CHAPTER 1

Introduction

Chapter contents

1.1 Introduction

The Head and Neck (HN) area is one of the most complex regions of the body because of its anatomical and functional diversity. Diseases of the HN, both primary and systemic, rarely go unnoticed; patients either notice changes themselves, or are alerted to them by the diagnostic investigations, often done for unrelated conditions.

HN cancer is the ninth most common cancer in the USA, accounting for 3.3 % of all cancers. The incidence of HN cancer has plateaued recently; however, morbidity and mortality continue to remain high. Despite the decline in overall mortality rates since 2001 a ratial disparity between the whites and the African Americans, both in inclidence and mortality, still exists [1].

Tobacco and alcohol use are the most important risk factors for most HN cancers. In addition, infection with certain types of human papillomavirus (HPV) is thought to be the cause of an escalating incidence of HPV-related oropharyngeal squamous cell carcinoma predominantly among middle-aged adults [2].

1.2 Fine needle aspiration cytology of the head and neck

Fine needle aspiration cytology (FNAC) has been recognised as one of the core activities for the management of HN disease [3–23]. Sites in the HN that are amenable to FNAC include the thyroid, cervical masses and nodules, salivary glands, intraoral lesions and lesions in the paraspinal area and base of skull [24].

FNAC has a high overall diagnostic accuracy: 85–95% for all HN masses, 95% for benign lesions, and 87% for malignant ones [25, 26]. Diagnostic accuracy is dependent on the site of aspiration as well as the skill of the individual performing and interpreting the FNAC [24]. Each site undergoing FNAC within the HN is associated with its own set of differential diagnoses and diagnostic challenges. There are virtually no contraindications, and complications are minimal [27].

FNAC allows an immediate diagnosis to be available to the clinician so that appropriate treatment can be discussed with the patient. It is recommended as a first line of investigation in palpable HN masses. FNAC is the preferred first-line pathological investigation of salivary gland and thyroid lumps because of the risk of recurrence and complications, respectively, associated with tissue biopsies [28].

The majority of aspirates from the HN will be to confirm an otherwise suspected diagnosis, for example a reactive lymphadenopathy or to confirm clinical staging for a metastatic carcinoma. However, there are a number of occasions where an unsuspected condition may be revealed, such as lymphoma or a salivary gland tumour. Whilst the diagnosis of lymphoma may need further tissue work up, the diagnosis of salivary gland lesions is often definitive in that it guides the surgical or non-surgical management. FNAC can diagnose majority of thyroid enlargements and help reduce the rate of surgery for benign thyroid disease. Ancillary techniques, namely immunocytochemistry, flow cytometry and molecular techniques, can greatly broaden the diagnostic range and specificity of FNAC. They are particularly useful in the diagnosis of lymphoproliferative processes and in determining the precise nature of lesions as variable as rhabdomyosarcoma, olfactory neuroblastoma and granular cell tumour. The prudent use of these techniques can be cost-effective and avoid the need for more invasive diagnostic procedures [29].

1.3 Ultrasound guided FNAC

Ultrasound imaging is a dynamic and readily available technique that is particularly useful in the examination of superficial structures. Modern machines combined with high frequency linear probes (7.5–12 MHz) produce high definition images in multiple planes. The spatial resolution that is achieved surpasses that of both multislice computed tomography (CT) and magnetic resonance imaging (MRI). Images are rapidly acquired, artefacts are few, and the technique is highly acceptable to most patients. As an adjunct to structural imaging, colour (directional) and power Doppler (non-directional but more sensitive) are often used to assess blood flow and the vascularity of tissue. These techniques add value in detecting abnormal peripheral or chaotic flow patterns in malignant lymph nodes, in assessing the patency of normal vessels, and in the investigation of vascular and lymphatic malformations.

Cytopathology of the Head and Neck: Ultrasound Guided FNAC, Second Edition. Gabrijela Kocjan.

