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Metastasis of Head and Neck Squamous Cell Carcinoma

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1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide and accounts for approximately 650,000 new diagnoses and 350,000 cancer deaths every year (Parkin, et al., 2005). In the United States, HNSCC accounts for approximately 5% of all cancer cases diagnosed per year. Even with significant advances in operative skills such as reconstructive microvascular free tissue transfer, and in adjuvant therapies such as hyperfractioned radiotherapy and concomitant chemoradiation, the 5-year survival of the HNSCC has not been markedly improved in the past three decades. The number of annually diagnosed cases amounts to over 42,000 individuals and results in more than 12,000 deaths per year in the United States. As is known, HNSCC is a locoregional disease notoriously for regional and distant metastases, representing the leading cause of death in HNSCC patients. Although surgical resection of isolated metastases is beneficial for some patients, the overall efficacy of surgery, chemotherapy or radiotherapy is still limited. The main reason for the poor 5-year survival may be that the most important prognostic factors for these patients are not only local control, but regional and distant metastases as well.

2. Development of metastasis

Metastasis is defined as the spread of disease from one organ or part to another not directly connected with it through the blood, lymph, or serosal surfaces. Recent investigations disclose the mysterious aspects of the cancer metastasis. The development of metastasis of tumor is a multi-step process, in which multiple genes participate in and play different roles. With regard to the regional lymph node metastasis, several important gene proteins related to mirovascular angiogenesis and lymphogenesis function as promoters of regional lymph node metastasis. For the regional metastasis to occur, it is necessary for tumor cells to enter the microvessels to gain the pathway to the lymphatic channels. After entering the tumor-draining lymphatic channels, the tumor cells migrate to the regional lymph nodes in the neck, in which they settle and form the foci of micrometastasis. In the event of distant metastasis, several processes determine the tumor spreading to other organ systems, including angiogenesis, tumor invasion into local stroma and vascular system, circulation of tumor cells, arrest of tumor cells at distant site, and colony formation at secondary site. It is obvious that tumor invasion into stroma and vascular system is a prerequisite to the

development of distant metastasis, which involves attachment of tumor to the basement membrane, degradation of extracellular matrix components, migration of malignant cells to the stroma and ultimate invasion to the surrounding blood vessels or lymphatic channels. Recently, results from several studies indicate that the disseminated cancer cells alter their adjacent stroma into a ''metastatic'' microenvironment that is similar to the primary tumor microenvironment in which they can survive and proliferate. A better understanding of the gene expression pattern and molecular biologic mechanisms of metastasis in HNSCC may be beneficial for exploration of new effective therapies to prevent the development of metastasis and to improve the survival of these patients.

2.1 Genes involved in metastasis

Development of metastatic carcinoma is associated with masses of molecules involved in cell adhesion, migration, and invasion in HNSCC. Further insight into the molecular basis of metastasis in HNSCC could lead to advances in screening, diagnosis, and treatment with improved clinical outcome. Multiple gene products are involved in angiogenesis, all of which have been demonstrated to be critical for regulating angiogenic phenotype. This has raised the need for comprehensive analysis of the angiogenic phenotype using microarray analysis and global proteomic approaches. Complex interplay between positive and negative regulators determines the degree of neovascularization in and around the tumor. And now emerging evidence suggests that the lymphangiogenic factors may also play important roles in lymph node metastasis in many cancers.

2.1.1 Vascular endothelial growth factor (VEGF)

As a key regulator of angiogenesis, the role of VEGF has been extensively studied. Tumor cells enter the circulation by penetration through proliferating capillaries that have fragmented basement membrane. Further progress in this multi-step cascade is controlled by the positive and negative regulators of angiogenesis. Recent studies have shown that VEGF receptor-expressing cells from the bone marrow arrive at a specific site of future metastasis even prior to arrival of metastatic cells (Ellis, 2008). First and foremost, VEGF is a highly potent angiogenic agent that acts to increase vessel permeability and enhance endothelial cell growth, proliferation, migration and differentiation (Johnstone & Logan, 2007). In addition, VEGF promotes angiogenesis in many different tumor types. VEGF levels may affect tumor growth, metastatic potential, and response to radiotherapy. VEGF expression may prove to be an important prognostic factor in head and neck cancer (Smith, et al., 2000); VEGF positivity is the most significant predictor of poor prognosis. Accordingly, the potent role of VEGF in angiogenesis has spurred interest in using this molecule as a therapeutic target in antiangiogenetic therapy.

2.1.2 Matrix metalloproteinases (MMP)

As is known, MMP has the ability to degrade connective tissues such as the basement membrane, which is a crucial step in the initiation of metastatic process, thus serving as a positive regulator of metastasis. Expression levels of molecules involved in tissue remodeling and extracellular matrix (ECM) adhesion, especially *MMP-1* and *integrin-3,* can provide an accurate biomarker system for predicting the risk of cervical lymph node

metastasis in oral squamous cell carcinoma (Nagata, et al., 2003). In order to breech the basement membrane and invade the connective tissue stroma, HNSSC must produce enzymes capable of degrading the extracellular matrix. General classes of these proteolytic molecules include MMPs, named for their dependence on Zn^{2+} as a catalyst, and the plasminogen activators. The MMPs are a large group of secreted proteinases that require zinc for catalytic activity. MMP-2 and MMP-9 are the largest members of this gene family. They are able to degrade connective tissue, among other substrates, the basement membrane collagen, which appears to be very crucial in tumor cell invasion and in the process of metastasis.

The association of the expression of MMP-9 and MMP-2 with mode of tumor invasion and nodal involvement has previously been found in squamous cell carcinoma, and recently its utility has been proven in oral cancers (Miyajima, et al., 1995, Patel, et al., 2007). However, some studies have shown that the activation of MMP-2 was more prominent as compared with MMP-9 in malignant oral SCCs. Elevated activation ratio of MMP-2 has also correlated significantly with lymph node metastasis in oral SCCs. Accordingly, MMP-2 was considered by some investigators as more selective molecular marker for prediction of metastatic potentials of oral SCCs (Patel, et al., 2007). Certain other studies have shown results favoring the use of MMP-9 as a prognostic indicator (Ruokolainen, et al., 2004). Association between MMP-9 and vascular endothelial growth factor expression or micro vessel density has been found in head and neck carcinoma (Riedel, et al., 2000). The summary of MMPs produeced by HNSCC is illustrated in table 1.

MMP	Name	Substrate
Collagenases		
MMP-1	Interstitial	Collagens I, II, III, V, IX
	collagenase	Collagens I, II, III, V, IX
MMP-8	Neutrophil	Elastin
MMP-12	collagenase	Collagen III
MMP-13	Metalloelastase	
	Collagenase3	
Stromelysins		
MMP-3	Stromelysin 1	Proteoglycans, collagen IV, gelatins
MMP-7	Matrilysin	Fibronectin, collagen IV
MMP-10	Stromelysin 2	Proteoglycans, collagen IV, gelatins
MMP-11	Stromelysin 3	Laminin and fibronectin
Gelatinases		
MMP-2	Gelatinase A	Gelatin, collagens IV and V
MMP-9	Gelatinase B	Gelatin, collagens IV and V

Table 1. MMP produced by HNSCC

2.1.3 Endostatin

Endostain exhibits specific inhibitory action on the proliferating endothelial cells of newly formed blood vessels, representing one of the better defined and most potent negative

regulators of angiogenesis (O'Reilly, et al., 1997). Earlier studies have shown that plasma levels of endostatin in patients with HNSCC have been associated with histologic grade, recurrence, and survival rate (Homer, et al., 2002). However, the immunohistochemical expression of endostatin and collagen XVIII in SCC tissues and their significance for the growth and metastatic potential of these tumors have not been widely studied. In a recent study, the levels of endostatin were lower in the primary tumors of cases with multiple metastatic lymph nodes compared with non metastatic tumors. The differences in endostatin expression between these tumors corresponded well with the levels of collagen XVIII, suggesting that the reduction in endostatin expression in the node positive group is because of decreases in the production of the precursor molecule collagen XVIII. On the other hand, these results contradict with those of Homer *et al* (Homer, et al., 2002), who observed a positive trend between higher levels of endostatin and nodal metastasis and an association between increased endostatin expression and higher tumor grade, recurrence, and death in patients with HNSCC. The authors attributed this discrepancy to differences in methods used, as these investigators measured the circulating levels of endostatin, whereas this study assessed the levels in tissue samples (Nikitakis, et al., 2003).

