Review Article

"Insight in to Squamous Cell Carcinoma of Head and Neck Region: Current Statistics"

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Abstract

Background: Literature wires a rise in incidence of oral cancer despite advancements in the diagnostic modalities and technologies. For centuries it was believed to be the disease of elderly age group but recently this has increased in the early age group males specially. Methodology: This review critically examines many publications devoted to squamous cell carcinoma's risk factors, diagnostic and prognostic markers. All the data from the last ten years with latest updates has is being organized and statistics presented.

Observations and Results: Striking reports are evident that younger individuals who have never smoked or consumed alcohol, which are recognized risk factors in older groups, or the consumption and duration of exposure of the risk factors are too short for malignant transformation are still suffering from this fatal disease. The information on etiological factors of this disease including occupational, familial risk, immune deficits and virus infections are insufficient. The genetic abnormality seen in the younger age group is seen to be similar to that of the older age group although the studies supporting this evidence are rare; however, there is a conflict in regards to gender distribution.

Conclusion: Knowledge of the global demography, current statistics and risk factors, diagnostic and prognostic markers is very important in order to accelerate further progress in this field, improvise effective prognostic system and anticancer therapy and reduce the mortality rates.

Keywords: Squamous cell carcinoma; Head and Neck; Prevalence; Morbidity; Ethnicity; Statistics; Carcinogenesis; Dysplasia

Introduction

Squamous cell carcinoma is defined as, "a malignant neoplasm of stratified squamous epithelium that is capable of locally destructive growth and distant metastasis" [1].

Head and neck squamous cell carcinomas (HNSCC's) make up the vast majority of head and neck cancers, and arise from mucosal surfaces throughout this anatomic region. These include tumors of the nasal cavities, paranasal sinuses, oral cavity, nasopharynx, oropharynx, hypopharynx and larynx [2].

The cause of SCC is multifactorial [3], no single causative factor has been clearly defined. Both intrinsic and extrinsic factors have been seen to play an important role [4].

Incidence and prevalence

In developed countries, oral cancer is less common but is the sixth most common form of cancer overall [1]; however, the incidence varies great deal among countries [7,8]. The annual age-adjusted incidence rates per 100 000 in several European countries vary from 2.0 (UK, south Thames Region) to 9.4 in France. In the Americas the incidence rates vary from 4.4 (Cali, Colombia) to 13.4 in Canada [9]. During the period of four years i.e., from 2004 to 2008, the average incidence of oral cancer in U.S alone was estimated to be 10.6 cases per 100,000 persons per year [10]. However, it is expected to increase as it is reported that in the United States alone in 2014 there

will be 42,440 new cases of oral cancer and 8,390 deaths due to the same [11]. The incidence is high in south central Asia and Melanesia countries and is attributable to excessive betel quid chewing whereas in Australia it is due to solar irradiation [12]. In Asia, it ranges from 1.6 (Japan) to 13.5 (India). In Australia and New Zealand, it varies from 2.6 (New Zealand - Maori) to 7.5 in South Australia. In Papua New Guinea, in the Lowlands and the Highlands the incidence per 100 000 among men was 6.8 and 1.0 and among women 3 and 0.4, respectively. In Iran the incidence was reported to be 1.1 per 100 000 per year [13,14]. In India, oral cancer represents up to 50% of all cancers [15], compared to just 4% in the UK [7]. In Pakistan, the prevalence of oral SCC is from 7- 9.94 [16] and it represents 8.55% of all the cancers [16].

Mortality/Morbidity

Mortality rates for oral squamous cell carcinoma (OSCC) have increased, primarily in many East European countries [9]. In Germany, Czech Republic and Hungary, almost a 10-fold increase in mortality from oral cancer in men aged 35-44 years occurred within one generation [17]. Systematic analyses of cancer mortality data for 28 European countries showed pronounced upward trends in oral cancer mortality in persons aged 35-64 years from 1955-1989 [9]. Inspection of age-specific mortality rates revealed substantial increases at younger ages in most European countries, thus indicating the existence of strong cohort effects that will lead to increasing levels of oral cancer among males during future decades. The recently

estimated mortality rate of U.S from 2003-07 are 2.5 per 100,000 persons per year [11].

