

REVIEW

Types of Cancers Prevailing in Pakistan and their Management Evaluation

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Abstract

Cancer is basically a class of disorder marked by uncontrolled proliferation of cells which have the potential to interfere with different systems of body like digestive, central nervous and circulatory systems by releasing hormones. Tumors that reside only in a specified location and show restricted growth are commonly characterized as benign tumors. When tumor cells grow and effectively spread to other body parts and potentially invade and damage healthy tissues they show various degrees of malignancy. Cancer may be caused by different factors like gene mutations, carcinogens and some medical factors that harm the immune system of the body. Symptoms of cancer are relatively varied and classified according to location, progression pattern and size of tumors as well. Different diagnostic tests are used for evaluation that depends on the type of cancer. Cancer management and chemo protocols also depend on the progression and site where it develops. Cancers like breast, lung, liver, colorectal, prostate, head and neck carcinoma are most commonly diagnosed in Pakistan. This review briefly describes the three most common cancers prevailing in Pakistan and their management evaluation.

Keywords: Cancer prevalence - cancer progression - breast cancer - colorectal cancer - lung cancer

Asian Pac J Cancer Prev, 16 (9), 3605-3616

Introduction

Generally cancer may be defined as a cluster of diseases marked by unrestrained enlargement and proliferation of uncharacteristic cells that can influence any body part (Mancini et al., 1997). Uncontrollable proliferation of abnormal cells can lead to death of an individual suffering from cancer. Abnormal cells have potential to invade adjacent body parts and can reach to other organs either by lymph node or blood vessels. This process of rapid invasion is usually referred to as metastasis (Leber and Efferth, 2009). Factors primarily involved to cause cancer, are internal and external factors. In internal factors: hormone, immune condition, metabolic and hereditary mutations are involved. External factors include tobacco or alcohol use, malnourishment, obesity, physical inactivity, exposure to radiation, chemicals, pollution of air, human papilloma virus (HPV) hepatitis B virus (HBV), human immunodeficiency virus (HIV) and other infections caused by bacteria (*H. Pylori*) and parasites (Montesano and Hall, 2001; Ferber et al., 2003; Mimi and Yuan, 2004; Hashibe et al., 2009). Mostly, progression of cancers may involve many steps that take place over several years (Huber et al., 2005). Cancer can be preventable in certain cases by reducing contact with tobacco use and other factors that step up this process. Surgical procedure, chemotherapy, radiotherapy, hormones (Peters et al., 2000), immunosuppressant and

certain antibiotics are usually involved in the management/treatment of cancers (Baselga et al., 1998). Cancer is considered to be the primary cause of death in urbanized countries like USA, Australia, Canada, China etc and second main reason of death in un-urbanized countries for example in Pakistan, India, Bangladesh and Nepal (Ferlay et al., 2010; Jemal et al., 2011). According to the WHO, it was estimated that 7.5 million people died in 2005 because of cancer and in future if any action is not employed for its prevention then 84 million people will die in the subsequent 10 years (Jemal et al., 2009). More than 70% deaths in developing countries occur due to cancer because of absence and inadequate availability of resources for its diagnosis, prevention, management and treatment (Anderson et al., 2011).

Tobacco, in particular, is one of the most important preventable risk factor that is responsible for one-fourth of cancer deaths globally (Danaei et al., 2009). Worldwide one-third of the 12 foremost cancers can be prevented via intake of balanced diet and good physical fitness by maintaining healthy body weight (Beck et al., 2010). Around 15% of all unpleasant cancer incidents occur due to infections (Cavalli, 1998). This proportion is approximately three times higher (26%) in urbanized countries as compared to (8%) in un-urbanized countries (Parkin, 2006). In 2012, it was anticipated that approximately 14.1 million most recent cancer cases and 8.2 million cancer causing deaths has been reported

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in contrast to 12.7 million cancer cases and 7.6 million cancer deaths in 2008(Thomas and Gustafsson 2011). Worldwide most commonly cancers are breast cancer in females, lung cancer, colorectal cancer, prostate cancer in males, stomach cancer, liver cancer, cervix uteri cancer, esophageal cancer, cancer of urinary bladder, Non Hodgkin Lymphoma and childhood cancer(Jemal et al., 2011). Some recent studies has reported most frequently diagnosed cancers and cancer related deaths (Table 1) Ferlay et al., 2010; Bray et al., 2013).

Progression of Cancer

More progressively it is anticipated that reactive oxygen and nitrogen radicals play a very important role in the advancement and progression of cancer in human beings in particular as affirmation is increasing that commencement of various types cancer might be averted or obstructed by the use of antioxidants (Byers and Perry, 1992; Watson, 2013). In reactive oxygen species, oxygen radicals(peroxy, alkoxy, superoxide) and certain non radicals (oxidants) are included. Radicals of nitric oxide, nitrogen dioxide and other nitrogenous oxides are included in reactive nitrogen species (Cerutti, 1994). These both types of reactive oxygen and nitrogen radicals play a crucial role to initiate cancer by means of mutagenesis (Waris and Ahsan, 2006). These reactive species can encompass following consequences:

i) Initiate the modification of genetic makeup, e.g. base pair alteration, reshuffling, removal, addition and strengthening of order (Halliwell, 1994). ii) Have an influence on signal transduction pathways of cytoplasm and nucleus. (Schreck et al., 1992; Valko et al., 2007). iii) Activity pattern of proteins and genes are transformed that react in response to stress conditions which can leads to abnormal propagation, discrimination and apoptosis of

cells. (Jackson, 1994)

Evaluation of Cancer Progression

To evaluate cancerous growth, TNM staging system is usually employed by 3 approaches: Degree and extent of primary cancer (T); Insufficient or excess participation of localized lymph node (N); Lack and have acquire of isolated metastases (Edge and Compton, 2010).

Breast Cancer

Internationally tumor of breast tissues is most commonly diagnosed cancer in females and exceptionally uncommon in males. Worldwide it is reported that breast cancer is 23% of nearly all cancer cases (McPherson et al., 2000; Jemal et al., 2011; Benson and Jatoi, 2012). All women are endangered to develop breast cancer regardless of their cultural or traditional basis (Naeem et al., 2008). According to the facts and figures of WHO, globally every year above 1.2 million people are routinely diagnosed having breast cancer (Asif et al., 2014)). In Pakistan, females suffer from this medical condition, with highest prevalence rates in Asia (Sohail and Alam, 2007). According to the reported documentation from Shaukat Khanum Memorial Cancer hospital and research centre, prevalence rate of breast cancer is about 21.5% among all and 45.9% among females (Badar et al., 2011). Most frequently, it begins from internal lining of milk ducts tissue that contributes to milk production (Sariego, 2010). For breast cancer, rate of diagnosis and continued existence depend upon the nature of cancer, its stage, management or treatment protocol and geological position of patients. Prevalence of breast cancer is 2.5 times higher in Pakistan than that in nearby countries like India and Iran (Asif et al., 2014). Most commonly risk factors related to breast cancer

Table 1. According to the International Agency for Research on Cancer (IARC)

Cancers That Are Most Frequently Diagnosed	Most Frequently Cancer Related Deaths
Lung cancer(1.8 million, 13.0% of the total cases)	Deaths due lung cancer (1.6 million, 19.4% of the total reported deaths)
Breast cancer (1.7 million, 11.9% of total cases),	Deaths because of liver cancer (0.8 million, 9.1% of the total reported deaths)
Colorectal cancer (1.4 million, 9.7% of total cases).	Deaths proportion due to the reason of stomach cancer (0.7 million, 8.8% of the total reported deaths).

