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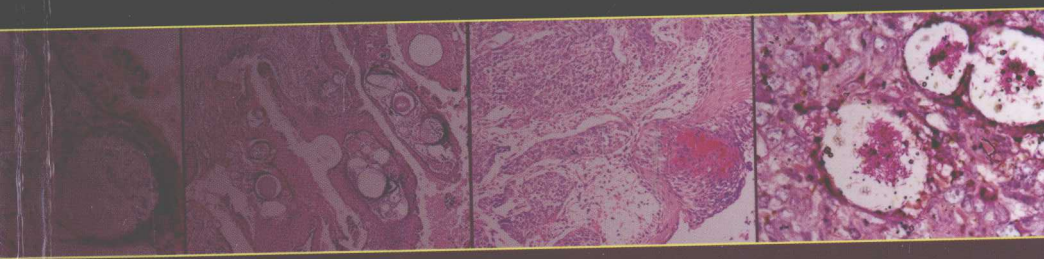
Pathology Atlas of nasopharyngeal carcinoma (NPC) and other diseases of nose and nasopharynx

鼻、鼻咽疾病病理图谱



天津科技翻译出版公司
TIANJIN SCIENCE & TECHNOLOGY TRANSLATION & PUBLISHING CORP.

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天津科技翻译出版公司出版

图书在版编目(CIP)数据

鼻、鼻咽疾病病理图谱:英文 / 陆献瑜编著. --
天津:天津科技翻译出版公司,2010.4
ISBN 978-7-5433-2691-0

Ⅰ.①鼻… Ⅱ.①陆… Ⅲ.①鼻咽肿瘤—病理学—图谱—英文 Ⅳ.①R739.63-64

中国版本图书馆 CIP 数据核字(2010)第 055303 号

出　　版:天津科技翻译出版公司
出 版 人:蔡 颢
地　　址:天津市南开区白堤路 244 号
邮政编码:300192
电　　话:022-87894896
传　　真:022-87895650
网　　址:www.tsttpc.com
印　　刷:山东临沂新华印刷集团有限公司
发　　行:全国新华书店
版本记录:880×1230　32 开本　4.25 印张　180 千字
2010 年 4 月第 1 版　2010 年 4 月第 1 次印刷
定价:45.00 元

Introduction of editor-in-chief

Lu Xian-yu, Professor of Pathology at Sun Yat-sen University Cancer Center, was born in December 1928. She has been engaged in clinical diagnosis; teaching and research work for several decades, and made a great achievement.

Prof. Lu worked precisely and accumulated abundant experience on diagnosis of difficult cases. She differentiated many specious cancer cases and rectified many wrong diagnoses to avoid unnecessary radiotherapy, chemo-therapy and radical operations. Also she compiled textbooks and held many training lessons of tumors. A lot of professionals specializing in pathology have been trained. Prof. Lu devoted herself to the research of nasopharynx, liver, breast, thyroid carcinomas and malignant lymphoma. Remarkable successes have been achieved. 58 research papers were published. She compiled the electrical teaching material of clinical pathology which was entitled "Nasopharyngeal Carcinomas, Nasal and other Nasopharyngeal Diseases" and won the 2nd prize of audio-visual aid textbook of higher education. She also took part in the compiling of "The Clinical and Experimental

Research of Nasopharyngeal Carcinoma", which got the 1st prize of the National Science and Technology Publication. The finding of four pigs with early NPC out of 17923 pigs made she got the 3rd Science and Research award of Guangzhou. The research papers about nasopharynx, liver, breast thyroid carcinomas and malignant lymphoma also won 2nd, 3rd, and 4th Research Prize of Guangdong province, Guangzhou respectively.

Prof. Lu enjoys a special allowance granted by the State Council of Chinese Government.

Hou Jing-hui

Preface

Sun Yat-sen University Cancer Center is a well known institution for diagnosis, treatment and research work on nasopharyngeal carcinomas (NPC). The affiliated hospital has admitted and treated thousands of patients coming from all over the country and the southeastern Asia. In order to providing more facilities and references in contributing to training of medical professionals and to raise further the diagnosis and research level of NPC, the authors compiled this atlas by collecting photographs with either gross or microscopic findings from 211 248 biopsies and 8,848 autopsies. Among them, a few cases are from Sun Yat-sen College of Medical Sciences. We hope it will enrich further the documents of pathology, oncology and otorhino laryngology.