Signs and symptoms

Squamous cell carcinoma has a number of different clinical presentations [18]. The most common early presentations of intraoral squamous cell carcinomas are leukoplakia and erythroplakia [19]. The more advance lesions may first appear as painless ulcer, reddish skin, a tumorous mass, or a verrucous (papillary) growth with intermittent bleeding [20]. Squamous cell carcinoma that has penetrated deep into the connective tissue may have few surface changes but appears as firm indurated area with associated loss of tissue mobility [21]. On the floor of the mouth this commonly causes fixation of the tongue or inability to fully open the mouth [22]. Carcinoma that arises from the gingiva invades into the underlying bone of maxilla or mandible and can result in loosening or loss of teeth [23]. If nerve is involved by the tumor, it causes paresthesias of that area [24]. The tumor commonly presents on sun-exposed areas (e.g. back of the hand, scalp, lip, and superior surface of pinna) [25,26]. Evidence of chronic skin photodamage, such as multiple actinic keratoses (solar keratoses) can be seen [27]. Cervical lymph node enlargement and hardness is present in case of metastasis [28].

Demographic factors (Sex, Age and Race Distribution)

Oral cancer predominantly affects men [14,29]. The sex differences in some population groups could be a direct consequence of the sex distribution of certain habits like tobacco and alcohol usage [30]. In U.S males are affected 2.5-2.8 times higher than females [10]. In South African Blacks, a high male: female ratio (7:1) was reported which has been related to the differences in tobacco usage between the sexes [29,31]. In Pakistan, there was a male predominance with a ratio of 1.5:1 [32]. SCCs affect the individuals in the higher age group, most of the patients being over the age of 40 [33]. The peak occurrence, however, varies in different population groups. In Western countries the peak occurrence is in the sixth and seventh decade, whereas in Asia it is generally earlier [34]. In Iran and India, the peak occurrence appears to be in the fifth and sixth decades [14]. In Pakistan, the peak occurrence is in the 4th-6th decades of their age group [16]. The load of SCCHN is seen greater for blacks' race than for whites, especially in oropharyngeal cases [35]. This is the reason that disease free survival rate is reported to be greater in white patients than black [36]. This is likely attributable to HPV-related cancer at this subsite in black ethnicity is more keeping the treatment and staging factors under control [37]. Another study however demonstrates no disparity between the Chinese and the White patients [38].

Extrinsic factors (Tobacco & Alcohol)

The habitual use of tobacco in its various forms for example, cigarettes, cigars, pipe tobacco and quid are reported to be important factors associated with the transformation of normal mucosal epithelial cells to squamous cell carcinoma [38-40]. Snuff and chewing tobacco are also associated and implicated. Tobacco chewing in people from parts of Asia appears to predispose to OSCC, particularly when it is started early in life and is used frequently and for prolonged periods [41]. Studies from India have confirmed the association between tobacco chewing and OSCC, particularly cancer of the buccal and labial mucosa [42]. It has been seen that 8 out of every 10 patients with oral cancer are long term heavy smokers. Compared

with persons who do not smoke, the risk of oral cancer in persons who smoke low/medium-tar cigarettes and high-tar cigarettes was 8.5 and 16.4 fold greater, respectively [9]. (Note that cigarettes are classified as low/medium if the tar yield is less than 22 mg and high tar if the tar yield is greater than 22 mg).

Betel quid contains a variety of ingredients, including betel vine leaf, betel (areca) nut, catechu, and, often, slaked lime together with tobacco. Some persons chew the nut only, and others prefer paan, which includes tobacco and sometimes lime and catechu [43]. In 1986, the International Agency for Research on Cancer has deemed betel-quid chewing an important risk factor, and the areca (betel) nut habit with or without tobacco use can cause cytogenetic changes in oral epithelium [9].

Excessive alcohol consumption has been implicated in oral cancer development [44]. It is uncertain that alcohol can alone initiate carcinogenesis, although it is well established that alcohol in combination with tobacco is a significant factor for oral cancer development [45]. Heavy tobacco smokers have a 20-fold greater risk; heavy alcohol drinkers a 5-fold greater risk and those who do both have a 50-fold greater risk [46].

The incidence of head and neck carcinoma is undoubtedly associated with the use of ethanol [47]. In 1998, the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) concluded that evidence was sufficient to show that alcoholic beverages are carcinogenic in humans.[48] Growing evidence is associating increased alcohol consumption with the risk of developing OSCC [1,49].