2.1.4 Others

E-cadherin is an important molecule that promotes cell to cell adhesion which serves as a positive regulator of metastasis. Low expression of E-cadherin should be considered as a high-risk group for late cervical metastasis when a wait-and-see policy for the neck is adopted (Lim, et al., 2004). The plasminogen activators (PAs) are another class of proteases that have been confirmed to play important parts in invasion and metastasis of HNSCC. PAs are neutral serine proteases which catalyze the synthesis of plasmin from plasminogen. Plasmin is a fibrinolytic enzyme, also active in degrading type IV collagen and laminin.

2.2 Molecular pathologic changes during development of metastasis

HNSCC will progress from carcinoma in situ, to microinvasive carcinoma, to an invasive tumor with stromal invasion, and to a deeply invasive tumor with lymphatic metastasis. The essential element in the transition from carcinoma in situ or preinvasive to invasive carcinoma is the destruction of the underlying basement membrane.A reasonable interpretation of these studies is that increased degradation of basement membrane correlates with increased invasion and metastasis. Adherence to the basement membrane and extracellular matrix components is another method by which tumor cells can facilitate local invasion and metastasis. Alterations in tumor cell adherence and the expression of these cell surface ligands may facilitate invasion, metastasis, and neovascularization.

2.2.1 Detachemnt and migration of tumor cells

Essential characteristics of cancer are the ability to invade surrounding tissues and metastasize to regional and distant sites. The events attendant to local invasion by an epithelial tumor include loss of adhesion to surrounding tumor cells and basement membrane, production of enzymes and mediators which facilitate the incursion of malignant cells into the subjacent connective tissue. Therefore, the late stages of cancer involve progressive tumor invasion and metastasis, which are the stages that ultimately affect vital functions and cause death in patients. Many important histopathologic and

molecular events associated with tumor progression and metastasis. Development of invasive carcinoma is associated with focal dissolution of the basement membrane and extracellular matrix (ECM), detachment, and migration of cells into the submucosal tissue. HNSCCs that exhibit a streaming pattern of small clusters of cells through the ECM are associated with more aggressive behavior and poor prognosis. HNSCCs exhibit alterations in expression of a repertoire of cell adhesion molecules and ECM substances that function in attachment and migration.

2.2.2 Angiogenesis

In 1972, Folkman first articulated the hypothesis that tumor growth was angiogenesis-dependent. Characteristics of prevascular tumors include a linear growth phase, absence of intratumoral vessels, and size limited to < 1 mm^3. Once tumors become vascularized, obtaining nutrients and exchanging metabolic waste products with the host become more efficient and the growth properties of the tumor change. Characteristics of tumors in the 'vascular phase' are histological demonstration of intratumor capillary networks, size> 1 mm^3, and an exponential growth phase (Folkman, 1990, 1992). Tumor progression to a size that becomes visible and has an effect on adjacent structures requires an increase in supply of oxygen and nutrients and removal of waste, which implies that new blood vessel formation is critical in cancer progression (Folkman, 1996). Enlargement of tumors to a size beyond 0.5 cm exceeds the range for diffusion of oxygen from existing vessels and necessitates new blood vessel formation, called neoangiogenesis. Angiogenesis is increased in various human cancers, including HNSCCs, and correlates with tumor progression and metastasis. Vascular endothelial growth factor (VEGF) has been shown to be a key regulator of angiogenesis.

The ability to stimulate new blood vessel growth (neovascularization or angiogenesis) is an integral part of organogenesis, reproduction, and wound healing and repair, and in this context it is short term and self-limiting. Pathologic angiogenesis is not autoregulated and results from alterations in growth control, which are parts of particular disease processes. However, the ability of a tumor to stimulate an angiogenic response should directly determine the capability of a tumor to metastasize and ultimately kill the host. The evidence regarding microvessel density as a predictor of nodal metastasis, or response to treatment in HNSCC remains conflicting, furthermore initially good correlations between microvessel density and outcome recently being challenged. Tumors invade local connective tissues by the production of proteinases and the expression of cell surface markers which facilitate attachment to components of the extracellular matrix. Tumor size is limited by the diffusion of nutrients from adjacent blood vessels, however, tumors circumvent this limitation by recruiting host capillaries to form an intratumor blood supply.

2.2.3 Lymphoangiogenesis

Lymphangiogenesis is associated with locoregional disease recurrence in early-stage oral carcinoma (Munoz-Guerra, et al., 2004). The presence of intratumoral lymphangiogenesis is a useful discriminator in predicting the outcome of patients with absence of lymph node metastasis. Various studies has stressed on the impact of tumor thickness as a significant factor that had predictive value for local disease recurrence, survival and neck metastasis. The rationale was that the depth of invasion would determine proximity to blood and lymphatic vessels and facilitate the ability of the tumor to expand. In most cases, metastasis

in squamous cell carcinoma occurs via the lymphatic vessels and dilation of lymphatic vessels is frequently found in oral tumors with lymph node involvement. However, the influence of intratumoral or peritumoral lymphangiogenesis on squamous cell carcinoma of the oral cavity is still controversial.

Several markers have been utilized in the study of lymphangiogenesis. The main disadvantage of this method is that it relies on quantitative rather than qualitative differences between lymphatic and blood vessels and therefore requires a certain amount of subjective interpretation. In addition, most antibodies used react with both blood vessels and lymph vessels (Hannen & Riediger, 2004). Some of these studies have correlated the presence of VEGF-C in the tumor cells with an increased likelihood of lymph node metastasis in oral SCC, which seems promising (Kishimoto, et al., 2003, Shintani, et al., 2004, Warburton, et al., 2007). An association between lymphangiogenic growth factors, intralymphatic growth and tumor metastasis has been suggested. However, the role of intratumoral lymphangiogenesis in the progression of squamous cell carcinomas has not been studied. Tumor invasion of capillaries and lymphatics leads to dissemination of tumors and the establishment of histologically identical tumors at secondary sites.

2.2.4 Cellular components of tumor microenvironment

It has been shown that during progression, squamous cell carcinomas undergo additional changes needed for growth and metastasis that depend on the host (Chen, et al., 1997). Inflammatory cells infiltrating squamous cell carcinomas are one of the host components that promote growth and metastasis. New vessel formation is commonly associated with an increase in inflammatory cells. Growth of the tumor epithelia and angiogenesis is also accompanied by increased infiltration of inflammatory cells and proliferation of fibrous stroma. These inflammatory cells bear a stem cell marker called CD34 and appear to differentiate into granulocytes and endothelial cells that form new blood vessels. Granulocytes have been found to promote growth and metastasis. Granulocytes from the host can release growth factors and proteases that stimulate growth and invasion of tumor cells. Several studies have suggested that tumor cells capable of inducing host inflammatory and stromal cell responses grow, invade, and metastasize more rapidly.

Squamous cell carcinomas also induce proliferation of stromal fibroblasts. Fibroblasts also secrete factors and ECM substances that can promote growth. The establishment of metastases requires cell arrest and vessel formation in a new location. HNSCC shows a predilection for metastases to the lymphatics, lungs, liver, and bone marrow, suggesting that the cells and substrate of the reticuloendothelial system provide a favorable environment for arrest and formation of squamous cell carcinoma metastases. Non-malignant cells within the tumor microenvironment also play important roles in modulating tumor progression and metastases. Functional studies have identified several tumor-promoting functions for macrophages in primary tumors. These include promotion of angiogenesis, tumor cell invasion, migration and intravasation.

Local tissue invasion and migration into the subjacent connective tissue matrix by HNSCC are dependent of the production of cell surface molecules, enzymes and motility factors. In addition to the production of these locally active molecules, HNSCC produces growth factors or cytokines which target other cell types. Cytokines are low molecular-weight

proteins which affect cell-cell communication and signal cellular proliferation, differentiation, activation, and migration.

