

# Cytology, Pathology, Frozen Section and Occult Primaries in Head and Neck Cancers

Roshni Chinoy

Department of Pathology, Prince Aly Khan Hospital, Nesbit Road, Byculla, Mumbai, Maharashtra, India

**Correspondence:** Roshni Chinoy, Department of Pathology, Prince Aly Khan Hospital, A/4 Amalfi, LD Ruparel Road, Malabar Hill, Mumbai 400006, Maharashtra, India, Phone: 23673833, Mob.: 9821242778, e-mail: roshchinoy@gmail.com

## Abstract

Whilst squamous cell carcinomas take center stage in the head and neck area, almost any mass disease that can occur in the rest of the body can theoretically occur here too. This includes the spectrum of adenocarcinomas, lymphomas, melanomas and sarcomas, not forgetting the diversity of salivary gland and thyroid tumors. Diagnoses by FNAC, open biopsy or frozen section have their own inherent, site specific, individualistic problems, and some of the basic principles will be highlighted. Frozen sections for resection margins and staging will be dealt with. Finally the challenge of the occult primary with metastasis in the head and neck, and understanding the need for immunohistochemistry are also touched upon.

**Keywords:** Head and neck cancers, squamous cell carcinoma, immunohistochemistry.

## INTRODUCTION

The head neck region is an anatomic site rich in diverse structures ranging from lymph nodes, nerves, veins, arteries, muscles, and mucosal epithelium to salivary glands, thyroid, and a host of developmental tissues. Almost any of these tissues can become pathological, resulting in a mass. The pathologist enters the arena of diagnosis when the clinical concern of a tumefaction calls for an FNAC or a biopsy.

The need for an accurate timely and well structured pathology report has become increasingly important in this age of super-specialization, never forgetting a society that is both erudite and critical, and consequently, increasingly litigious.

To diagnose a tumor in the absence of clear and relevant clinical and if necessary, radiological information, is foolhardy dangerous and can lead to inaccurate diagnosis and treatment.

Keeping in mind the fact that the readership of this journal caters to the needs of clinicians and not pathologists, I will refrain from the temptation to launch into a full blown discourse on the microscopic features of different lesions. The approach will be targeted for clinicians, and a few broad principles of head and neck pathology, and the 'why' and 'what' of some of our problems will be tackled.

## CYTOLOGY/FNAC OF HEAD NECK LESIONS

Head neck aspirates form approximately 65% of the total work load of cytology at our institute. The large numbers are a reflection of the high incidence of head and neck cancers in our country, which form 27% of all cancers.<sup>1</sup>

Neck lymph nodes take precedence over salivary and thyroid lesions, though we receive samples from almost all other sites like the scalp, orbit, parapharynx and other deep seated locations.

A neck mass in an adult, that is present for longer than a week is pathological until proven otherwise.<sup>2</sup> In our country, tubercular lymphadenitis is not at all uncommon but even so, a large percentage of all persistent adult neck masses turn out to be malignant, whereas in the pediatric population, neck masses are only rarely malignant.

Lumps in the head and neck are soft targets for the needle aspiration as many are superficially located and are accessible to the fine needle. FNAC is safe, simple, rapid and relatively cheap. They leave no scars, neither is there any risk of seeding tumors along the needle tract. Patients of all age groups can be subjected to this procedure. The procedure is incredibly cost effective and free of complications, well tolerated by the patient, done on an outpatient basis and it is repeatable. India is imminently suited

to use this procedure, and this is borne out by the fact that it has flourished both in large institutions, in peripheral small community hospitals and in private clinics. More than 90% of head neck lesions are diagnosed by the initial aspiration.

The aspirator could be the clinician, radiologist or the pathologist, provided that they are all familiar with the banal but important task of preparing well spread smears and fixing them quickly in cytological fixatives, or quickly drying smears meant for Romanowsky stains. FNAC is performed using a 23 or 24 gauge needle. An average of 2 to 3 passes are performed and a minimum of 3 slides are prepared. One slide is rapidly air dried and stained by Giemsa stain, while the remaining 2 slides are fixed in an alcohol ether mixture and then stained with PAP stain and routine hematoxylin eosin respectively. Hemorrhagic smears can occlude the precise cells which require diagnosis, and they also hamper good fixation and preservation of cells.