Companion website: www.wiley.com/go/kocjan/clinical_cytopathology_head_neck2e

Ultrasound (US) guidance is a useful adjunct to either FNAC or needle core biopsy (CB), and its use is expected to increase. US combined with US guided FNAC, rather than a tissue biopsy, can be recommended as a method for evaluating possible regional metastases in HN cancer patients, for both those with and those without a known primary tumour [30, 31].

US and, if necessary, FNAC, should continue to be the investigation method of first choice for HN lesions. The main indication for CB is after repeated failures of FNAC to provide a diagnosis. It can also be performed in patients who are not surgical candidates or in those who refuse surgery. Kraft et al. found CB was superior to FNAC in providing a specific diagnosis (90 vs 66%), and achieved a higher accuracy in identifying true neoplasms (100 vs 93%) and detecting malignancy (99 vs 90%). However, the sensitivity and specificity did not differ significantly between the two methods [32]. Khalid et al. found that the use of US-guided FNAC as the initial modality for tissue sampling of a thyroid nodule is more effective than traditional FNAC at an additional cost of $289 per additional correct diagnosis [33].

In our own experience, the adequacy rate of US guided FNAC is critical for the success of the service. In our institution the adequacy of US guided FNAC in the HN clinic is 97% [34]. Computed tomography and magnetic resonance imaging do not appear to add any advantage to FNAC in terms of specificity, sensitivity or accuracy of a malignant diagnosis [34]. As with rapid-diagnosis clinics, US-guided FNAC sessions benefit from attendance of cytopathology medical and non-medical staff to assess adequacy of the samples and make decisions about collecting appropriate material for ancillary tests.

1.4 A Combined US/FNAC approach

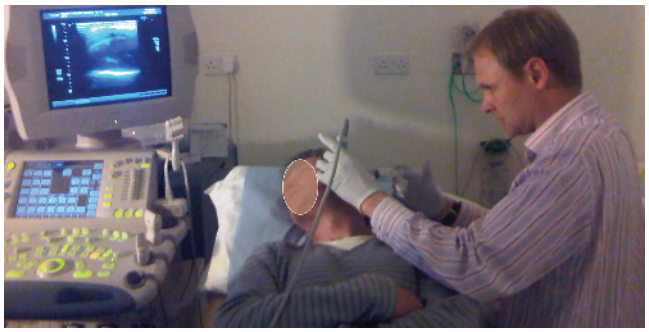
Recently, some cytopathologists have learned to use ultrasound machines to assist them in performing FNAC procedures. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were 96, 50, 98, 33 and 94% in palpation guided (PGFNAC) versus 100, 86, 97, 100 and 97% in the US guided (USGFNAC) group, respectively. USGFNACs performed by a cytopathologist could significantly improve the specificity and NPV ($P = 0.04$) while preserving virtually the same excellent sensitivity and PPV as those of PGFNACs. With US guidance, a cytopathologist is able to perform FNACs in smaller, non-palpable lesions and target complex lesions with confidence and accuracy, thus achieving a better outcome [36].

In our experience, even better results are obtained when an experienced radiologist takes the FNAC and has a cytopathologist close by to process the material and interpret the slides (Fig. 1.1).