3. Biological processes of the metastatic cascade

Tumor metastasis is ultimately the result of an imbalance between forces favoring and opposing the development of secondary tumors. The first steps in the development of distant metastases involve (1) the initiation of the primary tumor in a genetically susceptible host, (2) the promotion and progression of malignant cell gene mutations favoring clone expansion, and (3) uncontrolled proliferation of these malignant clones of cells due to the actions of autocrine growth factors and growth factor receptors.

The risk of distant spread is related to primary tumor site, its local and regional extension, and the phenotype (Li, et al. 2009). Distant metastases are particularly important in supraglottic laryngeal and pharyngeal cancers (Buckley, 2000). Factors which favor the development of metastases include the primary tumor's ability to activate oncogenes, downregulate tumor suppressor genes, express cell-surface adhesion molecules, synthesize and respond to autocrine and paracrine growth and motility factors, secrete proteases, and produce angiogenic and immunosuppressive cytokines. Factors opposing the development of metastases include activated tumor suppressor and antimetastasis genes, enhanced host immune responses, synthesis of protease and angiogenesis inhibitors by both the tumor and the host, and anatomic and structural barriers. All of these phenomena are the result of multiple gene mutations culminating in the development of secondary tumors at distant sites.

Fidler and colleagues (Fidler & Hart, 1982) articulated the principal of tumor heterogeneity, which is now widely accepted. The development of local-regional and distant metastases begins with the initiation of the primary tumor and ends with the establishment of metastatic clones throughout the host. Several processes including the differential expression of cell adhesion molecules, release of metalloproteinases, and angiogenesis occur at multiple points in the metastatic cascade. This cascade involves an sequential process including tumor invasion into local stroma and vascular system, circulation of tumor cell and arrest at the distant site, and clonal formation at secondary site.

3.1 Invasion into local stroma and vascular system

The process of tumor invasion involves attachment of the tumor to the basement membrane, degradation of extracellular matrix components, and migration of the malignant cells into the surrounding stroma. We will refer again the process when we consider the establishment of the tumor at a secondary (distant) site.

3.2 Circulation of the tumor and arrest at the distant site

Metastatic tumors, regardless of how they exist in the circulation, will establish distant metastases either by mechanical impaction or attachment to the endothelial cell surfaces. Mechanical impaction of the tumor/lymphocyte/platelet emboli will occur when the diameter of the embolus approaches that of the vessel. The tumor will then adhere to the lumen surface of endothelial cells and begin to grow. The second mechanism is the

attachment of single tumor cells to the exposed basement membrane on the subendothelial side of the capillary lumen.

3.3 Colony formation at the secondary site

The common theoretical mechanisms exist for determining the locations of distant metastases were first articulated by Fidler as the 'seed and soil hypothesis' of tumor metastasis. These mechanisms include: (1) tumor metastasis equally to all organs, but preferentially only grow in locations which provide appropriate growth factors (soil); (2) circulating tumor cells have receptors specific for the endothelial cells of only certain target organs (seed), and (3) circulating tumors have receptors for specific chemotactic factors produced by the target organ. These factors result in the preferential attraction of the tumors to the target organ (seed soil) (Markus, 1988).

4. Lymph node metastasis of HNSCC

The status of the regional lymphatics is one of the most important prognostic indicators in patients with head and neck cancer. HNSCCs that are localized to the primary site without regional lymph node metastasis have excellent cure rates with either surgery or radiation therapy. The presence of regional metastases results in cure rates that are approximately half of those obtainable if metastasis to the regional lymphatics is not present. Thus the treatment of the neck has become one of the most actively debated topics in the field of head and neck oncology.

4.1 Patterns

The primary sites for HNSCC are mainly in the oral cavity, oropharynx, hypopharynx and larynx. In 1972, Lindberg published the location of nodal metastases in patients with squamous carcinoma of the upper aerodigestive tract as determined by clinical examination (Lindberg, 1972). This review consisted of 2,044 previously untreated patients with HNSCC. The presence of nodal metastasis and its location was assessed and correlated with the location and stage of the tumor at the primary site. Primary sites were divided into oral tongue, floor of mouth, retromolar trigone/anterior faucial pillar, soft palate, tonsillar fossa, base of tongue, oropharyngeal walls, supraglottic larynx, hypopharynx and nasopharynx. Fifty-seven percent of patients presented with clinical evidence of metastasis in the cervical nodes. Lindberg showed that for lesions of the oral tongue, floor of mouth, retromolar trigone/anterior faucial arch and soft palate, the incidence of cervical nodal metastasis increased with the size of the primary tumor. However, the incidence of nodal metastasis did not correlate with the size of the primary in tumors of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx.

Clinicopathological studies on the specimens from surgical removal of primary tumors and the associated treatment neck dissection tissues revealed patterns and impacting factors of cervical lymph node metastasis in HNSCC (Li, et al., 1996). For oral cavity cancers, the most common neck regions for neck node metastasis are level I to level III. Whereas, cervical lymph node metastasis from the cancers of oropharynx, hypopharynx and larynx are most frequently found in level II to level IV. Lindberg demonstrated that squamous cell carcinomas of the upper aerodigestive tract tend to metastasize to the neck in a predictable

pattern. By far, the most common site of metastasis by all tumors is to the ipsilateral level II nodes. Tumors that lie within the oral cavity anterior to the circumvallate papillae have a propensity to metastasize to levels I through III, with levels IV and V seldom involved. Tumors of the oropharynx have a low propensity to metastasize to level I; metastasis is most common to level II with decreasing incidence of metastasis in levels III and IV. These tumors have a higher rate of metastases to level V than oral cavity tumors but the rate is still low. Tumors of the supraglottic larynx and hypopharynx rarely metastasize to level I, again metastases were most common to level II with a decreasing incidence in levels III and IV and metastases to level V were infrequent. Contralateral metastases were uncommon in cancers of the floor of mouth, oral tongue, hypopharynx, and retromolar trigone/anterior faucial arch. In contrast, tumors of base of tongue, oropharyngeal walls, soft palate, supraglottic larynx, and tonsil have substantial rates of contralateral metastases.

Lindberg's data clearly showed that in cases of squamous cell carcinoma of the upper aerodigestive tract, with the exception of nasopharyngeal carcinoma, nodal metastasis occurs in a predictable pattern and it may, in certain instances, be sound to exclude dissection of the level V lymph nodes. However, this study provides only information on clinically positive nodal metastasis—it provides no information on the incidence and location of occult nodal metastasis. Such information on microscopic metastasis can only be obtained from a surgical specimen. Byers and colleagues published one such study (Byers, et al., 1988) in 1988. They examined the specimens of 428 patients undergoing 648 modified neck dissections and correlated the location of the pathologically positive lymph nodes with the primary site. The majority of these neck dissections were selective neck dissections and therefore not all of the lymph node levels at risk were examined in each patient. This study essentially confirms the clinical data of Lindberg (Lindberg, 1972) that lesions anterior to the circumvallate papillae are most likely to metastasize to lymph nodes levels I through III and lesions within the hypopharynx and larynx to levels II through IV. It must be pointed out, however, that the majority of these dissections were less than comprehensive and therefore the low incidence of metastasis to certain nodal levels may simply reflect the lack of sampling of those levels.

In order to fully assess all the lymph node levels at risk for a particular primary site, surgical specimens should include all lymph node levels (comprehensive neck dissection). Just such information is provided in a series of studies by Shah and colleagues, (Candela, et al., 1990, Candela, et al., 1990, Shah, et al., 1990) which involved 1,081 previously untreated patients who underwent 1,119 classic RNDs for squamous carcinoma of the upper aerodigestive tract. The operations consisted of 343 elective RND in the clinically N0 setting and 776 therapeutic RND in the clinically N+ setting. In patients with primary tumors of the oral cavity undergoing therapeutic RND, the majority of metastatic nodes were located in levels I to III; level IV was involved in 20 percent of specimens and level V in only 4 percent. In those with primary oropharyngeal tumors, the majority of metastases were located in levels II to IV; levels I and V were involved in 17 percent and 11 percent of the specimens respectively. Therapeutic neck dissection in hypopharyngeal tumors showed that the majority of metastases were located in levels II to IV, while levels I and V were involved in 10 percent and 11 percent of the specimens, respectively. Primary tumors of the larynx metastasized to levels II through IV with levels I and V being involved in 8 percent and 5 percent of the specimens, respectively.