Prof. Liang Bo-qiang is one of the founders of pathology in China. He had initiated the work on study/diagnosis/treatment of NPC in China. He had made great pioneer achievements in the field of histopathological classification, biological behavior, origin of NPC and put forward the Liang's classification of NPC, which is significant for further investigation of NPC. Hundred thousands of biopsies and autopsies had been reported according to Liang's classification for several decades,

which has become a routine classification for NPC clinically. The NPC cases reported in this atlas were classified under the principle of Liang's classification.

This atlas serves as a reference book for teaching, clinical practice and research programs of NPC in pathology or otorhinolaryngology of medical colleges, hospitals and institutions. It is hard to avoid oversight, criticism and correction are welcome.

Thanks for the help of Prof. She Ming-peng, Zhen Yong-su, Zhong Shi-zhen, Zeng Yi-xin, Wu Qiu-liang. Also thanks to Prof. Sun Zhen-quan and Zhu Jia-zhen for providing some their precious pictures.

Lu Xian-yu ***Editor-in-chief***

2008

1 General outline

1. The pathologic category of Nasopharyngeal carcinoma (NPC)

Any malignant tumor which originates from the epithelium of nasopharynx including the tubular glands and acinus under the mucosa are termed as nasopharyngeal carcinoma (NPC). Histologically, the mucosa locating near by the oral pharynx, the lower half of the posterior wall, the lateral and inferior walls of nasopharynx is covered by squamous epithelium while the area near by the posterior nares is covered by pseudostratified ciliated columnar cell epithelium. Flat shaped transitional cells and squamous cell islands are obtained at the border between the squamous and columnar cell epithelia. There are cuboidal epithelial cells of excreting snot (nasal discharge) and columnar epithelial cells lining the gland tubules underneath the nasopha-ryngeal mucoas. All these epithelial cells might be infected or undergoing malignant change by repeated stimulation of certain pathogens or carcinogenic factors. Carcinomas originating from different epithelial cells might give a different pathological feature and so to have a different corresponding therapeutic regimen. For example, the morphology of well-differentiated carcinoma cells is somewhat close to normal epithelial cells, such

as keratinizing squamous cell carcinoma, basal cell carcinoma, papillary adenocarcinoma originating from the columnar cell of gland tubules, and adenoid cystic carcinoma originating from the gland acinar cells. All of these cells are insensitive to radiation therapy, so that, it's important to have an earlier pathologic diagnosis and an effective corresponding therapeutic plan.

Tumors originating from other tissue in nasopharynx are not termed as NPC. The malignant tumors originating from lymph tissue under the nasopharyngeal mucosa are called lymphoma, of which the principle treatment is chemotherapy. The malignant tumors originating from soft tissue or blood vessels under the nasopharyngeal mucosa are called sarcoma and the therapeutic principles are different. Therefore, in addition to different types of NPC, the author had also enumerated the benign and malignant tumors of both nasopharynx and nose as well as different kinds of inflammatory and tumor-like lesions for differential diagnosis. It's important to ensure the biopsy diagnosis before to make a therapeutic regimen for the cancer patients.

2. Problems concerning pathohistological classification of NPC

The principle of histopathological classification for NPC of this atlas is according to Liang Bo-qiang's histopathological classification. In order to make an easlier comprehension of this classification for the readers, the authors have listed the latest version of WHO's histopathological classification[3] in contrast as follows:

Histopathological classification of NPC

(based on Liang Bo-qiang's histopathological classification)

2.1 Undifferentiated Carcinoma (Fig.61–64)

Pleomorphic cell carcinoma (large cell type and small cell type)

2.2 Poorly differentiated Carcinoma

2.2.1 Giant round cell carcinoma (distant metastasis com-

mon) (Fig.68–71)