The cytologist interpreting the smears needs to have a clear indication of the terrain being sampled as this is crucial for interpretation. In case of lymph nodes, information of the level of lesion is vital for the diagnosis. Most of the positive upper level neck aspirates are generally metastatic from the upper aero digestive tract, thyroid and salivary glands, or may present as occult primaries. Occasionally a lower level neck node harbors metastasis from a distant site located in the gastrointestinal tract, kidney or the lung. Other primary sites below the clavicle, which may metastasize to the neck, are the cervix, ovary and sometimes even the bladder. Germ cell tumors, melanomas, small cell tumors are also part of the metastatic load in the head neck location. FNAC is also of considerable value in disease staging and documentation of recurrence.

In a previous study of 1255 patients by the author, as many as 184 specimens (i.e. 9%), were unsatisfactory: 496 samples, i.e. 25% were negative or reactive. Samples suspicious or positive for malignancy were reported in 1299 specimens (65.67%). The most common metastasis to the neck nodes was of squamous cell carcinoma arising in the oral cavity.<sup>3</sup>

The false-positive rate of lymph node FNAC for the detection of metastasis is quite low (in the range of 0.9-1.7%).<sup>4</sup>

Avoiding false-positive diagnosis is of obvious importance since therapeutic and surgical decisions are often based exclusively on cytology results. Cystic metastasis and aspirates of unusual low grade malignancies compose most of the false-negative cases.<sup>5,6</sup>

Deep seated masses especially those in relation to the craniofacial bones or in the orbit, posterior oropharynx and larynx require imaging techniques like USG or CT guidance. Such aspirates are particularly rewarding, as biopsies are difficult or even impossible from such awkward sites.

In case of salivary gland swellings, there is a formidable diversity of lesions, which necessitates information regarding duration of the swelling, the texture of the swelling (cystic or solid) and prior knowledge of the histopathology of these tumors. FNA diagnosis is useful in avoiding surgery (inflammatory lesions) or limiting surgical procedures (benign tumors). Mixed tumors and obviously malignant growths are easily recognized, however, cellular variants of mixed tumors and low grade tumors like polymorphous low grade carcinomas are difficult variants which may necessitate a frozen section diagnosis. Tumors like Acinic Cell carcinomas and low grade lymphomas are notoriously unreliable in that recognition of their malignant potential is difficult.<sup>7</sup>

The thyroid has been increasingly needled over the years, and there is reliable evidence that papillary carcinomas and medullary carcinomas can be accurately diagnosed in most cases. Diagnosis of follicular adenomas and carcinomas are the domain of the histopathologists, as cytology can be bland in both entities. Diagnostic evidence that stamps the lesion as malignant are, presence of angio-invasion and capsular invasion: both are architectural details that cannot be visualized in the cytology smears. Frozen sections are useful in guiding the intraoperative management for patients with unilateral thyroid nodules with benign or indeterminate preoperative FNAC.

## **GENERAL FACTS ABOUT FNAC OF USE TO THE CLINICIAN**

### **Screening for FNAC?**

Well performed needle aspiration cytology, whether done directly or with image guidance, should by its very nature be representative of the lesion in question. The needle is expected to be in the mass, and therefore the smears should contain material from the lesion. Unlike the exfoliated gynec PAP smears which need extensive screening for scanty hidden pre-neoplastic cells, the FNAC is not really a screening procedure in that sense.

A positive report of a malignancy or a specific disease process like tuberculosis, is usually forthcoming if the choice of patients requiring FNA is properly done. Patients

who have no mass lesion are unlikely to benefit from an FNA. A vague nodularity or diffuse induration in a tissue seldom yields sufficient cells for a diagnosis.

If on the other hand, the needle is definitely in the mass, and still a negative report has been rendered, and smears are poorly cellular, then there are 2 possibilities: A) the aspiration is poorly and inadequately performed, and the procedure has possibly missed the target site altogether, because FNAC is prone to sampling errors. B) The lesion is fibrotic and possibly genuinely poorly cellular. If the mass is superficially located, a repeat aspirate would be preferable. If the lesion is deep seated, a repeat aspirate requires visualization and whatever few cells that may be obtained in the needle, must be quickly smeared and fixed without any delay.