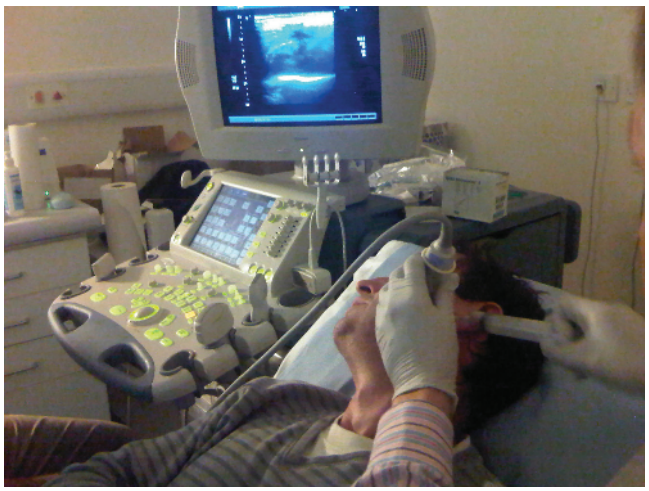
According to the British Society for Clinical Cytology (BSCC) Code of Practice, the combination of physical examination/clinical history, radiological assessment, careful needle sampling, appropriate cell preparation, subsequent interpretation and multidisciplinary clinical discussion are essential for a successful outcome [37]. The lack of skill, clinical information and communication can be detrimental to the result.

1.5 Sampling technique

Sample collection is a major factor influencing both the adequacy and the accuracy of FNAC [38,39]. It is our experience and experience of others that a good sampling technique is essential for



(A)



(B)

Figure 1.1 Ultrasound guided FNAC. (A) The radiologist, Dr Morley, uses the ultrasound probe in the left hand and injects the anesthetic into the lesion with the right hand. (B) Observing the monitor and using the ultrasound probe for guidance, the aspirator uses negative pressure to extract cystic fluid from the parotid gland lesion.

successful interpretation of FNAC. Comparing the material obtained by the cytopathologist with the material sent from various aspirators, Wu et al. found that the sensitivity of HN FNAC procedures is significantly better in the cytopathologist-performed group than in the non-cytopathologist-performed group (96 versus 67%) [40, 41]. Greater experience of the operator appears to improve the accuracy rate [42–44]. In experienced hands, palpation-guided FNAC is an excellent diagnostic tool. However, there is a movement towards using imaging guidance to target all masses [45].

The best results are obtained with a cytopathologist-led FNAC service, where the pathologist reviews the specimen immediately, in relation to the clinical context, thereby deciding on adequacy and the need for further sampling (Fig. 1.2) [46, 47].

With the FNAC procedure having been explained (Fig. 1.3), the patient is put in a supine position. The choice of whether to apply anaesthetic or not largely depends on the patient, the site involved and the extent of FNAC sampling planned. Since the average FNAC does not involve more than one pass with a 22+ G needle, most patients do not require local anaesthetic. However, if the patient is needle-phobic or a child, or if the site is particularly tender, for example, lip, nose, areola, or if it is expected that several passes will be necessary, a local anaesthetic is applied in the form of subcutaneous injection of 0.5 ml of 2% lignocaine. More recently we have

Figure 1.2 Examination of the glass slides in the clinic. This gives an orientation of adequacy and indicates whether further samples need to be taken for special techniques and/or for microbiology cultures. Results are usually not discussed with the patient at this preliminary stage of the investigations.