2.2.2 Spindle cell carcinoma (with a tendency of invading base of the skull commonly) (Fig.65–67)

2.2.3 Squamous cell carcinoma grade III (invasion of base of skull and distant metastasis) (Fig.54– 60)

2.2.4 Clear cell carcinoma(Fig.79–82)

2.2.5 Mixed–cell Poorly differentiated Carcinoma (Fig.87)

2.3. Well differentiated Carcinoma.

2.3.1 Squamous cell carcinoma grade I (Fig.48–51)

2.3.2 Squamous cell carcinoma grade II (Fig.52)

2.3.3 Adenosquamous carcinoma(Fig.85)

2.3.4 Columnar cell adenocarcinoma (including tubular adenocarcinoma and Papillary adenocarcinoma) (图 88, 89, 99–103)

2.3.5 Cuboidal cell carcinoma (including Acinar cell carcinoma) (Fig.91–98)

2.3.6 Mucoepidermoid carcinoma(Fig.104,105)

2.3.7 Adenoid cystic carcinoma(Fig.106–117)

2.3.8 Basal cell carcinoma(Fig.46,47)

Since the photographs published in this atlas are the representative cases of NPC which were selected from 211,248 biopsy and 8,848 autopsy cases, so that the number of types classified was expanded and more than that in the before. Some tumors are rarely seen in the past, such as adenosquamous carcinoma, cuboidal acinar cell carcinoma that originate from the gland acinus and tubules under the nasopharyngeal mucosa, as well as adenoid cystic carcinoma. These tumors are not sensitive to radiation therapy and metastasis also rarely occurs. In figures'110–113, the primary adenoid cystic carcinoma was resistant to radiation therapy, and unfortunately in this case, another malignant fibrous histocytoma developed in stroma after radiation therapy. It seems important to emphasize that for those well differentiated and non-metastasized NPC, completely removal of the primary tumor mass is recommended and further

therapeutic regimen is suggested in trial.

Basing on the data of analysis of 50 NPC autopsy cases reported by Liang Bo-qiang et al[2], types or features of the secondary or metastatic tumors might be different from that of the original ones. For instance, Squamous cell carcinoma or spindle cell carcinoma originally seen in biopsy specimens might be changing into pleomorphic cell carcinoma in the metastatic nodules and occasionally, different diagnosis might appear in the autopsy findings. Recently immunohistochemical detection confirmed that cytokeratin (CK)is positive in spindle cell carcinoma, pleomorphic cell carcinoma and most giant round cell carcinoma indicating that NPC mostly originate from squamous cell epithelium or from malignant change of squamous cell metaplasia of the columnar epithelium[4-6]。

Basal cells of squamous epithelium as showed in Fig.s.68 and 69 and cells in stratum basalis of the gland tubules lining with columnar cells as showed in Fig.70, all are able undergoing atypical hyperplasia; then malignant change to transform into giant round cell carcinoma. The author considered that giant round cell carcinoma belonged to an undifferentiated type. It might originate from cells of stratum basalis of squamous epithelium or from the basal cells of glands and tubules.

【Remarks 1】the author considered that the term "differentiated non-keratinizing carcinoma" raised in WHO NPC pathological classification, reflected the clinical feature, and seem worth to be preserved. Practically, malignant tumors occur from transitional cells of squamous epithelium and well-differentiated columnar epithelium. They are non-keratinizing, mitosis scanty, and developed slowly, similar to lympho-epithelioma or the transitional cell carcinoma.

【Remarks 2】WHO histological classification of tumours of the nasopharynx is too simple to express cytomorphological characters and is not in favour to clinic study of treatment pro-

WHO NPC pathohistological classification[3] tumours of the nasopharynx	
Malignant epithelia tumours	
NPC	
Non-keratinizing carcinoma	8027/3
Keratinizing squamous cell carcinoma	8071/3
Basaloid squamous cell carcinoma	8083/3
Nasopharyngeal papillary adenocarcinoma	8206/3
Salivary gland-type Carcinoma	

jects of all kinds of NPC. Therefore, cytomorphological characters and differentiated degree of cancer cells are taken as the base of histological classification in this book.

【Remarks 3】In order to express cytomorphological characterstics in favour to cilinical study of treatment projects of all kinds of NPC, cytomorphological characteristics and differentiated degree of cancer cells are taken as the base of histological classification in this book. Moreover, Liang's classification depended on lots of biopsy and anatomy datas is recommended. For example, giant round cell carcinoma of the nasopharynx was used to being called clear nuclear cell carcinoma. The author considers that the nucleus of most adenocarcinoma nuclear is clear; however it has been confirmed that cases of giant round cell carcinoma of the nasopharynx may originate from glandular and squamous epithelia (see Fig. 68–71).

3. Clinical symptoms and diagnosis of NPC

3.1 Symptoms of first visit to a doctor

If mucosa is involved in early stage, nasal hemorrhage and blood sputum may emerge. Nasal obstruction and nasal hemorrhage may appear if parietal wall or nearly posterior naris is involved. Headache, tinnitus, hypoacusis, exudative tympanitis

may appear if parietal wall of nasopharynx, auditory tube, protuberance and pharyngeal recess is involved. Some patients didn't have any auris and nasus symptoms. They didn't see a doctor until they had cervical lumps of lymph nodes, or diplopic, goggle-eye, exophthalmus, hypoacusis and one-side temporal, parietal or/and occipital migraine due to the base of skull is invaded.