Apart from poor cellularity, the other common causes for non-diagnostic smears can be technically suboptimal quality of the smears due to drying artifacts or admixture with blood. Cells which are allowed to dry slowly or unevenly on glass slides tend to spread and flatten themselves out, with the result that their sizes and contours get distorted. Such smears can get misinterpreted. Nuclear distortion is particularly distressing, as the basis of all cancers is largely on the nature of the nuclei, and often by the nuclear to cytoplasmic ratios. On the other hand, when we utilize the Giema smear for air dried cells, we dry the smears quickly by gently fanning the glass, and then staining them.

### FRAMING A CYTOLOGY REPORT

Documentation of the cytology findings in the report does not necessitate a thesis on the phenotypic details; neither should any report fail to give a final impression. Clinicians have little patience with our “pink and blue cells” and often skip the entire descriptive section, to leapfrog into the final impression. However, features regarding adequacy of the sample, degree of cellularity and architectural patterns if any, should be looked at critically by the discerning clinician. The cell morphology deserves a brief description, which should match with the final impression being signed out.

A report needs to be contributory and helpful to the clinician and should suggest the future line of management.

There are 4 general categories of reports:

1. Positive
2. Suspicious
3. Negative
4. Unsatisfactory

Every institute is expected to audit their years work and if there are more than 5-10% of unsatisfactory samples, then techniques should be improved and remedial steps taken.

If clinicians are dissatisfied with their pathologist's reports, or the pathologist is not getting adequate clinical information, they need to talk to each other and discuss each others problems and needs.

Most pathologists and clinicians need to be reminded that a report is also a form of a legal document which patients read, and often show around to other members of the professional world. There is need for clarity and openness in a report.

### RESULTS AND RELIABILITY OF FNA DIAGNOSIS IN THE HEAD NECK REGION

In our hands, FNAC had an accuracy rate of 83.5% thus proving to be a useful diagnostic test. One case diagnosed as metastasis of well-differentiated squamous carcinoma on FNAC, turned out to be an epidermal cyst on histology following excision. This was the only false positive case. In one patient with supraclavicular lymphadenopathy, a differential diagnosis of either a non-Hodgkin's lymphoma or metastasis of germ cell tumor was offered. Following excision biopsy, this was observed to be a metastasis of neuroendocrine carcinoma with a primary in lung.

Table of Cytology Diagnosis:

Cytology Results	Percentage of cases
Squamous Carcinoma	36.8
Adenocarcinoma	7.3
Poorly differentiated carcinoma	12.1
Small cell carcinoma	0.91
Non small cell carcinoma	1.1
Undifferentiated ca of nasopharyngeal type	1.82
Salivary gland tumors	0.70
Thyroid tumors	2.83
Reactive nodes	25
Uncommon metastasis like GCT, melanomas etc	1.52
Inadequate aspirates	9
Total (1978 patients)	100

In conclusion, cytology is an invaluable tool in the head neck region and yields valuable information rapidly and accurately.

### SURGICAL PATHOLOGY

The Royal College of Pathologists describes pathology as ‘*the hidden science at the heart of modern medicine, vital for the diagnosis and clinical management of disease*’.<sup>8</sup>

In our part of the world, head neck cancers form approximately 27% of all cancers.<sup>9</sup> The implications of accurate diagnosis staging and management call for a team effort between radiologists pathologists and clinical oncologists.

The majority of tumors are squamous cell carcinomas, but there are thyroid and salivary gland tumors to contend with, besides the lymphomas, melanomas and soft tissue masses.

Pathologists are advised to use the Royal College of Pathologists standards and minimum data set as a minimum standard of reporting head and neck cancer.

#### Primary Tumor

- Tumor site
- Tumor type
- Tumor grade
- Maximum tumor dimension
- Maximum depth of invasion
- Margin involvement by invasive and /or severe dysplasia
- Pattern of infiltration
- Perineural invasion
- Lymphatic/vascular invasion

Histopathology reporting of metastatic disease should include:

- Number of involved nodes versus total number nodes
- Level of involved nodes
- Extracapsular spread of tumor
- Type of nodal dissection
- Size of largest tumor mass<sup>10</sup>

There are several subtle nuances for different sites which call for continuing dialogues between pathologists and clinicians.