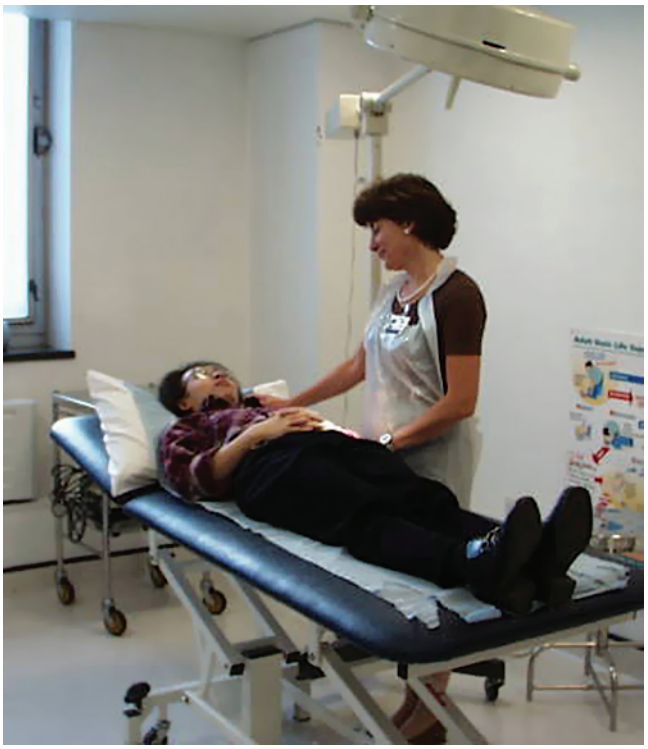
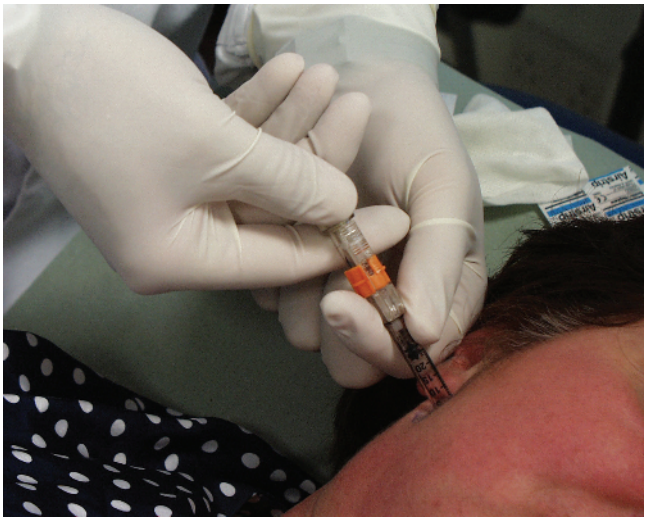
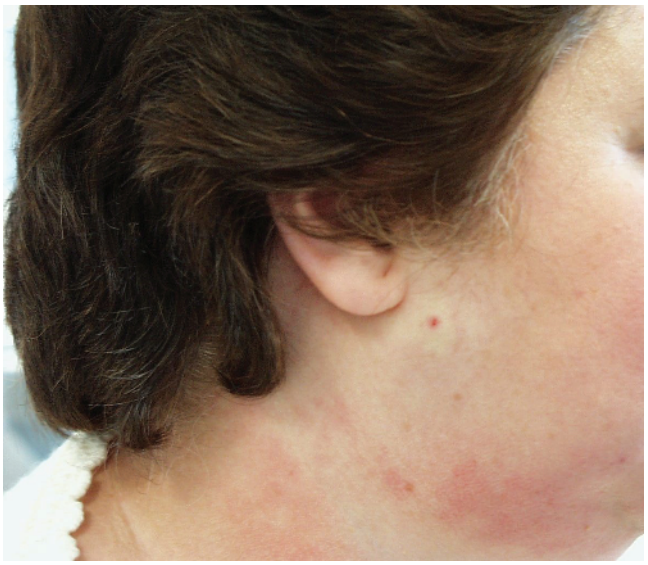


Figure 1.3 Clinical history and examination. The pathologist at the bedside examines the area referred to by the specialist and also asks the patient further relevant questions about the duration of the swelling, level of pain and any other associated systemic symptoms.

been using a needle free syringe where the pressurised air expels the anaesthetic, penetrating the skin, without the needle (Fig. 1.4A) [48]. Anaesthetic forms a small white ring through which the subsequent test needle is applied, once or more (Fig. 1.4B). Patients do not experience any pain on application of the anaesthetic and experience no or minimal pain at FNAC.



(A)



(B)

Figure 1.4 (A) Needle free anaesthetic system.Designed for patients who need daily injections, e.g. insulin, but also applicable to the local anaesthesia. This is particularly useful in children, in needle-phobic patients, in sensitive sites and where multiple needle passes are anticipated. (B) Needle-free anaesthetic system. A pale ring indicates the area of subdermal infiltration. A test needle should be passed through this area.