3.2 Auris and nasus symptoms

Because of NPC invading, enlarging and projecting from surface, patients commonly have purulent and bloody snot due to infection, except nasal hemorrhage for ulcerated, nasal obstruction and tinnitus. Few patients with NPC under mucosa had nasal hemorrhage. If olfactory nerves involved, patients may have hyposmia or anosmia; if Ⅷ pair of cranial nerves involved, patients may have deaf and vertigo.

3.3 Eyes symptoms

NPC may invade the basal skull and cavernous sinus region, and damage the cranial nerves. For example, if trochlear nerve (Ⅳ pair of cranial nerves)is damaged, superior oblique muscle is involved, the patients will have problem of depression in nasal-down direction. If oculomotor nerver (Ⅲ pair of cranial nerves) is damaged, superior rectus muscle, inferior rectus muscle, medial rectus muscle and inferior oblique muscles will be involved, the eyes may be fixed except abduction. If levator palpebrae muscle is involved, patient may have ptosis (blepharoptosis). When the sphincter muscles are involved, pupil dilatation may present. Since abducens nerves (VI pair of cranial nerves) pass a comparatively long distance and through the region that NPC oftens invade, they usually are affected early and result in paralytic diplopia as the first symptom. The patient often go to see oculist first. If NPC invades sphenoid bone, sphenoidal sinus, posterior ethmoidal cells, hypophysial fossa upwards, the region between optic chiasm and optic fora-

men can be invaded, the patients would have partial blindness and monocular or binocular blindness with optic nerve damage. Optic nerve atrophy may be seen by fundus examination.

NPC could invade orbit through many routes: it can enter the orbit through inferior and superior orbital fissure; come into pterygopalatine fossa along pterygoid canal; enter inner orbit though orbital apex. Posterior ethmoidal cells are involved through posterior naris, thus entering the orbit. If areas around auditory tube are involved frequently, thus invading petrosphenoidal space along fasciae and Ⅲ, Ⅳ and Ⅴ pairs of cranial nerves, the patients may have paralysis of eye movement. What's more, if trigeminal nerve or optic nerve is involved, the patients may have sensory disturbance of nasociliary nerve, eyeball, face, nasal cavity mucosa, lacrimal gland and upper eyelid. Finally, the patients may become blind in one or both eyes. If cervical sympathetic ganglia is involved, the patient may have Horner's Sign, which includes myosis, blepharophimosis and endoophthalmos. If NPC enters the orbit by way of extracranial passageway, the patients may have exophthalmia first, may be with or without cranial nerves symptoms.

3.4 Headache

Headache is one of the more common symptoms of NPC. It may be the earliest or unique symptom. Statistically 68.6% of the 1000 cases in the Tumor Hospital of Sun Yat-sen University complained of headache. Headache that appears in the early stage may be neurovascular reflex headache, or due to the stimulation of the first peripheral branch of trigeminal nerve, or related to backflow obstruction because of tumor internal cervical nerve compressed by. The headache is more common in single temporal, parietal or/and occipital region. The places of hemicrania are relatively steady. In the later stage the patients' neurogenic headache would he much more serious due to the involvement of basicranial bones, also associated with corre-

sponding symptoms of every pair of nerves involved. However, headache would dissapear if tumor involvement paralyed trigeminal nerve, while the symptoms of other pairs of involved nerves still exist.

3.5 The symptoms of mouth and other cranial nerves invided

If Ⅶ pair of cranial nerves (facial nerve) are involved, facial expression muscle may cause disappearence of frontal wrinkle, incompletely closed eyes, nasolabial sulcus shoaling and underlip deflexion. If (one side) IX pair of cranial nerves (glossopharyngeal nerve) are involved, patients may have sensory disturbance of the pharynx and posterio third of the tongue, secretory disturbance of parotid, palatine arches caved in. If X pair of cranial nerves (pneumogastric nerve) are involved, the patients may have anesthesia of hypopharynx and larynx, and that food may be aspirated into the trachea may cause tussis, voice hoarseness, vocal cords paralysis and sensory disturbanc of tragus's skin. If XI pair of cranial nerves (accessorius nerve), are involved, patients' trapezius muscle and sternocleidomastoid muscle may become atrophic and patients may shrug weakly. If XII pair of cranial nerves (hypoglossal nerve), are involved, patients may have unilateral tougue atrophy, and deviation towards the affected side.[6,7]