In the setting of elective RND in patients with primary tumors of the oral cavity, the majority of metastases were located in levels I to III; levels IV and V were involved in 9 percent and 2 percent of the specimens, respectively. In patients with primary tumors located in the oropharynx, the majority of metastases were located in levels II to IV; levels I and V were involved in 7 percent of the specimens. Patients with tumors of the hypopharynx undergoing elective RND had the majority of metastases in levels II to IV, while levels I and V were not involved in any of the specimens. Primary tumors of the larynx metastasized primarily to levels II through IV, while levels I and V were involved in 14 percent and 7 percent of the specimens, respectively. O'Brien et al.(O'Brien, et al., 2000) found occult metastatic disease in 30% of patients, and Lim et al (Lim, et al., 2006, Lim, et al., 2006) found it in 28%.

The question of metastasis to level V was addressed by another study by Davidson and colleagues. (Davidson, et al., 1993) They examined the specimens of 1,123 patients undergoing 1,277 RNDs and found metastases to level V in only 3 percent of patients. Level V metastases were highest in patients with hypopharyngeal and oropharyngeal primary sites (7% and 6% respectively). Only 3 of the 40 patients with level V metastases had these in the face of a clinical N0 stage. They concluded that the incidence of metastases to level V was small in general, and extremely unlikely in the clinically N0 patient.

4.2 Risk factors

Clinicopathologic factors associated with the development of cervical lymph node metastasis have been well studied for other locations like tongue, mouth floor, and cheek, in particular concerning tumor size (in tongue carcinoma≥3 mm), tumor depth (≥4 mm in tongue carcinoma), differentiation, mode of invasion, microvascular invasion, and histologic grade of malignancy (Kurokawa, et al., 2002, Sparano, et al., 2004, Wallwork, et al., 2007). The presence or absence of lymph node metastasis is a major prognostic factor for survival in patients with negative cervical lymph nodes (Hiratsuka, et al., 1997). A high incidence (20–30%) of cervical metastasis of cancer in the tongue/mouth floor has been well studied (Kurokawa, et al., 2002, Sparano, et al., 2004, Wallwork, et al., 2007). But very few studies have been performed concerning squamous cell carcinoma of the maxilla (Simental, et al., 2006). Sparamo et al(Sparano, et al., 2004) and Kruse et al (Kruse & Gratz, 2009) reveal that the higher the grading, the higher the risk of cervical metastasis. Therefore, regarding the proportion of late cervical metastasis, the question arises whether an elective neck dissection should be provided in early-stage squamous cell carcinoma. Capote et al. (Capote, et al., 2007) reported that in pT1N0 and pT2N0 oral squamous cell carcinoma, neck dissection therapy was a significant prognostic factor for recurrence and survival. Therefore, tumor size, tumor depth, and differentiation should be taken into consideration for the planning of neck dissection for squamous cell carcinoma of the upper jaw. Also the mode of invasion plays an important role in therapy planning because in certain localizations like the palate, the tumor does not need to invade very deeply before reaching the bone.

4.3 Prognostic factors

As an independent prognostic factor, cervical lymph node metastasis has a great impact on disease-free and overall survival of patients with HNSCC. Among various

clinicopathological factors, the most important prognostic factors are pN+, numbers of positive node (more than 3 positive nodes), lower level of invasion, and especially the extracapsular nodal spread (ECS) (Di, et al., 2009). A review of literature reveals the impacts of clinicopathological factors on neck recurrence. For example, if residual disease after neck dissection, 2 or more pathologic lymph nodes, extracapsular spread (ECS), more than 3 cm-diameter pathologic lymph node and invasion of soft tissue are found in neck dissection specimens, the risk of neck recurrence is considered to be high (Li, et al., 2009). Since treatment neck dissections for HNSCC vary from selective neck dissection (SND) to radical neck dissection (RND), it is necessary to analyze the clinicopathologic risk factors for regional recurrence in a group of positive-node patients treated with such neck dissections and postoperative radiotherapy (PORT) in order to determine which patients need further adjuvant therapy and further short-interval follow-up. However, the majority of the literatures draw these conclusions in the absence of adjuvant radiotherapy. Furthermore, some reports show that these factors have no statistical significance in predicting regional failure following neck dissection and adjuvant PORT. It is now well established that the development of cervical metastases, in particular those with extranodal extension of tumor, negatively impacts both regional control and survival of patients with laryngeal carcinoma (Myers & Fagan, 1999).

4.4 Modern concepts in management of cervical lymph node metastasis in HNSCC

The lymphatic system of the head and neck is complicated (Fisch, 1964). An extensive analysis of 2044 medical records of patients with HNSCC who had not received prior treatment led Lindberg to divide nine lymph node regions on each side and, additionally, the parited lymph nodes (Lindberg, 1972). The lymph fluid of the upper aerodigestive tract is drained via about 300 regional cervical lymph nodes, which are divided according to the current classification established by Robbins (Robbins, et al., 2002) into nine lymph node levels (level I–VI). It is well understood that an incomplete surgical resection margin is the most important single factor for tumor recurrence, which is determined not only by the experience of the surgeon but also by the limitation of surgical excision. For example, if multiple nodes or ECS of neck diseases are present, it may be difficult to obtain adequate surgical resection margins or to resect all metastatic lymph nodes in the neck. Recurrence in the neck is more likely to occur in patients with these neck situations. For this reason, it is widely accepted that ECS is a marker for biologically aggressive disease and patients with HNSCC who have evidence of ECS need aggressive multimodality therapies including surgery, PORT and, even chemotherapy.

4.4.1 Detection of lymph node metastasis

Most tumors of the head and neck initially metastasize to the regional lymph nodes. The presence of cervical metastases is the most significant oncological factor in the prognosis of HNSCC (SCC) because early detection and treatment may prevent distant metastases (Gray, et al., 2000). The assessment of cervical lymph nodes is known to be extremely difficult clinically. Despite recent advances in the fields of radio diagnosis, its utility to detect occult neck metastasis still lacks considerable power. Owing to the high number of undersized lymph node metastases, the non-invasive neck staging methods are limited to a maximum accuracy of 76% (Stuckensen, et al., 2000). Pre-surgical staging of the neck has become more

complex over the years. Clinical assessment of the neck by palpation, while providing critical information, is inadequate in its sensitivity for detecting metastatic disease to the cervical nodes. Error rates as high as 40 percent have been reported when physical examination alone is used to evaluate the neck (Teichgraeber & Clairmont, 1984). Patient factors such as a short, obese neck, as well as prior irradiation play a role in decreasing the accuracy of this technique. Clearly, radiologic assessment of the neck adds to the sensitivity and specificity of preoperative neck evaluation.

4.4.1.1 Comouterized tomography (CT) and magnetic resonance imaging (MRI)

Computerized tomography (CT) and magnetic resonance imaging (MRI) have become the workhorses of imaging modalities in HNSCC. Size criteria are frequently used as indicators of metastatic involvement. Other features such as central necrosis or ring-enhancement aid in specificity but are relatively infrequent findings. Generally, a subdigastric node measuring > 15 mm, a submandibular node > 12 mm, and other nodes > 10 mm are suspicious for involvement. Using criteria such as these, the accuracy of detecting neck disease approaches 90 percent (John, et al., 1993). Size, however, is certainly not pathognomonic for cancerous involvement of lymph nodes. Even in the patient with an identified squamous cell carcinoma of the upper aerodigestive tract, a myriad of alternative causes of enlarged lymph nodes exist. Further, microscopic foci of disease may exist in nodes of normal size. As CT or MRI is often employed to evaluate the primary lesion, inclusion of the neck in the area of study incurs nominal additional expense and no morbidity. Although CT and MRI provide excellent anatomic detail and are the current modalities of choice, they provide little information on the biology of the lymph node.

