 2003;21:421– 427.

Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995; 75:171.

Hamrick RE Jr, Liner FJ, Hastings PR, Cohn I Jr. Primary carcinoma of the gallbladder. Ann Surg 1982; 195:270.
Yamaguchi K, Chijiiwa K, Ichimiya H, et al. Gallbladder carcinoma in the era of laparoscopic cholecystectomy. Arch Surg 1996; 131:981.
Strom BL, Soloway RD, Rios-Dalenz JL, et al. A prospective analysis of 1518 laparoscopic cholecystectomies. The Southern Surgeons Club. N Engl J Med 1991; 324:1073. Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer 1995; 76:1747.
Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006; 118:1591.
Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001; 51:349.
Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004; 4:695.
Miquel JF, Covarrubias C, Villaroel L, et al. Genetic epidemiology of cholesterol cholelithiasis among Chilean Hispanics, Amerindians, and Maoris. Gastroenterology 1998; 115:937.
Serra I, Calvo A, Báez S, et al. Risk factors for gallbladder cancer. An international collaborative case-control study. Cancer 1996; 78:1515.

Rodney C. Richie, MD, FACP, FCCP; John O. Swanson, MD. Breast Cancer: A Review of the Literature. Journal of Insurance Medicine. J Insur Med 2003; 35:85–101.

Milind Javle1*, Chaitanya Churi1, HyunSeon C. Kang2, Rachna Shroff1, Filip Janku3, Rakesh Surapaneni4, Mingxin Zuo1, Christian Barrera1, Humaid Alshamsi1, Sunil Krishnan5, Lopa Mishra6, Robert A. Wolff1, Ahmed O. Kaseb1, Melanie B. Thomas7 and Abby B. Siegel8*. R E S EAR CH A R TIC L E - HER2/neu-directed therapy for biliary tract cancer. Journal of Hematology & Oncology (2015) 8:58; 1-9.

Heim E, Valach L, Schafner L. Coping and psychosocial adaptation: longitudinal efects over time and stages in breast cancer. Psychosom Med. 1997;59:408–18.

Bednarek A, Sahin A, Brenner A, Johnston D, Aldaz C. Analysis of telomerase activity levels in breast cancer: positive detection at the in situ breast carcinoma stage. Clin Cancer Res. 1997;3(1):11–6.

Segal R, Evans W, Johnson D, Smith J, Colletta S, Gayton J. Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. J Clin Oncol. 2001;19:657–65.

Moran M, Schnitt S, Giuliano A, Harris J, Khan S, Horton J. Society of surgical oncology–American society for radiation oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int J Rad Oncol Biol Phys. 2014;88:553–64.

Jacquillat C, Weil M, Baillet F, Borel C, Auclerc G, Maublanc M. Results of neoadjuvant chemotherapy and radiation therapy in the breast-conserving treatment of 250 patients with all stages of infltrative breast cancer. Cancer. 1990;66:119–29.

Neuman H, Morrogh M, Gonen M. Stage IV breast cancer in the Era of targeted therapy, Does surgery of the primary tumor matter. Cancer. 2015;116:1226–33.

PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION. PrXELODA® capecitabine tablets Tablets 150 mg and 500 mgManufacturer's StandardAntineoplastic Agent. Date of Revision:April 19, 2021. Hoffmann-La Roche Limited 7070 Mississauga RoadMississauga, OntarioL5N 5M8. ®Copyright 1998 – 2021 Hoffmann-La Roche Limited.XELODA® is a registered trade-mark of F. Hoffmann-La Roche AG, used under license. www.rochecanada.com

Coleman M, Quaresma M, Berrino F, Lutz JM, Angelis R, Capocaccia R, et al. Cancer survival in fve continents: a worldwide population-based study (CONCORD). Lancet Oncol. 2008;9:730–56..

Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.

Berry D, Cronin K, Plevritis S, Fryback D, Clarke L, Zelen M, etal. Efect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med. 2005;353:1784–92.