3.6 The symptyoms of basicranial bones invaded

79% of basicranial bones destroyed have headache, and 21% have no headache. 70% of patients with symptoms of III, IV, V, VI pairs of cranial nerves involved, will have basicranial bones destroyed. Most patients with descending-type NPC invading their cervical lymph nodes do not have basicranial bones destoyed.[6]

3.7 Enlargement of cervical lymph nodes

The metastatic ratio of cervical lymph nodes in NPC is

very high. According to the statistics provided by the Tumor Hospital of Sun Yat-sen University, of the 1000 NPC cases, the metastatic ratio of cervical lymph nodes is 78.9%, and the metastatic ratio of bilateral cervical lymph nodes is 34.1%. Metastatic ratio of NPC in parietal and basal walls is higher. Usually metastasis of parietal and basal walls is the primary symptom which precedes the symptoms of auris and nasus. Of the 1000 cases, the metastatic ratio of NPC in parietal and basal walls is 45.3%, while primay focus was not found in 18 cases (1.8%). It is possible that the primary focus is under mucosa near the pharyngeal recess of the prominance posterosuperior to the auditory tube. So some patients' primary symptom was the enlargement of cervical lymph nodes. Therefore, the nasopharynx of all patients who have enlargement of cervical lymph nodes should be checked. Enlargement of superior deep anterior cervical lymph nodes (under posterior belly of digastric muscle) or posterior cervical lymph nodes (under apex of papillary muscles and deep surface of sternocleidomastoid muscles) may occur first. If the patient's primary focus is located behind nasopharyngeal cavity, enlargement of accessor lymph nodes of posterior triangle of neck may occur firstly[7].

According to lymph drainage of nasopharyngeal cavity, enlargement of retropharyngeal and parapharyngeal lymph nodes may occur firstly; pharyngorhinoscopy shows retropharyngeal mucosa upheaving. If Ⅸ, Ⅹ, Ⅺ, and Ⅻ pairs of cranial nerves are involved, enlargement of retropharyngeal lymph nodes should be suspected as the cause. Metastasis of lymph nodes of descending NPC often occurs earlier than that of ascending NPC. According to the statistics of the Tumor Hospital of Sun Yat-sen University, of the 1000 cases, the metastatic ratio of one-side cervical lynph nodes is 43.3%, whereas the metastatic ratio of two-ide cervical lymph nodes was 34.1%. In ascending NPC, squamous cell carcinoma grade I and grade II

of NPC usually fewer cases have metastasis, with their ratio being 21.1%.Cervical lymph nodes through thoracic duct communicate with supraclavicular cervical large veins, so cancer cells enter into the blood vessels by this way and distant metastasis may occur. Autopsy showed that the metastatic ratio was 76%[8], and most mestastatic focuses are in bone, lung and liver.

Radiograph shows osteolytic, osteoblastic or mixed focus. Osteoblastic focus appears an even and dense image.Mixed-type appears mottling, radial or pectinal neogenetic bone, mostly seen in thoracic and cervical vertebrae. In the early stage of metastasis in liver, lungs and mediastinum, the patients have no symptoms. In the later stage, the patients may have hemoptysis, chest pain, hepatomegaly and hepatalgia, and mediastinal lymph radiograph may show nodular image, B-ultrasound and CT are helpful for diagnosis.

3.8 Problems of NPC early diagnosis

NPC early diagnosis can improve NPC treatment ratio. In early stage, NPC is limited in nasopharyngeal cavity, basicranial bones, cranial nerves and cervical nodes are all free from NPC no metastasis exist in other distant organs. For many years only 3%~6% of patients with stage I NPC were definitely diagnosed per year in Tumor Hospital of Sun Yat-sen University. The cure treatment ratio of stage I NPC is 76.9%.

In the early stage it is very difficult to find out focuses in pharyngeal recess and pharyngeal base due to a covered nasopharyngeal position. Headache, nasal obstruction, nasal hemorrhage and tinnitus are usually misjudged as indisposition. Many patients with those symptoms will delay seeing a doctor. Many patients come to see a oculist because of strabismus, diplopic or hypopsia. Some patients casually take Chinese medicine or anodyne for their headache. Some patients who