Table 2. Diagnosis and Management of Breast Cancer

Diagnostic Tests	Management	References
Physical examination	Chemotherapy for example cisplatin, carboplatin, docetaxel, doxorubicin, cyclophosphamide, methotrexate, and paclitaxel. Epirubicin in combination with paclitaxel, capecitabine+ docetaxel	(Pietras et al., 1998; Da-wood et al., 2010; Burris et al., 2011; Gøtzsche and Nielsen, 2011; Krop et al., 2012; Verma et al., 2012)
Imaging test like mammogram, MRI, breast ultrasound, ductogram,	Surgery	
Biopsy ((Excisional biopsy, a core biopsy or vacuum-assisted breast biopsy)	Hormone-blocking drugs	
Fine needle aspiration and cytology).	Monoclonal antibodies for example, trastuzumab alone or in combination with chemotherapy	

are age of patient, sex, infertility, overweight, high caloric food intake, family history of having breast cancer, use of alcohol, lack of physical activity, poor socioeconomic status, lack of knowledge about this disease, ingestion of hormonal combination (progestin and estrogen), exposure to industrial chemicals for example; polycyclic aromatic hydrocarbons, polychlorinated biphenyls, organic solvents and numeral pesticides (Brody et al., 2007).

Risk of breast cancer is also remarkably increased with elevation of Estrogen level (Thomas and Gustafsson, 2011; Hamedeyazdan et al., 2012). Mainly two kinds of Estrogen receptors (ER) exist; one is ER-alpha and second is called ER-beta (Toniti et al., 2011). Approximately, 70% of the primary breast cancer patients are affected by uncontrolled expression of ER-alpha which is considered

to be the major cause of breast cancer and play significant role in signaling network of this deadliest cancer (Fuqua, 2001; Ariazi et al., 2006; Izadi et al., 2012; Kumar et al., 2013; Xu et al., 2013). For breast cancer Tamoxifen, Raloxifene, Toremifene are the most frequently used anticancer drugs (Gutman et al., 2002). These drugs are responsible for causing some serious side effects for example blood clots, strokes, cancer of uterus, or cataracts (Andrew et al., 2011; Suganya et al., 2014). From recent studies, it has been demonstrated that some natural flavonoids containing compounds (Flavanols, Flavones, Anthocyanidins, Isoflavonoids) have been approved for having anticancer activity. Vegetables, cereals, tea, red wine, legumes and fruits are rich source of flavonoids (polyphenolic compounds) that have cancer reducing

Table 3. Chemotherapy Protocols for Breast Cancer According to BCCA

Sr. #	Protocol Code	Drugs	Recommended dose	Administration guideline	Cycle	References
1	BRAJAC	i) DOXOrubicin ii) cyclophosphamide	60 mg/m ² 600 mg/m ²	IV push IV in NS or D5W 100 to 250 mL over 20 min to 1 hour	4 cycle repeat every 21 days	(Fisher, Brown et al. 1990)
2	BRAJACT	i) DOXOrubicin ii) cyclophosphamide iii) PACLitaxel	60 mg/m ² 600 mg/m ² 175 mg/m ²	IV push IV in NS or D5W 100 to 250 mL over 20 min to 1h IV in NS 500 mL over 3 hours	4 consecutive cycles 4 consecutive cycles of PACLitaxel Start at 21 days after final cycle of DOXOrubicin & cyclophosphamide.	(Citron et al., 2003; Sparano et al., 2007)
3	BRAJ-CAFG	i) DOXOrubicin ii) fluorouracil iii) cyclophosphamide iv) filgrastim (G-CSF)	30 mg/m ² Days 1 and 15 500 mg/m ² Days 1 and 15 700 mg/m ² Days 1 and 15 5 mcg/kg/day Days 2 to 13 and Days 16 to 27 (or adjust as needed**)	IV push IV in NS or D5W 100 to 250 mL over 20 min to 1 hour* SC	Repeat every 28 days* 6 cycles total	(Hutchins et al., 2005)
4	BRAJCEFG (regimen at 100% doses)	i) epirubicin ii) fluorouracil iii) cyclophosphamide iv) filgrastim (G-CSF)	60 mg/m ² /day on Days 1 and 15 500 mg/m ² /day on Days 1 and 15 525 mg/m ² /day on days 1 and 15 5 mcg/kg/day on Days 2-13 and Days 16-27 (or adjust as needed)	IV push IV push IV in 100 to 250 mL NS or D5W over 20 min to 1 hour SC	Repeat every 28 days* 6 cycles total	(Levine et al., 1998)
5	BRAJTR	For cycle 1 i) trastuzumab For cycle 2/subsequent cycles. ii) trastuzumab (HERCEPTIN)	8 mg/kg 6 mg/kg	IV in 250 mL NS over 1 hour 30 min IV in 250 mL NS over 1 hour on the second dose. IV in 250 mL NS over 30 min on all subsequent.	Repeat every 21 days x 17 cycles	(Perez and Rodeheffer, 2004)

6	BRAJF-ECDT	Cycle 1-3				(Perez and Rodeheffer, 2004; Jones et al., 2009; Soong et al., 2009; Vandenberg et al., 2010; Chan et al., 2011)	
		i) epirubicin	100 mg/m ² on Day 1	IV push	Repeat every 21 days x 3 cycles		
		ii) fluorouracil	500 mg/m ² on Day 1	IV push			
		iii) cyclophosphamide	500 mg/m ² on Day 1	IV in 100 to 250* mL NS over 20 min to 1 hour			
		followed by cycle 4					3 consecutive cycles, repeat every 21 days after final cycle of first regimen
		iv) trastuzumab (HERCEPTIN)	8 mg/kg	IV in 250 mL NS over 1 hour 30 min Observe for 1 hour post-infusion.			
		v) DOCEtaxel	100 mg/m ²	IV in 250 to 500 mL* NS over 1 hour.	Repeat every 21 days *3 cycles total		
		followed by cycle 5,6					
vi) trastuzumab (HERCEPTIN)	6 mg/kg	A) IV in 250 mL NS over 1 hour on the second dose(cycle 5) B) IV IN 250 ml NS over 30 min on the third dose					
vii) DOCEtaxel followed by	6 mg/kg	(Cycle 6), Observe for 30 min post infusion	14 consecutive cycles of trastuzumab to start 21 days after the final cycle of DOCEtaxel/trastuzumab for a total of 1 year of trastuzumab treatment.				
viii) trastuzumab (HERCEPTIN)	100 mg/m ²	IV in 250 to 500 mL NS over 1 hour IV in 250 mL NS over 1 hour 30 min					