## FROZEN SECTIONS IN HEAD AND NECK PATHOLOGY

Ackerman describes the frozen section as *“one of the most important and difficult procedures a pathologist performs during his practice. It requires experience, knowledge of clinical medicine and pathology, the capacity to make quick decisions under pressure, good judgment, an attitude that is conservative but not excessively so, and a keen awareness of the limitations of the method”*.<sup>11</sup>

Though the FS procedure is the literal ‘hot seat’ for the pathologist, the flip side of the coin is that FS enjoy a privileged place in the consultation services between clinicians and pathologists. It is professionally stimulating,

challenging and of immense benefit to the patients who peacefully sleeps though the procedure.

In the field of head neck pathology as in other areas, the questions asked during a frozen section service are as follows:

1. **What is the nature of the disease process?** In most instances, the definitive diagnosis has already been made by an open biopsy or an FNAC report. However, there are always an irreducible number of cases, where a diagnosis has not been arrived at, and it is only ‘on table’ that adequate or representative tissue can be obtained. Not surprisingly, it is the difficult cases that land up in the frozen section room.
2. Is this neoplastic? and if so, is it benign or malignant?
3. **Is the extent of the excision adequate?** This is an intra-operative assessment of adequacy of the margins of resection.
4. **What is the stage of the disease?** In the head neck area staging has become an issue of importance and interest in the management of patients ‘on table’.
5. **Is there representative tissue for confirming cancer and for IHC studies?** This is particularly relevant for our patients with suspected occult primaries, hemato-lymphoid neoplasms, in pediatric patients and patients with mesenchymal tumors.

In the final analysis, the only real reason for requesting an intra-operative consultation is epitomized in the statement written by Dr Lauren Ackerman *“There is only one purpose in the frozen section and that is to make a therapeutic decision.”*

Today the modern cryostat machine in the hands of experienced technicians, can offer tissue sections of excellent quality, which may be closely match the final paraffin sections. However, frozen sections are not permanent sections. Freezing creates its own set of artifacts which are uniquely different from the artifacts of routine processing. There are sampling errors, ice crystal artifacts drying artifacts and of course the limitation of time and number of sections that can be frozen.

The element of urgency itself places stress on the technician and the pathologist both.

The single most important first step in the frozen section procedure involves choosing the right area for sampling. It requires training to look at the gross appearance of organs and lesions and identity which area is likely to yield the best results. Having selected the area, it is important that neither surgeon nor pathologist should inadvertently squeeze the

tissue, or crush it, in an attempt to identify firm or suspicious areas. This can render a tissue useless for both the FS and the final paraffin sections.

A good technician will be able to produce a section which closely approximates the final paraffin section, and that too within a time space of 5-7 minutes. In the case of head neck samples, the commonest samples are lymph nodes sent for staging and surgical margins of resection.<sup>12-14</sup>

Intraoperative assessment of the clinically negative node with frozen sections is accurate with a specificity and positive predictive value approximating 98%. The negative predictive value is about 91%.

### Evaluation of Margins of Resection

Margins of resection evaluation can be accurately and reliably predicted on frozen sections. Basically there are two types of margins, the shave cut margin and the radial margin, both of which have merits and some demerits. The shave cut margin offers a long stretch of the outermost edge of the resected lesion for study, but here there is no way to measure the actual free distance between the tumor and the edge. In the case of the radial margin, the section includes tumor, a free area and the extreme edge of resection. Here the free distance between the two can be measured in millimeters and documented. The surgeon is in the best position to judge the areas s/he is worried about and the tissue sent to the FS room is best sampled by the operating surgeon in the theatre itself.

Inking of the edge which requires study is often a very good option and both pathologists and surgeons are accustomed to this exercise. Tumor actually reaching the inked surface, or within 1 mm of the tumor is reported 'positive'. In the case of shave margins, the entire tissue which includes the epithelium and the underlying sub-epithelium must be scrutinized and only if there is no tumor in any of the planes, then only is the margin is reported to be negative. Changes of dysplasia amounting to *in situ* carcinoma are documented, and the pathologist requests for a revised wider margin.