Sun exposure

Sun exposure is causally linked to squamous cell carcinoma of the skin, as well as to melanoma and basal cell carcinoma [50]. Radiation causes DNA damage in the following 3 ways: directly (breaks DNA), indirectly through changes in oxidative enzyme systems (buildup of free radicals damages DNA), and indirectly to DNA repair mechanisms (causes faulty DNA) [51]. Similarly, irradiation has been shown to increase the risk for radiation-related sarcomas and thyroid cancer [52]. The component of sunlight believed to be most important in cutaneous carcinogenesis is UVB (290-320 nm) [53], which is both an initiator and a promoter of carcinogenesis. In animal models, UV-induced photo carcinogenesis appears to involve the UVB and UVA-2 spectral ranges [54].

Occupational hazards

Numerous studies have been undertaken to ascertain the risks of head and neck cancer associated with various occupations and exposures. Studies have demonstrated that individuals working in the heavy-metal, textile, or electronic industry or those exposed to asbestos or wood dusts have increased cancer risks [55-57].

Intrinsic factors (Nutritional deficiencies)

Nutritional deficiencies like severe, chronic form of iron deficiency are associated with an increased risk of SCC of esophagus, oropharynx and posterior mouth [58]. Similarly vitamin A deficiency produces excessive keratinization of skin and mucous membrane and it is suggested that vitamin A plays an important role in preventive

and protective role in oral precancerous and cancerous lesions [59]. The role of nutritional status as a single factor is difficult to ascribe with certainty, so it is often associated with numerous cofounders, such as tobacco exposure, lifestyle-related viral exposure, alcohol use and oral hygiene [9].

Genetic factors

In oral squamous cell carcinoma (OSCC), modern DNA technology, especially allelic imbalance (loss of heterozygosity) studies, have identified chromosomal changes suggestive of the involvement of tumor suppressor genes (TSGs), particularly in chromosomes 3, 9, 11, and 17 [60]. Functional TSGs seem to assist growth control, while their mutation can unbridle these control mechanisms. Most commonly identified TSGs are:-

TSG termed *P16* on chromosome 9

TSG termed *TP53* on chromosome 17

As well as damage to TSGs, cancer may also involve damage to other genes involved in growth control, mainly those involved in cell signaling (oncogenes), especially some on chromosome 11 (*PRAD1* in particular) and chromosome 17 (Harvey ras [H-*ras*]). Changes in these and other oncogenes can disrupt cell growth control, ultimately leading to the uncontrolled growth of cancer [60,61].

Genetic profiles are associated with an increased susceptibility for oral carcinoma [62]. Patients with xeroderma pigmentosum, polydysplastic epidermolysis bullosa or Bloom syndrome are at increased risk for oral cancer [63]. These conditions are fairly uncommon. Familial associations of head and neck cancers have been investigated. Studies have demonstrated many cases of head and neck cancers, and a case report describes identical twins with oral carcinoma [63].

Human Papilloma Virus (HPV) & Epstein Bar Virus (EBV)

One of the most exciting developments in oncology within the last 20 years is the investigation of viral oncogenesis [64,65]. In head and neck cancer, EBV and human papilloma virus (HPV) are seen to be prominent. HPV has been demonstrated to be a cause of cancer in pharyngeal tonsils, larynx, esophagus, uterine cervix, vulva and penis. HPV subtypes 16, 18, 31, 33 and 35 are closely associated with dysplasia and SCC [66,67].

Chemical carcinogens

Chemical carcinogens like arsenic are a well-established cause of cutaneous squamous cell carcinoma and internal cancers [68]. Today, the main source of arsenic is contaminated well water, although arsenic may also be found in traditional Chinese medicines [69]. Other carcinogens associated with squamous cell carcinoma include polycyclic aromatic hydrocarbons such as tar, soot, and pitch [9].

Other factors

Chronic irritation due to ill-fitting dentures has shown an association with oral cancer. Precisely defining the role of poor oral hygiene in SCC of the oral cavity is difficult; however, they are associated. Some studies have demonstrated an association with ill-fitting dentures with oral cancer [33,70].