Table 4. Diagnostic Tests and Possible Treatment for Colorectal Cancer

Screening Tests	Possible Treatment	References
Flexible Sigmoidoscopy	Surgery	(Lokich et al., 1989; Cunningham et al., 1998; Rougier et al., 1998; Douillard et al., 2000; Saltz et al., 2000; Hoff et al., 2001; Tunio et al., 2010; Schoen et al., 2012; Zauber et al., 2012). References
Colonoscopy	Permanent colostomy	
	High dose rate intraluminal brachytherapy (HDR-ILBT(dose escalation technique in preoperative chemora-diation for rectal cancers)	
	Chemotherapy (mostly used)and radioherapy	
Double-contrast Barium Enema	i. fluorouracil (5-FU) alone or in combination with radiotherapy	
	ii. 5-fluorouracil and folinic acid	
	v. irinotecan	
	iv. oral capecitabine	
	v. irinotecan.	
	vi. Combination of irinotecan, 5-fluorouracil and 5-folinic acid	
Computed Tomographic Colonography	Polypectomy	
Fecal Occult Blood Test	Surgical resection	
Stool DNA Test	Targeted monoclonal antibodies therapy e.g., Bevacizumab, cetuximab, panitumumab	

ability (Jarzabek et al., 2009; Hamedeyazdan et al., 2012; Stapel et al., 2013).

Colorectal Cancer

Colorectal cancer basically arises from parts of large intestine like rectum or colon. Generally, it grows

gradually around a period of 10 to 15 years (Kelloff et al., 2004).This cancer naturally originates as noncancerous tumor that grows on inside layer of colon or rectum that has the ability to become a cancer. Worldwide, it is 3rd most frequently diagnosed solid cancer in males and 4th primary reason of cancer related deaths in both males and females (Jemal et al., 2011; Karaca et al., 2012; Chiu et

al., 2013). Frequency to develop colorectal cancer hits the highest point in 7th and 8th decennium of life, by only 5% documented in those with less than 40 years. Worldwide, Approximately 1.2 and 1.7 million cases of colorectal cancer were reported in 2008 and 2012 respectively. According to data of Karachi cancer registry (KCR), age standardized incidence rate (ASR) for all types of cancers are 179.0/100,000 in males and 204.1/100,000 in females. In Pakistan, ASR particularly for colon cancer is 3.2/100,000 in males and 2.8/100,000 in females (Bhurgri et al., 2000; Bhurgri et al., 2006a).

Colorectal cancer has been proved as a significant problem for global health as it is the main reason of morbidity and mortality (Zhang et al., 2014). Prevalence rate of colorectal cancer is more than 9% in contrast

to other cancers. Its prevalence rate fluctuates up to 10 folds between countries with highest incidence risk and countries with low incidence risk. Countries like New Zealand, Canada, Australia, the United States, and some parts of Europe are at highest risk to develop colorectal cancer. Countries with low incidence rate for colorectal cancer are India, China, some parts of Africa and Southern America. It varies from more than 40 for every 100,000 people in the United States. Australia, New Zealand, and Western Europe having less than 5 for every 100,000 people in Africa and various parts of Asia. Colorectal cancer at an early phase is often having no symptom but as disease progresses it may frequently cause following symptoms for example; blood ooze out from rectum, stool with bleeding, abdominal pain with muscle cramping,

Table 5. Chemotherapy Protocols for Colorectal Cancer According to BCCA

SR. #	Protocol Code	Drugs	DOSE	Administration Guidelines	Cycles	References
1	GIAJCAP	Capecitabine	1250 mg/m ² BID x 14 days	PO with food	Repeat every 21 days for 8 cycles.	(Scheithauer et al., 2003)
2	GIAJCAPOX	i) oxaliplatin ii) capecitabine	130 mg/m ² 1000 mg/m ² BID	IV in 500 mL* of D5W over 2 hours PO x 14 days	Repeat every 21 days for a maximum of 8 cycles.	(André et al., 2004; Kuebler et al., 2007)
3	GIAJFFOX	i) oxaliplatin ii) leucovorin iii) fluorouracil (5-fu) iv) fluorouracil	85 mg/m ² 400 mg/m ² 400 mg/m ² 2400mg/m ²	IV in 500 mL of D5W over 2 hours. IV in 250 ml D5W over 2 hours IV bolus, after leucovorin IV over 46 h in D5W to a total volume of 92 mL by continuous infusion at 2 mL/h via appropriate infusor device.	Repeat every 14 days for 12 cycles	(André et al., 2004)
4	GIAJFL	i) folinic acid (leucovorin) ii) fluorouracil iii) fluorouracil	400mg/m ² 400mg/m ² 2400mg/m ²	IV in 250 ml D5W over 2 hours IV bolus, after Folinic Acid. IV over 46 h in D5W to a total volume of 92 mL by continuous infusion at 2 mL/h via appropriate infusor device.	Repeat every 14 days for 12 cycles.	(André et al., 2004)
5	GIAVCETIR	i) cetuximab (first dose) ii) irinotecan	500 mg/m ² 180 mg/m ²	IV over 2 hours using a 0.22 micron in-line filter. IV in 500 mL D5W over 1 hour 30 min	Repeat every 2 weeks* 10 cycles.	(Cunningham et al., 2004; Martin-Martorell et al., 2008; Pfeiffer et al., 2008; Wilke et al., 2008)
6	GIAVPANI (As Palliative Third Line Treatment for Metastatic Colorectal Cancer)	Panitumumab	6 mg/kg	IV in 100 mL NS over 1 hour using a 0.22 micron in-line filter	Repeat every 2 weeks.	(Van Cutsem et al., 2007; Fakih, 2008; Melosky et al., 2009)
7	GICAPIRI	i) irinotecan ii) capecitabine	200mg/m ² 800mg/m ² bid	IV in 500 mL of D5W over 1 hour 30 min PO x 14 days	Repeat every 21 days for a maximum of 16 cycles.	(Wasserman et al., 1997; Bajetta et al., 2004)

dark colored stools, feeling of uneasiness or compel to have bowel passage when it does not require, new episode of diarrhea and constipation that persist for many days, unintended weight loss, excessive blood loss from cancerous parts leads to anemic condition. Majority of the colorectal cases are diagnosed at an advanced stage/ inoperation stage and approximately 60-80% of the colorectal patients develop recurrence which can be distant or local (Siegel et al., 2012). Factors that contributes to increase risk for colorectal cancer are, family history of having tumor of colon and rectum especially first degree relatives, overweight (abdominal obesity), smoking, lack of physical activity, excessive intake of alcohol and red meat, low consumption of milk, ingestion of unbalanced diet, low blood level of calcium, deficiency of vitamin D, disease like diabetes (Cho et al., 2004; Chao et al., 2005; Larsson et al., 2005; Levin et al., 2008; Huxley et al., 2009; Wolin et al., 2009; Campbell et al., 2010; Chan and Giovannucci, 2010; Cross et al., 2010). Tumor stage and predictive markers are the most significant indicators for colorectal cancer (Colussi et al., 2013; Yang et al., 2014). The most important prognostic markers from candidate (patient suffering from colorectal cancer) are circulating tumor cells, tumor enzymes, blood antigens and gene expressions (Chan et al., 2010; Firestein et al., 2010; Fang et al., 2012; Imamura et al., 2012; Liao et al., 2012; Morikawa et al., 2012; Li et al., 2013).