Problems arise when there are skip lesions, or when deeper sections studied in the paraffin sections reveal subtle *in situ* or invasive changes, not seen in the original frozen tissues. The problems can be somewhat obviated by taking frozen sections from the superficial as well as the deep planes, and the technicians are taught to offer 2 sections for every margin. In spite of such precautions, there will be instances when the final paraffin sections will reveal tumor.

Clinicians and pathologists have to learn to live with some of the limitations that biology imposes on some of these diagnostic issues.

## CANCER OF UNKNOWN PRIMARY SITES (CUP)

### Role of FNAC/Biopsy in the Diagnostic Work-Up

It is only natural for a patient to be in a state of shock when s/he has been diagnosed with cancer. It is a verdict harder to accept, when doctors cannot identify where the cancer is. This is a fairly rare situation, but one which calls for a dialogue between clinician radiologist and pathologist.

### Definition

CUP is the acronym for metastasis of unknown origin, and is defined "as a metastatic tumor for which the site of origin is not suggested on admission, even after a clinical history, thorough physical examination, or chest X-ray, adequate blood and urine tests, and initial histologic evaluation".<sup>15</sup> The word 'histologic' is pertinent as many clinicians, discourage the use of cytologic examination. Yet in a country like India, the FNA forms the first method of cell diagnosis, and there is a wealth of useful clinically relevant information that can be obtained thereof.

### Incidence and Mortality

CUP is one of the 10 most frequent cancers worldwide, constituting 3-5% of all human cancers, and accounting for a fourth cause of cancer deaths. It is a varied heterogeneous group of mainly epithelial cancers, recognizable on good cytology and histopathological preparations.

There are a number of possible reasons for why the primary might not have been found:

- The primary tumor may have disappeared spontaneously because the immune system may have destroyed the primary tumor, but not the secondaries.
- The secondaries may have grown and spread very quickly, while the primary is still too small to be seen on X-rays or scans.
- The primary tumor may be impossible to see on X-rays or scans because it is hidden by several larger secondaries that have grown close to it.
- The primary may have been expelled as happens with polypoidal growths in the colon.

There are no obvious etiological or risk factors that contribute to the pathogenesis of this syndrome. In general, CUP follows an aggressive biological and clinical course but there are sub-sets of patients with somewhat favorable outcomes.<sup>16</sup>

CUP often manifests as cervical lymphadenopathy, or as a carcinomatosis with disseminated neoplasm and multi-organ involvement. Early localization of the hidden primary is the combined effort of all diagnostic aids, and is important for 3 reasons:

- It helps in a possible ‘curative therapy’,
- It helps in effective palliation, and
- Thirdly it improves the quality of life of these patients.

The value of imaging modalities and endoscopic examination cannot be undermined. However, cytologic or histological analysis is virtually mandatory, because imaging techniques will only determine the extent of the disease rather than the source of the primary tumor. The pursuit for a very extensive and expensive work-up is often outweighed by the limited applicability of treatment options. Even when an extensive work-up is carried out, less than 20% of patients with true CUP have a primary site identified ante mortem. Moreover, it is a sobering fact of oncology, that even after autopsies, the primary remains occult in as many as 70% of cases.

Yet there are subsets of patients who have “favorable prognosis and in such patients should be treated with curative intent. Pathologists should make every attempt at discovering the occult primary. Such cases include Hodgkin’s diseases, germ cell tumors, metastatic ovarian cancers, small cell carcinomas and pediatric sarcomas, all of which could be found in head and neck nodes. Diseases amenable to excellent and often long-term palliation include breast endometrial and prostate carcinomas and head and neck tumors and some pediatric sarcomas.

## Cytology

The FNA is meaningful and justified if there is adequate cellularity and or tissue fragments are available in the smears for study. Paucicellular, badly processed and inadequate smears are of little use, and there must be an insistence from the senior pathologists on having 3-4 well spread air dried smears, at least 2 alcohol fixed smears, and some extra well fixed smears for future immunohistochemistry studies. Cell block preparation is of immense value, when material is abundant, and with fluid samples. In every case

requiring an FNAC, there should be some provision for keeping some smears apart for special tests and stains.

## Routine Cytology Smears are Often Adequate to Identify the 4 Main Cell Types of CUP, viz

- Adenocarcinomas (50-60%),
- Poorly differentiated carcinomas (30%)
- Squamous carcinomas (5-15%), and
- Undifferentiated malignant tumors (5%).