The palpable area in question is cleaned with an antiseptic agent and fixed between the two fingers of the non-dominant hand. 22 G, 23G or smaller needle is then passed into the lump using a non-aspiration technique (capillary sampling) with the aid of a needle only (without the syringe attachment) (Fig. 1.5). In a meta analysis comprising over 2000 thyroid FNAC samples, there was no difference between the aspiration and non aspiration technique in assessing thyroid nodules [29]. In cases where a fluid aspirate is expected, a syringe and a syringe holder are attached to the needle to help aspiration (Fig. 1.6) [29, 49–54]. The needle is passed round in a fan-shaped manner several times in the cases of non-thyroid lumps. In the case of thyroid, several vertical movements in the same direction are usually sufficient to gain representative material. When exiting the lump, if using syringe attachment, it is important

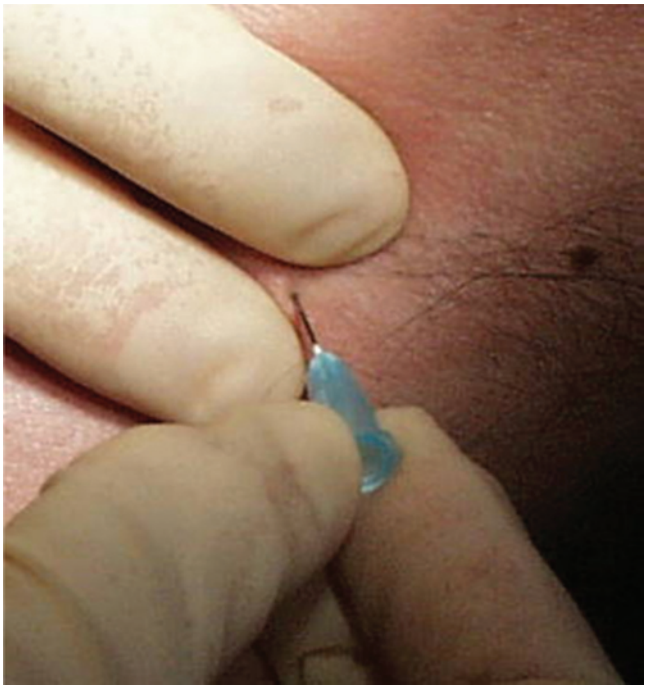


Figure 1.5 Free needle FNAC procedure. This, so called 'capillary technique', is particularly useful in very small, mobile lesions, e.g. lymph nodes. An aspirator has a much better feel of the tip of the needle and better control of the area sampled. It is not the method of choice for cystic or very sclerosed lesions.

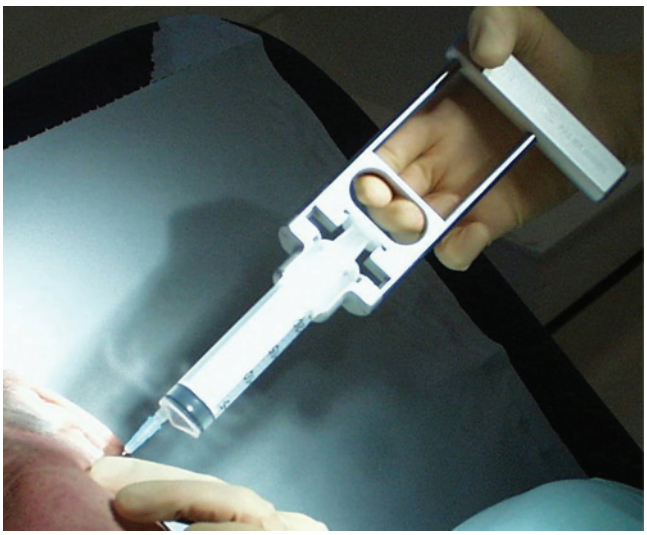


Figure 1.6 FNAC of fluids. A 20 ml syringe attached to a CAMECO (BELPRO MEDICAL, Canada), syringe holder A 23 G needle is used.

to release the negative pressure before exiting, otherwise the material is aspirated into the syringe and can only be retrieved by the aid of a needle wash.