Healthy human skin is constantly repairing UV-induced damage through DNA repair mechanisms. If DNA repairs failure occurs, as in patients with Xeroderma pigmentosum, due to a deficiency in an enzyme essential for normal DNA repair, individuals become more prone to develop innumerable squamous cell carcinomas, and, less commonly, other cutaneous tumors [9,71].

The use of immunosuppressive medications to prevent rejection in organ transplant rejection is associated with a 65- to 250-fold increased risk of developing squamous cell carcinoma compared with the general population [72].

Defects in cell-mediated immunity related to lympho-proliferative disorders predispose to the development of aggressive squamous cell carcinoma. The specific mechanisms by which immune suppression leads to squamous cell carcinoma development are poorly understood, but diminished immune surveillance is thought to be critical. CD8$^+$ T cells specific for the tumor suppressor gene TP53 have been observed in patients with squamous cell carcinoma, suggesting that a functional immune system may target keratinocytes expressing mutated TP53. Suppression of the immune system would presumably abrogate this response and might be expected to facilitate the development of squamous cell carcinoma [9].

Chronic infections have been associated with squamous cell carcinoma [9,73]. Chronic inflammation, irrespective of the underlying etiology, may lead to the development of squamous cell carcinoma. Both non-infectious inflammatory diseases and

Prognostic factors

Multiple factors are involved in determining the prognosis and there is no single marker which can accurately predict the final results. It is maybe due to the fact that the tumor development is a multifactorial and multistep process and therefore requires multiple markers. Still today the clinical studies for assessing the definitive usefulness of the biological marker has been slow and ineffective and therefore lacking the definitive implementation of it into our practices [74].

DNA microarray technologies is been used successfully in oral cancers along with many other cancers to assess the RNA expression, however it has a limitation of only analyzing the transcriptome and not the proteins who are the mediators of the biological functions, furthermore RNA levels does not always correlate with the proteins levels [75-77]. Other methods introduced recently are 2-D gel electrophoresis and mass spectrometry. They are used to study the salivary proteome; patterns have been established with the predicted outcomes [78,79]. The body fluid proteomic analysis has already been established therefore the health status, early diagnosis of the disease and its characterization can be monitored. In addition to this salivary biomarkers have been studied and can be of value for determining the links between the systemic diseases and the salivary proteins. Proteomic analysis of saliva has been done for since last two decades and over 100 such biomarkers are reported in the literature as potential salivary biomarkers for OSCC. Although this technique is relatively easy and non-invasive for diagnostic and health surveillance purposes it has its own limitations too. There is a lack of standardization in sample collecting, its processing and storage. Also there is wide variability in the levels of OSCC biomarkers and non-cancerous patients' biomarkers. There is a need of validation of salivary markers for the OSCC, especially for individuals having chronic inflammatory oral disease and other types of cancers but not OSCC [74].

Histological appearance

- The histological appearance of a usual invasive SCC varies with the degree of differentiation. In common to all are the following [80] Atypical squamous cells with enlarged, angulated nuclei.

- Increased nuclear-cytoplasmic ratio.

- Evidence of keratinization, more in well-differentiated and less in poorly differentiated lesions.

- Intercellular bridges or cytoplasmic projections that radiate outward from the cytoplasm and connect adjacent cells.

- Increased mitotic figures: No specific number is diagnostic of malignancy.

- Atypical mitotic figures: These are mitotic figures that do not fit into any of the known phases of cell division. Even anaphase-like mitotic figures demonstrate multipolarity, whereas normal cell division has 2 poles that the genetic material is oriented toward; atypical mitotic figures may have 3 or more poles.

- Hyperchromasia: The nuclei are darkly staining because of increased ploidy.

- Invasion below the usual level of the basement membrane: This may be in a large pushing front of dozens of cohesive squamous cells. It also may invade as small cell nests containing 5-10 cells per cluster, often with an elongated stabbing pattern. Finally, individual cells may be percolating through the stroma.

- Inflammation: Invasive carcinomas almost always have a surrounding and/or intermingling inflammatory response. This response may be exclusively of one cell type, eg, lymphocytes or plasma cells, or it may be a mixture of any combination of cells, including macrophages, neutrophils, eosinophils, lymphocytes, and plasma cells.

Histopathological characterization

The histopathological characterization of this interesting neoplasm also merits recognition as one of the more complicated and controversial in medical history. Although the 1991 classification of the World Health Organization (WHO) is now universally recognized, this lesion has been extensively recategorized and renamed throughout its history [81].