4.4.1.2 Positron emssion tomography (PET)

Several studies have evaluated fluorodeoxyglucose (FDG) PET in this setting, attempting to identify the patients who need neck dissection. In 3 studies totaling 48 patients, in which a sentinel node biopsy with immunohistochemistry was used as the gold standard, the detection rate of PET was between 0% and 30%, making PET an unreliable modality in this clinical setting (Civantos, et al., 2003, Stoeckli, et al., 2002). This is not unexpected, given that 40% of cervical nodal metastases are less than 1 cm in size and PET detection rate for nodes less than 1 cm is reported at 71% (Menda & Graham, 2005). Numerous promising pilot studies have evaluated sentinel node biopsy (SNB), up to 16% patients required additional immunohistochemistry (IHC) on the sentinel nodes to detect metastasis (Civantos, et al., 2006). Owing to these inadequacies in detection of occult nodal metastasis, surgical dissection and serial histologic examination are the currently accepted "yardsticks".

Another problem that should be considered seems to be the detection of micrometastasis. The assessment of the status of cervical lymph nodes is difficult, and therefore a treatment of patients with a clinical stage N0 neck is controversial. In most studies, the use of CT has an error rate ranging from 7.5 to 19%(van den Brekel, et al., 1990). In the late 1990s, the PET using F-18 FDG, a functional imaging methodology that provides information about tissue glucose metabolism, was applied. Consequently, a high FDG accumulation is manifested on PET images, but inflammation also reveals an increased FDG uptake and can lead to false-positive results. On the other hand, low tumor metabolic activity, the presence of small lesions, and hypoglycemia can lead to false-negative results (Murakami, et al., 2007). Concerning cervical lymph nodes, Ng et al. (Ng, et al., 2005) reported that sensitivity and

specificity of PET images were 75% and 93%, respectively. Sigg et al. (Sigg, et al., 2003) reported a sensitivity of 93% and a specificity of 100%. PET together with CT images showed a 15% increase in the accurate identification of nodal staging over using the PET images alone (Jeong, et al., 2007). PET/CT seems to have a higher sensitivity and specificity for detecting lymph node metastasis (Leong, et al., 2006, Wild, et al., 2006).

4.4.1.3 Ultrasound

Due to its non-invasiveness and affordability, ultrasound (US) has been investigated as a potential tool in evaluating neck disease. Factors such as size, irregular margins, and echo characteristics of lymph nodes have been shown to have predictive value in assessing involved nodes. The overall sensitivity of this approach, however, is limited due to the operator-dependant nature of ultrasound.(John, et al., 1993) Some authors have proposed ultrasound in combination with ultrasound-guided fine needle aspiration as an approach to diagnosis. Takes and colleagues (Takes, et al., 1998) examined, with ultrasonography, 64 necks staged N0 based on physical examination. Those with nodes greater than 5 mm in size underwent ultrasound-guided needle biopsy. Results were further verified with histopathologic examination and the findings compared with CT of the neck for detection of involved nodes. They found a 48 percent sensitivity, 100 percent specificity, and 79 percent accuracy for ultrasound versus 54, 92, and 77 percent respectively for CT. These results demonstrate that, in experienced hands, ultrasound can be a useful tool. Its widespread application, however, is limited by the technical expertise required for accurate interpretation.

4.4.2 Management

4.4.2.1 General principles

The type, grade, site and stage of the primary tumor determine the risk of cervical metastases and hence the type of treatment modality. Treatment of the neck in patients with clinical evidence of nodal metastasis has traditionally been surgical. In recent decades, this has been extended to include a combination of surgery and radiation therapy. The role of chemotherapy in the management of neck disease remains controversial and is currently being actively investigated. In oral tongue carcinoma, the risk of neck metastasis is significantly associated also with the depth of tumor invasion (Pentenero, et al., 2005). The patterns of spread of cancer to cervical lymph nodes are predictable, based on the anatomical location of the primary tumor. Therefore, in the absence of clinical evidence of neck disease, the pathological features of the primary tumor along with its site of origin and clinical T stage are used to stratify the risk of positive neck metastases and, consequently, the need for a neck dissection. When the risk for positive neck lymph nodes exceeds 15–20%, elective neck dissection is indicated – not only as treatment but also to evaluate the need for adjuvant therapy. A selective neck dissection, directed to the basins at risk for lymphatic spread, is commonly used for this purpose. The presence of palpable neck disease mandates comprehensive clearance of the lymphatic basins in the neck. Radical neck dissection was considered the primary modality for treatment of HNSCC with clinical evidence of cervical metastases. However, sacrificing vital structures during radical neck dissection causes severe disabilities in patients and a markedly reduced quality of life. Advances in the anatomic elucidation of the neck, enhanced understanding of the biological behavior of

tumors, and improved surgical methods have contributed to the emergence of the functional neck dissection technique, resulting in excellent survival and functional outcome(Shah & Gil, 2009). Exact knowledge of the anatomy of the neck and its adjacent structures and the risk and location of common cervical metastases is essential for the operative treatment of HNSCC.

Although primary tumor control is achievable in early tumors with minimally invasive surgery, such as transoral or robot-assisted procedures, the management of the neck is still an important consideration in the treatment of HNSCC. Surgical management of the neck in patients with pharyngeal cancers does not usually involve a dissection of the retropharyngeal lymph node (RPLNs). Neck dissections do not routinely address RPLNs, creating a potential for recurrence in the retropharynx and the need to address this nodal basin with radiotherapy (Tauzin, et al., 2010). Treatment of the neck in patients with clinical evidence of nodal metastasis has traditionally been surgical. In recent decades this has been extended to include a combination of surgery and radiation therapy. The role of chemotherapy in the management of neck disease remains controversial and is currently being actively investigated.

4.4.2.2 Adjuvant therapy

Although the practical value of postoperative radiotherapy (PORT) for improving survival in HNSCC is well acknowledged, it remains controversial whether this postoperative radiotherapy, an adjuvant treatment, could prevent recurrence in the neck in patients having ECS. Smeele et al. found that PORT dose of 62.5 Gy and more could increase neck control rates in patients with ECS treated with surgery and PORT for HNSCC. Peters et al. demonstrated that metastatic lymph nodes with ECS were adequately controlled by PORT at dosage of 63 Gy or more (Peters, et al., 1993). However, Prim et al. reported that the 3-year recurrence rates in the neck were 10.7% in patients without ECS and 49.6% with ECS in squamous cell carcinoma of the larynx with pathologically proven lymph node metastasis, and PORT did not appear to improve the outcome (Prim, et al., 1999). Shingaki et al. found that PORT did not decrease the rate of neck recurrence in patients of oral cavity carcinomas with ECS (Shingaki, et al., 2003). These findings suggest that the exact value of PORT in controlling neck recurrence needs to be further documented and recommended for adjuvant chemotherapy. Our findings suggest that the presence of ECS remains a determined risk factor for neck recurrence after surgery and adjuvant PORT in N^+ patients with HNSCC. There were no significant risk factors associated with regional failure in ECS^- group. Except for PORT, no additional adjuvant therapy is required for N^+ patients without ECS. However, more adjuvant therapies are to be considered after PORT in patients with ECS for the purpose of a more effective neck control.

4.4.2.3 Scenario in the management of an N0 neck

Due to the fact that the prognosis of patients suffering from squamous cell carcinoma of the upper aerodigestive tract depends significantly on the presence or absence of lymph node metastasis, the question of detecting clinically occult lymph node metastases is still important concerning the management of the clinical N0 neck. The published rate of lymph node metastasis depends on the location of the primary tumor, with values from 12% to over 50% (median, 33%) (Hosal, et al., 2000). Numerous authors favor elective treatment of the lymphatic region (neck dissection) if the presence of occult lymph node metastasis can

be expected with a probability of 20% or more. However, other authors prefer to adopt a "wait and see" strategy, although this requires both great compliance from the patient and great expertise on the part of the responsible physician to identify metastasis early. Another argument in favor of elective neck dissection versus a "wait-and-see" strategy is the significant deterioration of the survival rate when neck disscetion is due after clinical disease is detected (Godden, et al., 2002).

Regarding the current scenario in the management of an N0 neck, there are presently three policies advocated, which include elective neck irradiation, prophylactic neck dissection or close observation. The choice of therapy often takes into consideration T stage, site of primary, grade, compliance for follow-up, or the probability for occult metastasis [>20%]. Treatment of the neck, even when included with the primary treatment, often confers additional costs, morbidity and prolonged treatment time to the patient. Most often, a single modality treatment is used to treat the primary site and neck. The choice of which is dictated by the treatment of the primary site. There is no conclusive evidence to show if this elective neck treatment approaches contribute to improved overall survival for the patients with HNSCC and clinically negative neck.