Surgery is the most common therapeutic intervention for colorectal cancer. From some recent studies, it has been approved that Oxaliplatin in combination with fluoropyrimidines is used as first line therapy for metastatic colorectal cancer. Regardless of the demonstrated therapeutic efficacy, oxaliplatin may cause some serious side effects which indicates that efficacy of oxaliplatin has extensive range of interpatient variability (Boige et al., 2010; Yang et al., 2013). According to the NCCN Guideline, chemotherapeutic regimens for colorectal

cancer are fluorouracil, oxaliplatin, irinotecan, cetuximab, 5-FU. These agents may be used alone or in combination form such as FOLFIRI, FOLFOX, XELOX, irinotecan/oxaliplatin and UFT/LV (Xu et al., 2011). Among these regimens, FOLFOX is the most frequent and effective regimen (Chen et al., 2013) but the use of FOLFOX causes diarrhea of grade 3 or 4, nausea and vomiting (Ucu et al., 2013). Diarrhea is the dose limited toxicity of FOLFOX (Comeau and Labruzzo, 2012). In majority of the patients with colorectal cancer (approximately 80% cases), nausea, vomiting and diarrhea can be efficiently managed by administration of optimal doses of dexamethasone, indisetron and probiotic treatment with Lactobacillus spp respectively (Gibson et al., 2013; Nakatsumi et al., 2013).

Lung Cancer

Worldwide, lung cancer is the most common cause of cancer related deaths (Jemal et al., 2011). It is more or less characterized by carcinomas; these tumors basically originate from epithelial lining of trachea and bronchi. The most important histological types of lung cancers are, carcinoma of squamous cells (SCC), small cell carcinoma, adenocarcinoma. Histopathologically, primary lung cancer can be classified into two categories such as non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (Jemal et al., 2011). Globally it is the primary reason of cancer related deaths in males and 2nd important reason of cancer causing deaths in females with nearly 1.6 million new cancer cases diagnosed and in addition to 1.4 million deaths expected to occur in 2008 (Ferlay et al., 2010). In man, it accounts for highest prevalence rate in the United States as well as in eastern European countries. Lower risks of incidence are reported in Central and South America, South Central Asia and Africa (Jemal et al., 2010). In 2013, lung cancer has been account for 26% of all female cancer deaths (Siegel et al., 2013).

Table 6. Management/ Possible Treatment Protocols for Lung Cancer

Radiotherapy	Around 60 Gy, in divided dose among 30 sittings above a period of six weeks
Surgery	i) Resection (pneumonectomy or lobectomy) ii) And mediastinal-node mapping. iii) Complete lymph-node dissection.
Chemotherapy	i) Platinum agents for example: Cisplatin, Carboplatin ii) Nonplatinum agents for example: Etoposide, Topotecan, Irinotecan, Gemcitabine, Paclitaxel, Docetaxel Vinorelbine, Vincristine, Doxorubicin, Ifosfamide, Cyclophosphamide iii) Concomitant chemotherapy and radiotherapy after surgery for example: Cyclophosphamide, doxorubicin, and cisplatin vs immunotherapy Cyclophosphamide, doxorubicin, cisplatin, and radiotherapy vs radiotherapy alone Etoposide, cisplatin, and radiotherapy vs radiotherapy alone iv) Addition of chemotherapy to radiotherapy in inoperable cancer. Cisplatin, vinblastine, and radiotherapy vs radiotherapy alone Cisplatin, vinblastine, and concurrent radiotherapy vs cisplatin, vinblastine, and sequential radiotherapy v) Neoadjuvant chemotherapy in stage IIIA disease for example: Etoposide and cisplatin before and after surgery vs surgery and radiotherapy Mitomycin, ifosfamide, and cisplatin before surgery and radiotherapy vs surgery and radiotherapy vi) Chemotherapy for advanced disease of lung cancer : Cisplatin and paclitaxel vs cisplatin and gemcitabine, cisplatin and docetaxel and carboplatin and paclitaxel. Carboplatin, paclitaxel, and gefitinib vs carboplatin and paclitaxel.
References	(Holmes and Gail, 1986; Lad et al., 1988; Dillman et al., 1990; Rosell et al., 1994; Roth et al., 1994; Dillman et al., 1996; Roth et al., 1998; Rosell et al., 1999; Keller et al., 2000; Schiller et al., 2002; Curran et al., 2003).

In Pakistan, most frequent diagnosed cancer is squamous cell carcinoma. In Kashmir, most of the SCCs are associated with smoking with extremely poor diagnosis (Khan et al., 2006). The rate of incidence to develop lung cancer enhances with age, with a little bit high risk in males belonging to upper socioeconomic status and in females having lower socioeconomic status. Higher incidence risk of lung cancer was also found in men who were living along the seaside and for races belonging to Southern Pakistan living in south Karachi (Bhurgri et al., 2006b). Important risk factors that increases the incidence of lung cancer are excessive smoking, industrial exposure to carcinogenic materials (radon and asbestos, certain metals (chromium, cadmium, arsenic), coal smoke, indoor air pollution, and malnourishment (Behera and Balamughesh, 2004; Li and Hemminki, 2004; Matakidou et

al., 2005). Worldwide, it has been reported that 80% deaths in males and 50% deaths in females with lung cancer occur because of smoking (Ezzati and Lopez, 2003; Ezzati et al., 2005). Smoking is supposed to be accountable for 17.2% of NSCLC cases in males and 11.6% of cases in females as compared to nonsmokers with 1.3% in males and 1.4% in females. According to Xiao-Ming et al, it has been reported that cigarette smoking is definitely linked to hypermethylation of RASSF1A gene in tumor tissues of patients suffering from lung cancer. So, this hypermethylation is considered to be an early indicator for the diagnosis of lung cancer (Liu et al., 2013; Ge et al., 2014). People with lung cancer are often presented with permanent coughing, sputum splashed with blood, pain in chest, change in tone of voice, intermittent pneumonia or bronchitis. Most commonly diagnostic tests for lung