Peng J, Sengupta S, Jordan VC. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. Anti-Cancer Agents Med Chem. 2009;9:481–99.

Reeder J, Vogel V. Breast cancer prevention. Cancer Treat Res. 2008;141:149–64.

Dwivedi V, Shrivastava R, Hussain S. Comparative anticancer potential of clove (Syzygium aromaticum)—an Indian spice—against cancer cell lines of various anatomical origin. Asian Pac J Cancer Prev. 2011;12(8):1989–93.

Mary J, Vinotha P, Pradeep A. Screening for in vitro cytotoxic activity of seaweed, Sargassum sp. against Hep-2 and MCF-7 cancer cell lines. Asian Pac J Cancer Prev. 2012;13:6073–6.

Mukherjee P, Wahile A. Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. J Ethnopharmacol. 2006;103:25–35.

Zhu Y, Zhou L, Jiao S, Xu L. Relationship between soy food intake and breast cancer in China. Asian Pac J Cancer Prev. 2011;12:2837–40.

Han S, Guo Q, Wang T. Prognostic signifcance of interactions between ER alpha and ER beta and lymph node status in breast cancer cases. Asian Pac J Cancer Prev. 2013;14:6081–4.

Ferlay J, Soerjomataram I, Ervik M. Cancer incidence and mortality worldwide: sources,

methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136:359–86.

Haghighat S, Akbari M, Ghafari S, Yavari P. Standardized breast cancer mortality rate compared to the general female population of Iran. Asian Pac J Cancer Prev. 2012;13:5525–8.

Hanif M, Zaidi P, Kamal S, Hameed A. Institution-based cancer incidence in a local population in Pakistan: 9 year data analysis. Asian Pac J Cancer Prev. 2009;10:227–30.

Khoker S, Muhammad U, Masooma R, Naseem A, Afaf S. Clinico-pathologic profle of breast cancer patients in Pakistan: 10 years data of a local cancer hospital. Asian Pac J Cancer Prev. 2012;13:693–8.

Nadia Harbeck1*, Frédérique Penault-Llorca2, Javier Cortes3,4, Michael Gnant5, Nehmat Houssami6, Philip Poortmans7,8, Kathryn Ruddy9, Janice Tsang10 and Fatima Cardoso11. Breast cancer. Article in Nature Reviews Disease Primers · December 2019.

Moore M, Ariyaratne Y, Badar F. Cancer epidemiology in South Asia past, present and future. Asian Pac J Cancer Prev. 2009;10:49–67.

Jamal S, Mamoon N, Mushtaq S, Luqman M. Carcinoma of the male breast: a study of 141 cases from Northern Pakistan. Asian Pac J Cancer Prev. 2006;7:119–21.

Yang L, Parkin D, Ferlay J. Estimates of cancer incidence in China for 2000 and projections for 2005. Cancer Epidemiol Biomarkers Prev. 2005;14:243–50.

Torre LA, Sauer AM, Chen MS, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, native hawaiians, and pacifc islanders, 2016: converging incidence in males and females. Cancer J Clin. 2016;66:182–202.

Stark G, Grandel S, Spilker G. Tissue suction of the male and female breast. Aesth Plast Surg. 1992;16:317–24.

Tanis P, Nieweg O, Olmos R, Kroon B. Anatomy and physiology of lymphatic drainage of the breast from the perspective of sentinel node biopsy1. J Amer Coll Surg. 2001;192:399–409.

Thomsen S, Tatman D. Physiological and pathological factors of human breast disease that can infuence optical diagnosis. Ann N Y Acad Sci. 1998;838(1):171–93.

Jagannathan N, Sharma U. Breast tissue metabolism by magnetic resonance spectroscopy. Metabolites. 2017;7:25–30.

Hassiotou F, Geddes D. Anatomy of the human mammary gland: current status of knowledge. Clin Anat. 2013;26:29–48.

Goss, P. E. et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. N. Engl. J. Med. 375, 209–219 (2016).