4.4.2.4 Sentinel node and elective neck dissection

The elective treatment of the regional lymphatic drainage can generally be performed either surgically or radiotherapeutically. The choice of one of these procedures generally depends on the therapy of the primary tumor. An advantage of elective neck dissection over radiotherapy is that the histological examination of the neck dissection specimen can give important information for deciding therapy, as well as about the prognosis. Thus, the sentinel node concept for squamous cell carcinomas of the upper aerodigestive tract is quite appealing. Furthermore, limits and pitfalls of SLNs for HNSCC discussed elsewhere illustrate that an advanced intranodal tumor growth with extracapsular metastatic spread, leads to a significant reduction of the radiotracer uptake (Dunne, et al., 2001). Even small, clinically unsuspected lymph nodes may reveal extracapsular tumor growth with resulting lack of radiopharmacon accumulation (Coatesworth & MacLennan, 2002). The dominating metastatic region of pharyngeal and laryngeal carcinomas is mainly level II and less commonly, level III. Carcinomas of the anterior oral cavity drain mostly into level I and less commonly into level II. Accordingly, neck dissection of these lymph node levels can be expected to include the majority of clinically occult metastases. With this background, it must still be clarified whether the intraoperative identification of the radiolabeled SLN is appropriate to reduce the extent of selective neck dissection in the suspected N0 neck, or whether neck dissection can be completely avoided in the case of histologically-proven tumor-free SLN. Opponents of such a procedure argue that selective neck dissection already has a morbidity that must be considered. Supporters of sentinel lymphadenectomy stress both protecting the intact, i.e. non-metastatic, cervical lymph node systems and reducing the extent of surgery. Scarring contractures, paresthesia, and persisting lymph edemas can be reduced by a selective SLN dissection. Current research aims to optimize surgical access to the SLNs. The first results on endoscopically performed selective lymphadenectomy led to the assumption that this method of lymph node dissection could achieve some significance in the therapy of the clinical N0 neck, provided that it is based on the SLN concept (Werner, et al., 2004).

However, the techniques would have to be optimized. Furthermore, prospectively collected data should be gathered and analyzed. Within such an investigation, it would make sense to examine frozen sections of the excised lymph node. Depending on the histopathological result, a surgical resection of the lymphatic drainage in the form of a selective neck dissection could then be indicated. At present, the technical diversity and importance of endoscopic lymphadenectomy in the neck shows scientific and clinical potential. The question about the significance of the procedure, however, can not yet be answered conclusively.

5. Distant metastasis

Generally, distant metastasis is defined as tumor spread to other organ systems from its primary site. As a relatively rare but clinically relevant event, the development of distant metastasis is usually difficult to predict in clinic, especially when initial treatment planning is made.

5.1 Clinicopathlological features of distant metastasis in HNSCC

5.1.1 The incidence and common sites of distant metastasis in NHSCC

Alavi et al. (Alavi, et al., 1999) reviewed 342 patients with mucosal HNSCC, and 47 (13.7%) had distant metastases. Five patients (1.5%) had metastases to infraclavicular lymph nodes (axilla, inguinal and presternal). The clinical detection of metastatic foci occurs in 10% to 30% of cases, whereas autopsy studies yield an incidence of about 50% of cases with metastases below the clavicle (Amer, et al., 1979, Dennington, et al., 1980). Clinical data in recently reported studies indicates an incidence of 4% to 23.8%, whereas autopsy data documents that 12% to 57% of cases had disseminated disease(Dennington, et al., 1980). Merino and associates (Merino, et al., 1977) in an analysis of 546 of 5019 untreated patients with squamous carcinoma of the upper respiratory tract who completed curative treatments, found clinically manifested metastases below the clavicle in 10.9% of the cases. The risk of subpathological distant metastases has also to be considered. New and highly sensitive investigations (immunohistochemistry, molecular analysis and FDG-PET/CT) and serial sectioning of nonregional lymph nodes and at risk organs may increase the detection of distant micrometastases in head and neck cancer patients. Probably the different reported incidence depends on the selection criteria of screening for distant metastases and the characteristics of the patients included (Leon, et al., 2000).

The lungs, bones (especially the vertebrae, ribs, and skull) and the liver are the most common sites of hematogenous distant metastases from HNSCC (Gowen & Desuto-Nagy, 1963). During the follow-up period after the initial treatment, 6.2% of the patients were diagnosed of having distant metastasis. The most common sites of distant metastasis were the lungs (58%) and the bones (22%). The lung is clearly the most common site of distant spread. The incidence of pulmonary metastases is also high in patients who present with extensive soft tissue extension of the primary or metastatic regional nodal disease. Holsinger et al, from the Anderson Cancer Center in Houston, provided a panel of clinical and histopathological predictors that may identify patients at the greatest risk for development of distant metastases in HNSCC (Holsinger, et al., 2000). In their study, the 5-year incidence of distant metastasis was 15.1 % (94/622). Pulmonary metastases were most commonly

found: 65.9% to the lung, 4.2% to the mediastinum, 2.1 % to the pleura. Metastases to bone (22.3%) and to the liver (9.5%) were the next most commonly encountered. Thirty (31.9%) patients with distant metastases presented with more than one metastatic site. Lung was the most common site for solitary metastasis. The most common site for bony metastasis was the spine (12.7%), followed by skull (4.2%), rib (3.1 %), and axial bones (femur, humerus; 2.1 %). More than half of patients with osseous metastases presented with multiple sites. The patients who present with jugular vein invasion or extensive soft tissue disease in the neck clearly have a high incidence of pulmonary metastases. Other less common sites of metastases include the mediastinum, adrenal gland, brain, pericardium, kidney, and thyroid gland (Troell & Terris, 1995).

5.1.2 Risk factors

Taken into consideration to be relatively important factors in clinic, clinical T stage, N stage, tumor site, tumor thickness, differentiation, pattern of invasion, vascular and/or lymphatic invasion, bone and/or cartilage invasion, perineural invasion, and lymph nodal status have been reported to be associated with distant metastasis in HNSCC. However, the conclusions concerning the role of each independent factor differ among the various authors. In a recent study, we successfully demonstrated that primary tumor site, level of tumor invasion and numbers of levels with positive lymph node are closely related to the occurrence of distant metastasis in HNSCC (Li, et al., 2009).

The incidence of metastases is influenced by T and N stage, as well as control of the primary lesion. As local and regional control of head and neck cancer has improved, distant metastases have become an increasingly common cause of death. (Vikram, et al., 1984) The disturbance of the lymphatic system in the cervical region resulting from radiotherapy or neck dissection can result in alternative pathways of lymphatic drainage. These newly formed pathways of drainage can ultimately result in lymphatic dissemination of head and neck cancers to sites below the clavicles. Metastasis from head and neck carcinomas to infraclavicular lymph nodes has been reported very infrequently in the literature (Nelson & Sisk, 1994). Recognition of this phenomenon is crucial in the evaluation of patients with recurrent head and neck cancer, especially when salvage surgery is entertained.

The incidence of distant metastases is directly related to the clinical stage of the tumor, with high incidence of distant metastases in stage IV tumors, particularly in patients who present with advanced nodal disease. The distant metastasis ratio was much higher in patients with T3 to T4, N2 to N3 lesions who received postoperative radiotherapy. It is reported that locally extensive lesions T3 and T4 are most likely to metastasize and that nodal involvement is also associated with increased risk of distant spread. Lesions arising in the larynx and hypopharynx have a greater predilection to metastasize than oral lesions, although true vocal cord lesions infrequently metastasize as demonstrated by Snow and coworkers(Snow, et al., 1980). In data of Merino (Merino, et al., 1977), 8% of all patients who had local control developed metastases, while 23% of those with T3 to T4 lesions had local control and developed distant spread.

The incidence of pulmonary metastases is extremely high in patients who present with bilateral N3 disease. Disease stage showed a striking correlation with the risk for distant metastases (as follows): stage I, 1 %; stage II, 14%; stage III, 15%; stage IV, 20% ($p < 0.0003$).