Table 7. Chemotherapy Protocols for Lung cancer According to BCCA

Sr.#	Protocol code	Drugs	Dose	Administration guidelines	Cycles	References
1	LUAJNP (For NSCLC)	i) CISplatin ii) Vinorelbine	80 mg/m ² Day 1 30 mg/m ² days 1, 8, 15	IV in NS 500 mL with potassium chloride 20 mEq, magnesium sulphate 1 g, Mannitol 30 g over 1 hour. IV in NS 50 mL over 6 min	Repeat every 21 days*4 cycles	(Winton et al., 2005)
3	LUAVDC (first line treatment for advanced NSCLC)	i) DOCEtaxel ii) CISplatin	75 mg/m ² 75 mg/m ²	IV in 250 mL* NS or D5W over 1 hour. Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq KCl, 1 g magnesium sulfate, 30 g mannitol over 1 hour	Repeat every 21 days x 4 to 6 cycles	(Fossella, 2001; Fossella et al., 2003)
4	LUAVDOC (for advanced NSCLC)	DOCEtaxel	75 mg/m ²	IV in 250 mL NS or D5W over 1 hour	Repeat every 21 days x 6 cycles	(Shepherd et al., 2000)
5	LUAVERL (2nd and 3rd line treatment for advanced NSCLC)	Erlotinib	150 mg daily	PO		(Shepherd et al., 2005)
6	LUAVPG	i) gemcitabine ii) CISplatin	1250 mg/m ² /day on days 1 and 8 75 mg/m ² /day on day 1	IV in 250 mL NS over 30 min Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour	Repeat every 21 days x 4 to 6 cycles	(Brescia et al., 1997; Van Moorsel et al., 1997; Scagliotti et al., 2002; Schiller et al., 2002; Zatloukal et al., 2003)
7	LUSCCAV (for SCLC)	i) DOXOrubicin ii) vinCRistine iii) cyclophosphamide	50mg/m ² 1.2mg/m ² 1000mg/m ²	IV Push In 50 mL NS over 15 minutes IV in 100 to 250* mL NS over 20 min to 1 hour		(Livingston et al., 1978)
8	LUSCPERT (for SCLC)	i) CISplatin ii) etoposide	25 mg/m ² /day x 3 days (days 1 to 3) 100 mg/m ² /day x 3 days (days 1 to 3)	IV in 100 to 250 mL* NS over 20 to 30 Min IV in 500 mL NS over 45 min	Repeat every 21 days x 4 to 6 cycles	(Murray et al., 1993)

cancer are X-ray of chest, Sputum cell analysis, Fiberoptic examination of the bronchial passages, Positron-emission tomography, Molecular markers in sputum, Low-dose spiral computed tomography (CT) scans and lung biopsy (Pieterman et al., 2000).

References

- Anderson BO, Cazap E, El Saghir NS, et al (2011). Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. *Lancet Oncol*, **12**, 387-98.
- André T, Boni C, Mounedji-Boudiaf L, et al (2004). Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *New Engl J Med*, **350**, 2343-51.
- Andrew NF, Binbing Y, HG M (2011). Benefit/risk assessment for breast cancer chemoprevention with raloxifene or tamoxifen for women age 50 years or older. *J Clin Oncol*, **29**, 2327-33.
- Ariazi EA, Ariazi JL, Cordera F, et al (2006). Estrogen receptors as therapeutic targets in breast cancer. *Current topics in med chem*, **6**, 181-202.
- Asif HM, Sultana S, Akhtar N, et al (2014). Prevalence, risk factors and disease knowledge of breast cancer in Pakistan. *Asian Pac J Cancer Prev*, **15**, 4411.
- Badar F, Faruqui Z, Uddin N, et al (2011). Management of breast lesions by breast physicians in a heavily populated South Asian developing country. *Asian Pac J Cancer Prev*, **12**, 827-32.
- Bajetta E, Di Bartolomeo M, Mariani L, et al (2004). Randomized multicenter Phase II trial of two different schedules of irinotecan combined with capecitabine as first-line treatment in metastatic colorectal carcinoma. *Cancer*, **100**, 279-87.
- Baselga J, Norton L, Albanell J, et al (1998). Recombinant humanized anti-HER2 antibody (Herceptin) enhances the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast cancer xenografts. *Cancer Res*, **58**, 2825-31.
- Beck K, Thompson RL, Allen K, et al (2010). Policies and actions for cancer prevention: food, nutrition and physical activity. *Open Obes J*, **2**, 81-94.
- Behera D, Balamugesh T (2004). Lung cancer in India. *Indian J Chest Dis Allied Sci*, **46**, 269-81.
- Benson JR, Jatoi I (2012). The global breast cancer burden. *Future Oncol*, **8**, 697-702.
- Bhurgri Y, Bhurgri A, Hassan SH, et al (2000). Cancer incidence in Karachi, Pakistan: first results from Karachi cancer registry. *Int J Cancer*, **85**, 325-9.
- Bhurgri Y, Bhurgri A, Nishtar S, et al (2006a). Pakistan-country profile of cancer and cancer control 1995-2004. *J Pak Med Assoc*, **56**, 124.
- Bhurgri Y, Bhurgri A, Usman A, et al (2006b). Patho-epidemiology of lung cancer in Karachi (1995-2002). *Asian Pac J Cancer Prev*, **7**, 60.
- Boige V, Mendiboure J, Pignon J-P, et al (2010). Pharmacogenetic assessment of toxicity and outcome in patients with metastatic colorectal cancer treated with LV5FU2, FOLFOX, and FOLFIRI: FFCD 2000-05. *J Clin Oncol*, **28**, 2556-64.
- Bray F, Ren JS, Masuyer E, et al (2013). Global estimates of cancer prevalence for 27 sites in the adult population in 2008. *Int J Cancer*, **132**, 1133-45.
- Brescia FJ, Fontenot MRG, Johnson DH, et al (1997). Clinical practice guidelines for the treatment of unresectable non-small-cell lung cancer. *J Clin Oncol*, **15**, 2996-3018.
- Brody JG, Rudel RA, Michels KB, et al (2007). Environmental pollutants, diet, physical activity, body size, and breast cancer: where do we stand in research to identify opportunities for prevention? *Cancer*, **109**, 2627-34.
- Burriss HA, Rugo HS, Vukelja SJ, et al (2011). Phase II study of the antibody drug conjugate trastuzumab-DM1 for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. *J Clin Oncol*, **29**, 398-405.
- Byers T, Perry G (1992). Dietary carotenes, vitamin C, and vitamin E as protective antioxidants in human cancers. *Annu Rev Nutr*, **12**, 139-59.
- Campbell PT, Deka A, Jacobs EJ, et al (2010). Prospective study reveals associations between colorectal cancer and type 2 diabetes mellitus or insulin use in men. *Gastroenterol*, **139**, 1138-46.
- Cavalli F (1998). Rare syndromes in Hodgkin's disease. *Ann Oncol*, **9**, S109-S13.
- Cerutti PA (1994). Oxy-radicals and cancer. *The Lancet*, **344**, 862-3.
- Chan A, Fu WH, Shih V, et al (2011). Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. *Support Care Cancer*, **19**, 497-504.
- Chan AT, Baba Y, Shima K, et al (2010). Cathepsin B expression and survival in colon cancer: implications for molecular detection of neoplasia. *Cancer Epidem Biomar*, **19**, 2777-85.
- Chan AT, Giovannucci EL (2010). Primary prevention of colorectal cancer. *Gastroenterol*, **138**, 2029-43.
- Chao A, Thun MJ, Connell CJ, et al (2005). Meat consumption and risk of colorectal cancer. *Jama*, **293**, 172-82.
- Chen Q, Xia H-W, Ge X-J, et al (2013). Serum miR-19a predicts resistance to FOLFOX chemotherapy in advanced colorectal cancer cases. *Asian Pac J Cancer Prev*, **14**, 7421-6.
- Chiu J, Tang V, Leung R, et al (2013). Efficacy and Tolerability of Adjuvant Oral Capecitabine plus Intravenous Oxaliplatin (XELOX) in Asian Patients with Colorectal Cancer: 4-Year Analysis. *Asian Pac J cancer Prev*, **14**, 6585-90.
- Cho E, Smith-Warner SA, Spiegelman D, et al (2004). Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer I*, **96**, 1015-22.
- Citron ML, Berry DA, Cirrincione C, et al (2003). Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol*, **21**, 1431-9.
- Colussi D, Brandi G, Bazzoli F, et al (2013). Molecular pathways involved in colorectal cancer: implications for disease behavior and prevention. *Int J Mol Sci*, **14**, 16365-85.
- Comeau J, Labruzzo MB (2012). From bench to bedside: promising colon cancer clinical trials. *Am J Manag C*, **19**, SP32-7.
- Cross AJ, Ferrucci LM, Risch A, et al (2010). A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. *Cancer Res*, **70**, 2406-14.
- Cunningham D, Humblet Y, Siena S, et al (2004). Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *New Engl J Med*, **351**, 337-45.
- Cunningham D, Pyrhönen S, James RD, et al (1998). Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *The Lancet*, **352**, 1413-8.
- Curran W, Scott C, Langer C, et al (2003). Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. *Proc Am Soc Clin Oncol*, **22**, 621.