Cytological features do suffer from a limitation in that overlapping features and subtle features of individual tumor types add to the confusion in diagnosis of many carcinomas. The problems are compounded when the tumors are poorly differentiated or undifferentiated. Mimics of carcinomas abound in the real world, however cytologists must train to have a high index of suspicion for melanomas, neuroendocrine tumors, epithelioid sarcomas and lymphomas.

The demographic information of value for the clinician and the pathologist include the age sex and location of the cancer in the neck. Most cases are diagnosed in cervical nodes and a search for the probable primary could be instituted from this information:

Table showing probable source of primary by judging level of nodal involvement in cases of squamous carcinomas.

Level I	Oral cavity, submandibular gland
Level II	Oral and nasal pharynx, larynx, parotid
Level III	Oral pharynx, hypo pharynx, supraglottic larynx
Level IV	Supraglottic larynx, hypo pharynx, esophagus, thyroid
Level V	Pharynx, esophagus, lung, kidney, cervix, pancreaticobiliary tree

In the case of adenocarcinomas, the probable primaries are usually in the thyroid or salivary glands. If the nodal involvement is at level V, then there are chances of the primary being located below the clavicle, e.g. in lung, kidney, cervix or even from the GIT.

There is sometimes a close morphological similarity between poorly differentiated carcinomas, Adenocarcinomas and melanomas. Subtle features of differentiation like keratin, gland formation or melanin pigment need to be carefully looked for. However, when the tumor is really undifferentiated there is need for immunohistochemistry (IHC). Panels of IHC tests for different categories of tumors are now available for routine use.

Today immunohistochemistry (IHC) is the most useful tool in pinpointing a number of carcinomas and narrowing the diagnostic possibilities.

**TABLE 1:** IHC usage for broad categorization of tumors

Tumor Type	IHC
Carcinoma	CK, EMA
Lymphoma	LCA, CD20
Melanoma	S-100 HMB-45
Breast carcinoma	CK, ER, PR, Her 2
Germ cell tumors	B- HCG, APF, PLAP, CK, EMA
Sarcomas	Vimentin, Desmin, Actin, Factor VIII
Prostate cancer	PSA, CK, EMA
Thyroid	Thyroglobulin, TTF-1, Calcitonin
Lung	TTF-1, CK,
Neuroendocrine tumors	NSE, Chromogranin, Synaptophysin, CK, EMA

In the case of many adenocarcinomas, there may not be any diagnostic problem of labeling the type of tumor, but the primary needs to be unearthed as treatment options vary. In this area, the CK phenotypes are gaining importance and combined usage of two CK types helps in the identification of some primary sites.

**TABLE 2:** CK phenotypes

CK Phenotype	Tumors
CK 7 Negative and CK 20 negative	Head neck, liver, lung, small cell prostate, kidney
CK 7 + and CK 20 -	Biliary tract, pancreas, breast cervix, endometrium lung, ovary
CK 7 – and CK 20 +	Colon, Merkel cell carcinomas
CK 7 + and CK 20 +	Biliary tract and pancreas, Mucinous ovarian cancer and urothelial cancer

## Serum Tumor Markers

Some types of cancer release certain substances into the bloodstream. Testing for these substances in the blood can sometimes provide valuable clues about the origin of the cancer.

- **Prostate-specific antigen (PSA):** A high PSA level in a man suggests that a CUP may have started in the prostate gland.
- **CA-125:** A high CA-125 level in a woman suggests ovarian cancer may be the cause.
- **Human chorionic gonadotropin (HCG):** High levels of HCG suggest a germ cell tumor, a type of cancer that can begin in the testes, ovaries, the mediastinum, or the retroperitoneum.
- **Alpha-fetoprotein (AFP):** This substance is produced by some germ cell tumors as well as by some cancers that originate in the liver.

## Favorable Subsets

Pathologists and clinician understand the importance of recognizing favorable subsets, as many of these patients fare well. Their diagnosis and subsequent treatment will be governed by the pathology/cytology report.