Advanced disease (T stage> 3 and N stage> 2a) was significantly correlated statistically with the development of distant metastases ($p < 0.003$). The authors found that certain clinical features (extent of cervical metastasis or N stage) and histopathologic data (evidence of lymphatic or vascular invasion and extension beyond the confines of the lymph node) are associated with significantly increased rates of distant metastases.

Spector (Spector, 2001) report a retrospective tumor registry analysis of patients with HNSCC of the larynx and hypopharynx who were treated with curative intent between January 1971 and December 1991. In 2,550 patients, the mean age, sex and tumor differentiation did not affect the incidence of distant metastases. The overall incidence of distant metastases was 8.5% (217/2,550 patients) with the following distribution: glottis 4.4%, supraglottis 3.6%, subglottis 14%, aryepiglottic fold 16%, pyriform sinus 17% and posterior hypopharynx 17.6%. The overall 5-year disease-specific survival for distant metastases was 6.4%. Distant metastases were related to advanced local disease (T3 + T4), lymph node metastases at presentation (N+), tumor location (hypopharynx) and locoregional tumor recurrence ($p = 0.028$). A meta-analysis of variables which predispose to a higher incidence of distant metastases indicate that tumor location (hypopharynx> larynx), advanced primary disease (T3 + T4), regional disease (N+), locoregional recurrences, and advanced regional metastases (N2 + N3) are statistically significant. The salvage rate for distant metastases was poor (6.4%) and significantly worse than the salvage rate for delayed regional node metastases (42%) or second primary malignancies (38%) ($p = 0.001$). The onset period of distant metastases was greatest between 1.5 and 6 years post initial treatment with a mean of≤3.2 years.

Research for clinicopathlological features of distant metastasis in HNSCC is of clinical implications in the diagnosis and treatment of the disease. Strong prognostic indicators that predict development of distant metastases are the presence and number of lymph node metastases in the neck, and extranodal spread. Once distant metastases are detected, patients have a very poor prognosis. The time interval between the diagnosis of distant metastasis and death is less than 2 years in greater than 90% of such cases.

5.1.3 Retrograde dissemination

Alvarez reported a retrospective study of 633 patients with HNSCC to describe the clinical characteristics of the distant metastasis. During the follow-up period after the initial treatment, 6.2% of the patients were diagnosed of having distant metastasis (Alvarez Marcos, et al., 2006). The site of primary tumor was hypopharynx in 14.4%, unknown origin in 11.8% and oropharynx in 8.5%. Three year overall survival in patients with distant metastasis was 2.5% (versus 49,5% in the control group).

Nonregional lymph node dissemination should be classified as distant metastasis but axillary and mediastinal metastases can be part of a regional dissemination of HNSCC. Metastases to lymph nodes of the upper mediastinum are very common among patients with subglottic, hypopharynx and thyroid carcinomas. Axillary metastases are found at autopsy in 2–9% of the patients who died of HNSCC and are frequently associated with skin implantation in aggressive recurrent head and neck carcinomas. The possible explanations for this location of metastasis were retrograde dissemination due to lymph system blockage, further tumor dissemination after a parastomal recurrence, hematogenous dissemination, and metastasis from a second primary tumor (Kowalski, 2001).

5.2 Diagnose of distant metastasis in HNSCC

5.2.1 Schemes for screening

Because distant metastasis has an important impact on survival, early detection of this unfavorable status in HNSCC is substaintial for therapeutic strategy regulation. The metastatic workup for patients with head and neck cancer frequently includes examination of the cervical lymph nodes as well as chest radiography, liver function tests, and a serum calcium level determination. This evaluation may fail to detect metastases to distant lymph nodes in patients who present with recurrent or second primary cancers after previous therapy that has affected the cervical lymphatics. A predictable pattern of lymphatic metastasis based on tumor histology and site of origin has also been well documented for most cancers that arise in the head and neck region.

The diagnostic and screening procedures used for distant metastasis in HNSCCs are sometimes equivalent and sometimes complementary. The available methods for the assessment of tumor status include: (1) conventional radiographs (X-rays); (2) sectional imaging - CT, magnetic resonance imaging (MRI), positron emission tomography (PET); (3) ultrasound and ultrasound-guided fine needle biopsy; (4) radionuclide scanning; (5) endoscopic examination and (6) histological and cytological investigations - conventional histology, semiserial sections, immunohistochemistry, molecular analysis and techniques of cell culture.

As the lungs, bones and the liver are the most common sites of distant metastases from HNSCC, routine examination about these organs should be performed for high risk patients of metastasis in HNSCC. The prevalence of metastases at autopsy (37-57%) is much higher than in clinical studies (4-26%) (Leon, et al., 2000). This suggests that distant metastases in head and neck cancer are often asymptomatic, which raises the question of screening. Any investigations used for screening need to be sensitive, highly specific, inexpensive, noninvasive and readily available (Troell & Terris, 1995). In the absence of useful screening tests, metastases are usually detected by specific investigation of suspicious symptoms. Plain X-rays, computed tomography (CT) and bone scanning are the most frequently used investigations.

Chest CT is recommended for high-risk patients, especially during the follow-up period. Intensified evaluation and management are mandatory for indeterminate small solitary pulmonary nodules because of the high rate of malignant neoplasms (Hsu, et al., 2008). Otherwise, cross-sectional imaging with CT and MR imaging is commonly used for tumor metastasis detection.

Recently, PET using the radiotracer 18F FDG is widely used to evaluate patients with HNSCC. The combinated technique, PET/CT, provides anatomic and functional information and is useful for identification of an unknown primary tumor, detection of distant metastasis, establishing radiation-therapy planning, assessing therapy response, and long-term surveillance for recurrence. Positron emission tomography-computed tomography with fluorodeoxyglucose F18 (FDG-PET/CT) is widely used to evaluate patients with HNSCC. PET/CT can provide early, accurate detection of bone metastases from HNSCC and to determine the impact of detecting occult bone metastases on patient care. Use of FDG-PET/CT in restaging HNSCC allows for detection of occult lung, liver and bone metastases, and this early detection frequently influences therapeutic decision making (Basu, et al., 2007).

5.2.2 Confirmation of miscellaneous distant metastases

5.2.2.1 Pulmonary metastasis

Chest computed tomography (CT) scan is clearly more sensitive in identifying and localizing pulmonary metastasis than plain chest radiography, which can serve as a useful screening tool.

Treatment of pulmonary metastases requires some evaluations concerning control of the primary site and regional lymph nodes, and the general physiological and mental condition of the patients as well as the patient's willingness to be treated. In addition, to determine the optimal treatment, especially when considering surgical treatment, it is necessary to exclude other metastases and to precisely define the sequence after the surgery. Surgical excision is indicated as the optimal treatment for a solitary metastasis tumor of the lung when chemoimmunotherapy is ineffective. The patients who have jugular vein invasion or extensive soft tissue encroach in the neck clearly have a high incidence of pulmonary metastases.

5.2.2.2 Bone metastasis

Because metastasis to osseous tissue is the second most common presentation of distant metastases, bone scan is an important and sensitive test. However, because of its non specificity, CT-directed needle biopsies may be necessary to establish diagnosis.

5.2.2.3 Liver metastasis

Hematogenous spread to liver rarely occurs without evidence of pulmonary and bone disease. Although liver function tests may detect abnormality, elevation in liver enzymes ordinarily carries low sensitivity or specificity for liver involvement. Confirmation most often requires a diagnostic CT scan followed by ultrasound-guided needle biopsy.

5.2.2.4 Brain metastasis

Brain metastasis is a rare occurrence from head and neck cancer, it is particularly more probable in tumor involving the temporal bone simply because of its proximity to the cranial vault. CT scan and magnetic resonance imaging (MRI) provide the highest sensitivity of screening for intracranial disease well before neurological manifestations become apparent.

5.3 Management of distant metastasis in HNSCC

5.3.1 Prevention

It has been noted that, with the modern therapeutic regimens, the outcome of patients with distant metastasis from HNSCC remains dismal. Salvage therapy of metasesectomy or ionizing radiation is not sufficient to obtain a higher cure rate, when distant metastasis is at presence. It seems that optimal therapeutic strategies for distant metastasis may be adjuvant chemotherapy after surgery and postoperative radiotherapy at target groups of patients who are at high risk of developing distant metastasis. According to findings in our previous study (Li, et al., 2009), we propose that patients with multilevel nodal involvement in the neck, primary tumor localization at oropharynx, hypoparynx and larynx, and primary tumor invasion into muscle, bone or cartilage are at highest risk of developing distant

metastasis in HNSCC. Therefore, these subsets of patients with high risk factors should be considered for a more through evaluation for detecting distant metastasis and a more increasing utilization of adjuvant chemotherapy for preventing distant metastasis. However, it must be mentioned that screening for distant metastasis in the follow-up doses little help in improving the outcome, since there is mostly no possibility of a curative intervention.