- Danaei G, Ding EL, Mozaffarian D, et al (2009). The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. *PLoS Med*, **6**, 1000058.
- Dawood S, Broglio K, Buzdar AU, et al (2010). Prognosis of women with metastatic breast cancer by HER2 status and trastuzumab treatment: an institutional-based review. *J Clin Oncol*, **28**, 92-8.
- Dillman RO, Herndon J, Seagren SL, et al (1996). Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst*, **88**, 1210-5.
- Dillman RO, Seagren SL, Probert KJ, et al (1990). A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med*, **323**, 940-5.
- Douillard J, Cunningham D, Roth A, et al (2000). Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *The Lancet*, **355**, 1041-7.
- Edge SB, Compton CC (2010). The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol*, **17**, 1471-4.
- Ezzati M, Henley SJ, Lopez AD, et al (2005). Role of smoking in global and regional cancer epidemiology: current patterns and data needs. *Int J Cancer*, **116**, 963-71.
- Ezzati M, Lopez AD (2003). Estimates of global mortality attributable to smoking in 2000. *The Lancet*, **362**, 847-52.
- Fakih M (2008). Management of anti-EGFR-targeting monoclonal antibody-induced hypomagnesemia. *Oncol*, **22**, 74-6.
- Fang W-J, Zheng Y, Wu L-M, et al (2012). Genome-wide analysis of aberrant DNA methylation for identification of potential biomarkers in colorectal cancer patients. *Asian Pac J cancer Prev*, **13**, 1917-21.
- Ferber M, Montoya D, Yu C, et al (2003). Integrations of the hepatitis B virus (HBV) and human papillomavirus (HPV) into the human telomerase reverse transcriptase (hTERT) gene in liver and cervical cancers. *Oncogene*, **22**, 3813-20.
- Ferlay J, Shin HR, Bray F, et al (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, **127**, 2893-917.
- Firestein R, Shima K, Noshio K, et al (2010). CDK8 expression in 470 colorectal cancers in relation to β -catenin activation, other molecular alterations and patient survival. *Int J Cancer*, **126**, 2863-73.
- Fisher B, Brown AM, Dimitrov NV, et al (1990). Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate, and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. *J Clin Oncol*, **8**, 1483-96.
- Fossella F (2001). Docetaxel+Cisplatin (DC) and Docetaxel +Carboplatin (DCCb) vs Vinorelbine+Cisplatin (VC) in chemotherapy -naive patients with advanced and metastatic non-small cell lung cancer (NSCLC): Results of a multicenter, randomized phase III study. *Eur J Cancer*, **37**, 154.
- Fossella F, Pereira JR, von Pawel J, et al (2003). Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: The TAX 326 study group. *J Clin Oncol*, **21**, 3016-24.
- Fuqua SA (2001). The role of estrogen receptors in breast cancer metastasis. *J Mammary Gland Biol*, **6**, 407-17.
- Ge Y-Z, Xu L-W, Jia R-P, et al (2014). The association between RASSF1A promoter methylation and prostate cancer: evidence from 19 published studies. *Tumor Biol*, **35**, 3881-90.
- Gibson RJ, Keefe DM, Lalla RV, et al (2013). Systematic review of agents for the management of gastrointestinal mucositis in cancer patients. *Support Care Cancer*, **21**, 313-26.
- Gotzsche P, Nielsen M (2011). Screening for breast cancer with mammography. *Cochrane Database Syst Rev*, **1**, 1877.
- Gutman M, Couillard S, Roy J, et al (2002). Comparison of the effects of EM-652 (SCH57068), tamoxifen, toremifene, droloxifene, idoxifene, GW-5638 and raloxifene on the growth of human ZR-75-1 breast tumors in nude mice. *Int J Cancer*, **99**, 273-8.
- Halliwell B (1994). Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *The Lancet*, **344**, 721-4.
- Hamedeyazdan S, Fathiazad F, Sharifi S, et al (2012). Antiproliferative activity of Marrubium persicum extract in the MCF-7 human breast cancer cell line. *Asian Pac J Cancer Prev*, **13**, 5843-8.
- Hashibe M, Brennan P, Chuang S-c, et al (2009). Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Cancer Epidem Biomar*, **18**, 541-50.
- Hoff PM, Ansari R, Batist G, et al (2001). 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*, **19**, 2282-92.
- Holmes EC, Gail M (1986). Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. *J Clin Oncol*, **4**, 710-5.
- Huber MA, Kraut N, Beug H (2005). Molecular requirements for epithelial-mesenchymal transition during tumor progression. *Curr Opin Cell Biol*, **17**, 548-58.
- Hutchins LF, Green SJ, Ravdin PM, et al (2005). Randomized, controlled trial of cyclophosphamide, methotrexate, and fluorouracil versus cyclophosphamide, doxorubicin, and fluorouracil with and without tamoxifen for high-risk, node-negative breast cancer: treatment results of Intergroup Protocol INT-0102. *J Clin Oncol*, **23**, 8313-21.
- Huxley RR, Ansary-Moghaddam A, Clifton P, et al (2009). The impact of dietary and lifestyle risk factors on risk of colorectal cancer: a quantitative overview of the epidemiological evidence. *Int J Cancer*, **125**, 171-80.
- Imamura Y, Morikawa T, Liao X, et al (2012). Specific mutations in KRAS codons 12 and 13, and patient prognosis in 1075 BRAF wild-type colorectal cancers. *Clin Canc Res*, **18**, 4753-63.
- Izadi P, Mehrdad N, Foruzandeh F, et al (2012). Association of poor prognosis subtypes of breast cancer with estrogen receptor alpha methylation in Iranian women. *Asian Pac J Cancer Prev*, **13**, 4113-7.
- Jarzabek K, Koda M, Kozlowski L, et al (2009). The significance of the expression of ERR α as a potential biomarker in breast cancer. *J Steroid Biochem*, **113**, 127-33.
- Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. *Ca Cancer J Clin*, **61**, 69-90.
- Jemal A, Center MM, DeSantis C, et al (2010). Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidem Biomar*, **19**, 1893-907.
- Jemal A, Siegel R, Ward E, et al (2009). Cancer statistics, 2009. *Ca Cancer J Clin*, **59**, 225-49.
- Jones S, Holmes FA, O'Shaughnessy J, et al (2009). Docetaxel with cyclophosphamide is associated with an overall survival

- benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. *J Clin Oncol*, **27**, 1177-83.
- Karaca H, Deniz K, Berk V, et al (2012). Association of human epidermal growth factor receptor-2 expression and clinicopathological findings in patients with colorectal cancer. *Asian Pac J Cancer Prev*, **13**, 6221-5.
- Keller S, Vangel M, Adak S, et al (2000). A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. *N Engl J Med*, **343**, 1217-22.
- Kelloff GJ, Schilsky RL, Alberts DS, et al (2004). Colorectal adenomas a prototype for the use of surrogate end points in the development of cancer prevention drugs. *Clin Cancer Res*, **10**, 3908-18.
- Khan N, Afroz F, Lone M, et al (2006). Profile of lung cancer in Kashmir, India: a five-year study. *Indian J Chest Dis Allied S*, **48**, 187-90.
- Krop IE, LoRusso P, Miller KD, et al (2012). A phase II study of trastuzumab emtansine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer who were previously treated with trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine. *J Clin Oncol*, **30**, 3234-41.
- Kuebler JP, Wieand HS, O'Connell MJ, et al (2007). Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol*, **25**, 2198-204.
- Kumar P, Bolshette NB, Jamdade VS, et al (2013). Breast cancer status in India: An overview. *Biomed Prev Nutr*, **3**, 177-83.
- Lad T, Rubinstein L, Sadeghi A (1988). The benefit of adjuvant treatment for resected locally advanced non-small-cell lung-cancer. *J Clin Oncol*, **6**, 9-17.
- Larsson SC, Orsini N, Wolk A (2005). Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst*, **97**, 1679-87.
- Leber MF, Effertz T (2009). Molecular principles of cancer invasion and metastasis. *Int J Oncol*, **34**, 881-95.
- Levin B, Lieberman DA, McFarland B, et al (2008). Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology*. *Ca Cancer J Clin*, **58**, 130-60.
- Levine M, Bramwell V, Pritchard K (1998). Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. *J Clin Oncol*, **16**, 2651-8.
- Li H-Y, Zhang Y, Cai J-H, et al (2013). MicroRNA-451 inhibits growth of human colorectal carcinoma cells via downregulation of Pi3k/Akt pathway. *Asian Pac J Cancer Prev*, **14**, 3631-4.
- Li X, Hemminki K (2004). Inherited predisposition to early onset lung cancer according to histological type. *Int J Cancer*, **112**, 451-7.
- Liao X, Lochhead P, Nishihara R, et al (2012). Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *New Engl J Med*, **367**, 1596-606.
- Liu W-J, Tan X-H, Guo B-P, et al (2013). Associations between RASSF1A promoter methylation and NSCLC: a meta-analysis of published data. *Asian Pac J Cancer Prev*, **14**, 3719-24.
- Livingston R, Moore T, Heilbrun L, et al (1978). Small-cell carcinoma of the lung: combined chemotherapy and radiation: a southwest oncology group study. *Ann Intern Med*, **88**, 194-9.
- Lokich JJ, Ahlgren JD, Gullo JJ, et al (1989). A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. *J Clin Oncol*, **7**, 425-32.
- Mancini M, Anderson BO, Caldwell E, et al (1997). Mitochondrial proliferation and paradoxical membrane depolarization during terminal differentiation and apoptosis in a human colon carcinoma cell line. *J Cell Biol*, **138**, 449-69.
- Martin-Martorell P, Rosello S, Rodriguez-Braun E, et al (2008). Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer*, **99**, 455-8.
- Matakidou A, Eisen T, Houlston R (2005). Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer*, **93**, 825-33.
- McPherson K, Steel C, Dixon J (2000). ABC of breast diseases: breast cancer-epidemiology, risk factors, and genetics. *BMJ: Br Med J*, **321**, 624-8.
- Melosky B, Burkes R, Rayson D, et al (2009). Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. *Curr Oncol*, **16**, 14-24.
- Mimi CY, Yuan J-M (2004). Environmental factors and risk for hepatocellular carcinoma. *Gastroenterol*, **127**, 72-S8.
- Montesano R, Hall J (2001). Environmental causes of human cancers. *Eur J Cancer*, **37**, 67-87.
- Morikawa T, Kuchiba A, Liao X, et al (2012). Tumor TP53 expression status, body mass index and prognosis in colorectal cancer. *Int J Cancer*, **131**, 1169-78.
- Murray N, Coy P, Pater JL, et al (1993). Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, **11**, 336-44.
- Naeem M, Khan N, Aman Z, et al (2008). Pattern of breast cancer: experience at lady reading hospital, peshawar. *J Ayub Med Coll Abbottabad*, **20**, 22-5.
- Nakatsumi H, Komatsu Y, Yuki S, et al (2013). Optimal dose period for ondansetron tablets for preventing chemotherapy-induced nausea and vomiting with modified FOLFOX6: A randomized pilot study. *Chemother*, **58**, 439-44.
- Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*, **118**, 3030-44.
- Perez EA, Rodeheffer R (2004). Clinical cardiac tolerability of trastuzumab. *J Clin Oncol*, **22**, 322-9.
- Pfeiffer P, Nielsen D, Bjerregaard J, et al (2008). Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. *Ann of Oncol*, **19**, 1141-5.
- Pieterman RM, van Putten JW, Meuzelaar JJ, et al (2000). Preoperative staging of non-small-cell lung cancer with positron-emission tomography. *New Engl J Med*, **343**, 254-61.
- Pietras RJ, Pegram MD, Finn RS, et al (1998). Remission of human breast cancer xenografts on therapy with humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs. *Oncog*, **17**, 2235-49.
- Peters WA, Liu P, Barrett RJ, et al (2000). Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*, **18**, 1606-13.
- Rosell R, Gomez-Codina J, Camps C, et al (1999). Preresectional

- chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer*, **26**, 7-14.
- Rosell R, Gomez-Codina J, Camps C, et al (1994). A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *New Engl J Med*, **330**, 153-8.
- Roth J, Fossella F, Komaki R (1994). A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *J Natl Cancer Inst*, **86**, 673-80.
- Roth JA, Atkinson EN, Fossella F, et al (1998). Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer*, **21**, 1-6.
- Rougier P, Van Cutsem E, Bajetta E, et al (1998). Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *The Lancet*, **352**, 1407-12.
- Saltz LB, Cox JV, Blanke C, et al (2000). Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *New Engl J Med*, **343**, 905-14.
- Sariego J (2010). Breast cancer in the young patient. *Am Surgeon*, **76**, 1397-401.
- Scagliotti G, De Marinis F, Rinaldi M, et al (2002). Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol*, **20**, 4285-91.
- Scheithauer W, McKendrick J, Begbie S, et al (2003). Oral capecitabine as an alternative to iv 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. *Ann Oncol*, **14**, 1735-43.
- Schiller JH, Harrington D, Belani CP, et al (2002). Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *New Engl J Med*, **346**, 92-8.
- Schoen RE, Pinsky PF, Weissfeld JL, et al (2012). Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. *New Engl J Med*, **366**, 2345-57.
- Schreck R, Albermann K, Baeuerle PA (1992). Nuclear factor κ B: an oxidative stress-responsive transcription factor of eukaryotic cells (a review). *Free Radical Res*, **17**, 221-37.
- Shepherd FA, Dancey J, Ramlau R, et al (2000). Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol*, **18**, 2095-103.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al (2005). Erlotinib in previously treated non-small-cell lung cancer. *New Engl J Med*, **353**, 123-32.
- Siegel R, DeSantis C, Virgo K, et al (2012). Cancer treatment and survivorship statistics, 2012. *Ca Cancer J Clin*, **62**, 220-41.
- Siegel R, Naishadham D, Jemal A (2013). Cancer statistics, 2013. *Ca Cancer J Clin*, **63**, 11-30.
- Sohail S, Alam SN (2007). Breast cancer in Pakistan-awareness and early detection. *J College Physicians Surgeons Pakistan*, **17**, 711-2.
- Soong D, Hag R, Leung M (2009). High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. *J Clin Oncol*, **27**, 101-2.
- Sparano J, Wang M, Martino S, et al (2007). Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: results of Intergroup Trial E1199. *J Clin Oncol*, **25**, 516.
- Stapel J, Oppermann C, Richter D, et al (2013). Polyphenol compounds with anti-carcinogenic qualities: Effects of quercetin (flavonol), chrysin (flavon), kaempferol (flavanol), naringenin (flavanon) and hesperidin (flavanoid) on in vitro breast cancer. *J Med Plants Res*, **7**, 2187-96.
- Suganya J, Radha M, Naorem DL, et al (2014). In Silico Docking Studies of Selected Flavonoids-Natural Healing Agents against Breast Cancer. *Asian Pac J Cancer Prev*, **15**, 8155-9.
- Thomas C, Gustafsson J-A (2011). The different roles of ER subtypes in cancer biology and therapy. *Nature Rev Cancer*, **11**, 597-608.
- Toniti W, Suthiyotha N, Puchadapirom P, et al (2011). Binding capacity of ER-alpha ligands and SERMs: comparison of the human, dog and cat. *Asian Pac J Cancer Prev*, **12**, 2875-9.
- Tunio MA, Rafi M, Hashmi A, et al (2010). High-dose-rate intraluminal brachytherapy during preoperative chemoradiation for locally advanced rectal cancers. *World J Gastroenterol*, **16**, 4436.
- Uncu D, Aksoy S, Cetin B, et al (2013). Results of adjuvant FOLFOX regimens in stage III colorectal cancer patients: retrospective analysis of 667 patients. *Oncol*, **84**, 240-5.
- Valko M, Leibfritz D, Moncol J, et al (2007). Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell B*, **39**, 44-84.
- Van Cutsem E, Peeters M, Siena S, et al (2007). Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol*, **25**, 1658-64.
- Van Moorsel CJ, Peters GJ, Pinedo HM (1997). Gemcitabine: future prospects of single-agent and combination studies. *The Oncologist*, **2**, 127-34.
- Vandenberg T, Younus J, Al-Khayyat S (2010). Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice-a retrospective analysis. *Curr Oncol*, **17**, 2-3.
- Verma S, Miles D, Gianni L, et al (2012). Trastuzumab emtansine for HER2-positive advanced breast cancer. *New Engl J Med*, **367**, 1783-91.
- Waris G, Ahsan H (2006). Reactive oxygen species: role in the development of cancer and various chronic conditions. *J Carcinogen*, **5**, 14.
- Wasserman E, Myara A, Lokiec F, et al (1997). Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. *Ann Oncol*, **8**, 1049-51.
- Watson J (2013). Oxidants, antioxidants and the current incurability of metastatic cancers. *Open Biol*, **3**, 120144.
- Wilke H, Glynne-Jones R, Thaler J, et al (2008). Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. *J Clin Oncol*, **26**, 5335-43.
- Winton T, Livingston R, Johnson D, et al (2005). Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *New Engl J Med*, **352**, 2589-97.
- Wolin K, Yan Y, Colditz G, et al (2009). Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer*, **100**, 611-6.
- Xu C-Y, Jiang Z-N, Zhou Y, et al (2013). Estrogen receptor α roles in breast cancer chemoresistance. *Asian Pac J Cancer Prev*, **14**, 4049.
- Xu H-X, Huang X-E, Qian Z-Y, et al (2011). Clinical observation of Endostar® combined with chemotherapy in advanced colorectal cancer patients. *Asian Pac J Cancer Prev*, **12**, 3087-90.
- Yager JD, Davidson NE (2006). Estrogen carcinogenesis in breast cancer. *New Engl J Med*, **354**, 270-82.
- Yang Y, Zhang X, Yang M, et al (2014). Prognostic role of nucleophosmin in colorectal carcinomas. *Asian Pac J Cancer*

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Prev, **15**, 2021-6.

- Zatloukal P, Petruzelka L, Zemanová M, et al (2003). Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. *Lung Cancer*, **41**, 321-31.
- Zauber AG, Winawer SJ, O'Brien MJ, et al (2012). Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *New Engl J Med*, **366**, 687-96.
- Zhang H-Q, Lian C-H, Ping Y-D, et al (2014). Pemetrexed is mildly active with good tolerability for treatment of patients with colorectal cancer. *Asian Pac J Cancer Prev*, **15**, 8391-4.