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

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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 leads 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 particularly 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(peroxyl, alkoxyl, 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).	Deeaths 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; Dawood 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, Isofavonoids) have been approved for having anticancer activity. Vegetables, cereals, tea, red wine, legumes ad 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)cyclophos-phamide	60 mg/m² 600 mg/m²	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)cyclophos-phamide iii)PACLitaxel	60 mg/m² 600 mg/m² 175 mg/m²	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) DOXOubicin ii) fluorouracil iii)cyclophos-phamide iv) filgrastim (G-CSF)	30 mg/m² Days 1 and 15 500 mg/m² Days 1 and 15 700 mg/m² 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) cyclophos-phamide iv) filgrastim (G-CSF)	60 mg/m² /day on Days 1 and 15 500 mg/m² /day on Days 1 and 15 525 mg/m² /day on days 1and 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/sub-sequent 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 subse-quent.	Repeat every 21 days x 17 cycles	(Perez and Rodeheffer, 2004)

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

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)	
Double-contrast Barium Enema	Chemotherapy (mostly used)and radioherapy	
	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 4rth 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 fuorouracil, oxalipatin, irinotecan, cetuximab, 5-FU. These agents may be used alone or in combination form such as FOLFIRI, FOLFOX, XELOX, irinotecan/ oxalipatin 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 (Uncu 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 docetaxe 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 Balamugesh, 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/ 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, Fiber-optic 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).

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