Broadly SCC is classified as well differentiated, moderately differentiated and poorly differentiated. It is also called grading [82, 83].

Grade I Well differentiated < 25% undifferentiated cells.

Grade II Moderately differentiated < 50% undifferentiated cells.

Grade III Poorly differentiated < 75% undifferentiated cells.

Grade IV Undifferentiated > 75% undifferentiated cells.

Features indicating a well differentiated squamous carcinoma include the presence of large islands of infiltrating tumor cells with inter-cellular bridges, epithelial pearl formation and obvious keratinization of cell cytoplasm. Moderately differentiated carcinoma show consists of solid islands and smaller groups of polygonal cells. Keratinization and bridges are seen but are less obvious and pearl formation is not seen. Poorly differentiated carcinoma invades as sheets, islands and single cells. No definite squamous features are seen [82].

The current system has been further simplified as follows: (1) SCC (keratinizing SCC) or (2) nonkeratinizing carcinoma, which is subdivided as (a) differentiated or (b) undifferentiated [84].

Treatment

Several methods for treatment of cancer of the head and neck are acceptable, including surgery, radiotherapy, chemotherapy, new molecularly targeted agents and combinations of these [85]. New investigative treatments include immunotherapy and gene therapy [86,87]. Factors that influence the choice of treatment are the site, grade, and stage of the primary tumor; patient age and general medical condition [88]. Goals of treatment generally consist of removal of cancer load, maintenance of quality of life, and prevention of subsequent primary tumors [89].

Medical therapy

Curettage and cautery/electrodesiccation [90,91]: Performed using a curette to remove soft material from the tumour. The base of the tumour is then destroyed, using cautery. This may be used to treat small (less than 1 cm) in situ SCCs and precancerous lesions. It is safe and well tolerated, and usually produces a good cosmetic outcome. It is suitable for patients with multiple lesions.

The histology may be difficult to interpret as the lesion may be incompletely removed and margins of excision cannot be assessed optimally.

Cryotherapy/cryosurgery [92,93]**:** Is a cost-effective treatment and is well established for small in situ SCCs and precancerous lesions. Histology is not available unless an incisional biopsy is taken first.

Topical treatment [94-99]:

Imiquimod 5% cream is effective in treating actinic keratosis.

Fluorouracil (Efudix® 5% cream) is licensed for 'superficial malignant and precancerous skin lesions'.

Diclofenac 3% gel is licensed for the treatment of actinic keratoses.

Photodynamic therapy (PDT) [100,101]:

- Involves the use of light therapy in combination with a topical photosensitising agent to destroy cancer cells.

- Is used in the treatment of in situ SCCs and actinic keratosis.

- Evidence of efficacy for treating invasive squamous cell carcinomas is limited, recurrence rates are high, there is a risk of metastasis and retreatment may be necessary.

Radiotherapy

Nearly all patients with advanced disease require adjuvant radiotherapy, preoperatively or postoperatively. Preoperative radiotherapy has the risk of increased complications of surgery. Radiation dosage in excess of 6000 cGy is recommended with a boost to areas of high risk [102].

Indications for radiotherapy include a bulky tumor with significant risk of recurrence (T3 and T4), histologically positive margins, and perineural or perivascular invasion of tumor. For the neck, indications for radiotherapy include elective treatment of the N0 neck not treated surgically where risk of micrometastasis is high, gross residual tumor in the neck following neck dissection, multiple positive lymph nodes, and extranodal extension of tumor [103,104].

Chemotherapy

Adaptation of traditional chemotherapeutics to local and regional administration techniques in treating head and neck cancers is being actively pursued to provide higher local concentrations of otherwise systemically toxic drugs. Bleomycin with or without electroporation has been used [105].

Cisplatin is another chemotherapeutic drug of choice for head and neck cancers. Although cisplatin is one of the most successful agents in the treatment of cancer, it produces major toxicities to normal cells and organs at the concentrations necessary for effective treatment of malignancies. A combination of cisplatin with interstitial laser therapy has been reported. Hyperthermia produced by the laser is known to augment the cytotoxic effects of both radiation therapy and some chemotherapy drugs. Temperatures above 38°C enhance cisplatin therapy [106].