1. **Men with poorly differentiated carcinomas found near the midline of the head or other areas of the body:** Young men with undifferentiated or poorly differentiated carcinomas should be treated as extragonadal germ cell tumors even in the absence of elevated serum levels of AFP or B- HCG levels.
2. **Head and neck metastatic squamous carcinomas of the cervical lymph nodes.** The main culprit is often a head neck site and particularly the nasopharynx, post cricoid region or pyriform fossae. Patients with supraclavicular node involvement, often have the primary in the lung GIT, or lower esophagus.
3. **Poorly differentiated neuroendocrine tumors:** Most often the origin is unclear in these patients, but they respond to cisplatin based chemotherapy.
4. **Single isolated metastasis particularly in the head and neck sites:** Some of these patients achieve prolonged disease free intervals.<sup>17</sup>

Apart from some of these favorable subsets of patients, most patients with CUP have a poor prognosis and are relatively resistant to chemotherapy.

## REFERENCES

1. Cancer Incidence in Five Continents. Vol IX IARC Scientific Publication No 160 Editors Curado MP, Edwards B, Shin HR, Felay J, Heanue M, Boyle P, Storm H, IARC 2007.
2. McGuirt WF. The neck mass. *Med Clin North Am* 1999;83: 219-34.
3. Izhar N, Bagwan Shubadha V, Kane Roshni F Chinoy. Cytologic Evaluation of the Enlarged Neck Node: FNAC Utility in Metastatic Neck Disease: *The Internet Journal of Pathology* 2007;6(2).
4. Steel BL, Schwartz MR, Ramzy I. Fine needle aspiration biopsy in the diagnosis of lymphadenopathy in 1103 patients. Role, limitations and analysis of diagnostic pitfalls. *Acta Cytol* 1995;39:76-81.
5. Ustun M, Risberg B, Davidson B, Berner A. Cystic Change in metastatic lymph Nodes: A common diagnostic pitfall in Fine-Needle Aspiration Cytology. *Diagn Cytopathol* 2002;27:387-92.
6. Kusum V, Mandal S, Kapila K. Cystic change in lymph nodes with metastatic squamous cell carcinoma. *Acta Cytol* 1995;39:478-80.
7. Usefulness of fine needle aspiration in Parotid Diagnostics. Salgarelli AC, Cappare P, Bellini P, Collini M. *Oral Maxillofac Surg.* 2009 Oct 11.

8. [www.rcpath.org](http://www.rcpath.org).
9. Cancer Incidence in Five Continents. Vol IX IARC Scientific Publication No 160 Editors Curado MP, Edwards B, Shin HR, Felay J, Heanue M, Boyle P, Storm H. IARC 2007.
10. Royal College of Pathologists. Standards and Datasets for Reporting Cancers: Datasets for histopathology reports on head and neck carcinomas and salivary neoplasms, 2nd edition London. The Royal College of Pathologists 2005 (cited 11 August 2006 Available at [url:http://rcpath.org/resources/pdf/Head and Neck data set June 05.pdf](http://rcpath.org/resources/pdf/Head%20and%20Neck%20data%20set%20June%2005.pdf)).
11. Ackerman LV, Ramirez GA. The indications for and limitation of frozen section diagnosis. *Br J Surg* 1959;46:336-50.
12. Wick MR, Mills SE. Evaluation of margins in anatomic pathology: Technical, conceptual and clinical considerations. *Semin Diagn Pathol* 2002;19:207-18.
13. Howanitz PJ, Hoffman GG, Zarbo RJ. The accuracy of frozen section diagnosis in 34 hospitals.
14. *Arch Pathol Lab Med*. 1990;114: 355-59. 5 Dankwa EK, Davies JD. Frozen section diagnosis: an audit. *J Clin Pathol*. 1985;38:1235-40.
15. The Washington Manual of Oncology 2nd edition, ed T Ramaswamy Govindan, Lippincott Williams and Wilkins 2008.
16. Briasiykus E, Tolis C, Bergh J, et al. ESMO minimum clinical recommendations for diagnosis, treatment and follow up of cancers of unknown primary site (CUP) *Ann Oncol* 2005;16 (Suppl 1):75-77.
17. Van De Wouw AJ, Jansen RIH Speel EJM, et al. The unknown biology of the unknown primary tumor a literature review. *Ann Oncol* 2003;14:191-96.