5.3.2 Surgery

Treatment of metastases is generally difficult. The difficulty seems to be caused by the low sensitivity of metastatic tumor cells to anticancer drugs and radiation. Surgery and radiotherapy are the main treatment modality of morning metastases for HNSCC. Metastasized regional lymph nodes are usually controlled by surgical removal (Shah & Andersen, 1994). However, surgical removal of distant metastatic tumors is usually not easy, especially in patients with multiple organ metastases. Because of these difficulties in conservative and surgical treatments, distant metastases are lethal in most patients.

Treatment planning for cases with axillary metastasis must take in consideration the likelihood of other regional recurrences and/or distant metastasis. Also, the presence of a second primary tumor must be ruled out. Whenever axilla is the only site of cancer recurrence, a standard axillary dissection must be considered. Upper mediastinal metastases from subglottic and hypopharyngeal cancer are managed by paratracheal and mediastinal dissection through the neck and postoperative radiotherapy (Kowalski, 2001).

Surgery is sometimes useful in the treatment of bone metastases. For example, pulmonary metastasectomy of isolated metastasis has been shown to be of benefit in selected patients (Wedman, et al., 1996). Surgery is sometimes useful in the treatment of bone metastases, although radiotherapy is the standard first-line treatment. In metastatic brain tumor, surgical resection should also be considered for patients with solitary brain metastasis and no extracranial disease or controlled extracranial disease. Whole-brain radiotherapy is routinely administered postoperatively (Hoegler, 1997). Although surgical removal of isolated solid metastatic tumors in liver is sometime carried out, adjuvant chemoradiation is the mainstream in the treatment modalities.

Occasionally, surgical resection of metastases is useful for metastases that do not respond to radiotherapy and in weight-bearing or high-stress areas (subtrochanteric region of the hip, mid-femoral diaphysis, mid-humeral metaphysis). Surgical stabilization can improve the remaining quality of life in these patients if it is carried out early enough (Sim, et al., 1992). A brief, fractionated course of radiotherapy is usually given postoperatively (Hoegler, 1997).

5.3.3 Chemotherapy

Head and neck cancer metastases are responsive to chemotherapy and the use of multiple agents may increase response rate. Unfortunately, neither single agent nor combinations of drugs have any significant impact on survival (de Mulder, 1999). The exception may be nasopharyngeal carcinoma, where platinum-based chemotherapy may increase survival even in the presence of distant metastases (Gebbia, et al., 1993). Chemotherapy also acting as a radiosensitizer, increases survival in advanced metastasis in HNSCC.

Neoadjuvant chemotherapy with the cisplatin and fluororacil (PF) regimen in HNSCC patients has no effect on locoregional relapse. However, it shows a small but significant

benefit in reducing distant metastasis and improving the overall survival (Su, et al., 2008). Many new chemotherapy ways are attempted in a broader sense of targeted therapy.

Multi-modality treatment or targeted therapy-containing management does not significantly improve overall survival.

Systemic chemotherapy management of extensive metastasis in HNSCC patients is a major concern. The drugs most commonly used clinically are the platin compounds (cisplatin and carboplatin), taxanes (docetaxel and paclitaxel), 5-FU, methotrexate, and ifosfamide. In an effort to improve response rates and, hopefully, survival time, combination chemotherapy needs to be developed.

5.3.4 Radiotherapy

Radiotherapy is the standard first-line treatment of bone metastases in HNSCC. Radiotherapy also has a role in the infrequent patients with brain metastases, especially for solitary brain metastasis with no extracranial diseases or have been controlled. It relieves clinical symptoms in 70-90% of patients (Hoegler, 1997). The use of stereotactic radiosurgical treatment remains to be defined. It is most often used to treat solitary metastases in previously irradiated patients.

Radiotherapy is unlikely to cure even solitary lung metastases. However, it may have a palliative role and increase survival when there are a limited number of foci, small metastases and locoregional control (Sugawara & Kaneta, 1983). Approximately 50% of patients with cancer develop bone metastases, although they are relatively unusual in head and neck cancer. They can cause pain and affect weight-bearing areas and consequently have a significant impact on quality of life. The role of radiotherapy in the palliation of bone metastases is well supported in the literature, with reported response rates of around 70-90% (Arcangeli, et al., 1998, Hoegler, 1997). The pain relief is complete in nearly half of the responders (Uppelschoten, et al., 1995) (Steenland, et al., 1999). If patients fail to respond to the first treatment, then they may respond to re-treatment.

5.3.5 Associated targeting therapy

Recently, molecular targeting biologicals with a different toxicity profile and hopefully less late damage to functionally important tissues may open new strategies in primary and adjuvant treatment of HNSCC. The principal strategies currently being used to design antiangiogenesis agents are aimed at blocking angiogenic factors (or enhancing negative regulators) or acting on endothelial cells to block cell surface receptors or prevent them from breaking down the surrounding matrix.

Besides cetuximab and other EGFR targeting mAbs, there are other receptors and non-receptor tyrosine kinase inhibitors, which might play an important role in the future treatment of HNSCC. Many investigatons have been carried out to solve the problem of multi-drug resistance in HNSCC progenitor cells. Cetuximab, as an epidermal growth factor receptor-specific monoclonal antibody, plus radiation were shown to improve survival rate as compared to radiation treatment alone (Bonner, et al., 2006). However, one retrospective study suggests the duration of progression free survival and overall survival is shorter in patient receiving cetuximab plus radiation than those with cisplatin plus radiation (Pignon, et al., 2009).

It is prostulated that VEGF targeted therapy has the potential to fulfill both anti-angiogenic and anti-tumorigenic functions (Tong, et al., 2008). As reported, CD44 certainly posseses a valid target for anti-cancer therapy. CD44 targeting members of several relevant pathways might be used to induce apoptosis or inhibit tumour angiogenesis and metastatic spread. Immunotherapy for HNSCC is a relatively new but promising therapeutic strategy. In HNSCC, immunotherapy has been implemented successfully in patients, especially in patients with end-stage metastasising disease, who had undergone a variety of other therapeutic modalities. Despite this fact, both clinical and translational trials with cytokines, monoclonal antibodies, and various kinds of other strategies have yielded promising results with little evidence of host toxicity. Future efforts will be foucusing on finding ways to circumvent immune tolerance and overcome malignancy-related immune dysfunction to produce regimens with better efficacy.

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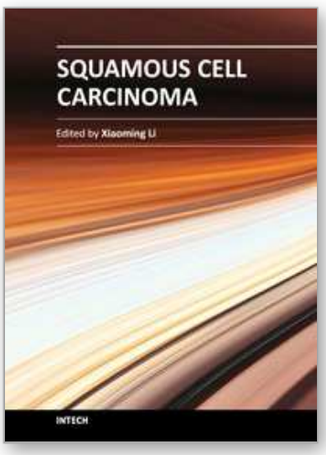
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This book points to some new areas for investigation on squamous cell carcinoma (SCC). Firstly, the features and management of some specific SCC is discussed to give the readers the general principles in dealing with these uncommon and sophisticated conditions. Some new concepts in adjuvant therapy including neoadjuvant therapy and gold nanoparticle-based photo dynamic therapy are introduced. Secondly, a detailed discussion of molecular aspects of tumor invasion and progression in SCC is provided with the emphasis on the roles of some important factors. The role of tumor microenvironment in head and neck SCC is specifically discussed. Thirdly, the roles of cancer stem cells (CSC) in cancer therapy of SCC are described. Molecular mechanisms involving therapeutic resistance and new therapeutic strategies targeting CSC are discussed in detail. Finally, other aspects concerning SCC are included, which involve the assessment, genetic manipulation and its possible clinical implications for the treatment of SCC.

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