Combination chemoradiotherapy with cisplatin and concurrent radiation therapy has improved locoregional control in locally advanced squamous cell cancer. Chemoradiotherapy is now considered the standard care in locally advanced disease following surgical resection and in unresectable disease [105].

Surgical therapy

Surgical resection remains the criterion standard for treatment of head and neck cancer. Management of all but the earliest confirmed neck metastases is best achieved with surgical removal [107]. Mohs micrographic surgery has become the "gold standard" for surgical excision of nonmelanoma skin cancers (SCC & BCC) for maximal preservation of normal tissue. Mohs micrographic surgery requires processing specimens in horizontal frozen sections with immediate examination under a light microscope [108]. This technique offers the examination of lateral and deep margins in the same plane in contrast to wide local excision. Success with Mohs micrographic surgery depends on accurate mapping of the tumor, correct interpretation of the histopathological sections, and appreciation of aggressive tumor characteristics [109].

Neck dissection

Lymphatic metastasis is the most important mechanism in the spread of head and neck squamous cell carcinomas. The rate of metastasis probably reflects the aggressiveness of the primary tumor and is an important prognostic indicator. Regardless of the site of the primary tumor, the presence of a single lymph node in either the ipsilateral or contralateral side of the neck reduces the 5-year survival rate by 50% [110].

Modified neck dissection is designed to preserve the spinal accessory nerve, the great auricular nerve and the sternocleidomastoid muscle. The jugular vein and submandibular gland also have been preserved. In addition, successful results can be achieved through less than complete lymph node removal, selectively removing only those lymph node levels likely to be involved by metastases. Modified radical neck dissection removes all 5 lymph node levels, preserving one or all of the spinal accessory nerves, jugular vein, and sternocleidomastoid muscle [111].

Selective dissection removes either levels 1, 2, and 3 (supraomohyoid neck dissection); levels 2, 3, and 4 (anterior neck dissection); or levels 2, 3, 4 and 5 (anterolateral neck dissection). Modified and selective neck dissections clearly have been demonstrated as oncologically equal to the radical neck dissection in treating N0 neck disease. However, when there is one positive node, the likelihood of another positive node in an unexpected location increases significantly. For this reason, selective neck dissection is usually limited to patients without pathologically involved lymph nodes on the side of the dissection [110,111].

Classic radical neck dissection was described by Crile in 1901 and includes removal of all 5 levels of cervical lymph nodes down to the deep muscular fascia. This removal includes the sternocleidomastoid muscle, submandibular gland, jugular vein and spinal accessory nerve. This operation remains the best procedure for definitive control of neck disease. Radical neck dissection can be combined with resection of the primary cancer and postoperative radiation therapy [112].

Radical neck dissection has significant morbidity because of the resection of the spinal accessory nerve and in bilateral dissection, the sacrifice of the internal jugular veins. Severing the spinal accessory nerve results in paralysis of the trapezius muscle in approximately 70% of patients. In most patients, the shoulder subsequently loses support, rotates forward, and droops, and the patient has pain and difficulty lifting his or her arm [112].

Molecularly targeted agents

Cetuximab is an IgG1 chimeric antibody directed against the epidermal growth factor receptor (EGFR). Early results with cetuximab plus radiation have shown similar response to cisplatin plus radiation, but no randomized trial has yet compared the 2 regimens. Current recommendations are to use cetuximab as an alternative to chemotherapy in patients who cannot tolerate chemotherapy [113].

Future Direction

The proposition to this disease is early prevention. The implementation of primary prevention is the need of the time. It will requires media inputs like films, television, radio, newspapers, posters and also intensive personal communication by doctors and social workers. While the advantage of primary prevention lies in tackling the problem at a grass-roots level, it has its limitations. One of them is that it requires long sustained efforts under close monitoring. Second, the achievement of a drop in the incidence rates of oral cancer requires a long time. These limitations point gives the importance to

the secondary prevention. This form of prevention consists of early diagnosis of oral cancer and management of suspected precancerous lesions. The treatment of early cancers will lead to better prognosis and the management of the precancerous lesions and conditions will prevent their progression to cancer.

Conclusion

Knowledge of the global demography, current statistics and risk factors, diagnostic and prognostic markers is very important in order to accelerate further progress in this field, improvise effective prognostic system and anticancer therapy and reduce the mortality rates.

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