Whilst adhering to the traditional technique of smearing the material ejected from the needle onto a slide and then either air drying or fixing it in alcohol, if necessary we also suspend the material from a separate needle pass in a liquid medium that can then be used for ancillary techniques including cell block

Figure 1.7 Rapid staining and examination. Slides are stained with one of the rapid stains and examined under the microscope for cellularity. This gives a good orientation if more material is needed or if different cell preparation technique should be applied.

(CBL). Air dried smears can be stained by a rapid staining technique to assess material adequacy in the One Stop clinic (Fig. 1.7). CBL provide a method for immunocytochemistry (ICC) that has revolutionised cytopathology by making it possible to apply panels of antibodies to multiple sequential sections of aspirated or exfoliated cellular material [55]. CBL can be prepared from virtually all varieties of cytological samples. CBL sections offer advantages over conventional cytological smears with respect to cellular architecture and archival storage. They also provide several sections, which can be utilised to perform special stains, immunophenotypic analysis, ultrastructural studies and molecular tests, including cytogenetic and polymerase chain reaction (PCR)-based techniques [56–59]. In today's era of personalised medicine, the ability to perform these tests augment the utility of cytological samples in analysing the molecular alterations as effectively as surgical biopsies or resection specimens. With the availability of molecular targeted therapy for many cancers, a large number of recent studies have used cytological material or CBL for molecular characterisation. Jain et al. described various methods of preparations of CBL and their application in cytology. The advantages and disadvantages of various methods of cell preparation are outlined in Table 1.1 [50].

One of the easiest way to prepare a CBL is the so-called 'Poor Man's cell block'. This method should be available to any laboratory and is able to produce very good results (Fig. 1.8) [61].

The final cytopathology report should be clear, written with the knowledge of the ultrasound and clinical findings, morphology and ancillary techniques (Fig. 1.9). Difficult cases should be discussed at the intradepartmental and multidisciplinary meetings and are also an important source of education and training [62] (Fig. 1.10).

Table 1.1 Comparison of different cytological preparation methods.

Direct smear[13]		Cytospin[25]		Cell block[2–4]		Liquid-based cytology[26]	
For	**Against**	**For**	**Against**	**For**	**Against**	**For**	**Against**
Diagnosis Fast		Optimal for cysts, urine and effusions	Cellular crowding	Additional to other slides	Needs time and histology skill	Easy to transport, collect and process	Low cellularity
Inexpensive	Needle handling	Multiple slides	Limited cellularity	Increased diagnostic yield		Reduced screening area	Cell shrinkage (methanol)
Routine process	Multiple slides	Air dried and/or alcohol fixed		More architecture		No air-drying artefacts	Less architecture
Permits rapid evaluation	Obscuring background			Archival storage		Clean background	Reduced or altered background material
Excellent cellular detail	Air-drying artefacts					Monolayer of cells	
ICC possible on fresh or destained slides	Adverse effect of stripped nuclei and cytoplasmic background	Routine laboratory method	Risk of FNs due to focal antigen expression	Easy to perform and compare with histology	Variable staining due to different fixatives	Equal or stronger than direct smears	Alcohol-based: may differ from formalin-fixed slides
Suitable for nuclear antibodies	Potential increased FNs			Routine histology controls Dual ICC possible		Equal distribution of staining Clean background	All antibodies not yet evaluated
Cytogenetic and molecular testing							
Potentially effective for preparation and storage	May be diluted by normal cells	Suitable for FISH	Cell crowding may hamper nuclear signals	Optimal results with current methods	Depends on cellular yield and fixation methods	Suitable for FISH and molecular analysis	Limited studies so far available
Routinely available and cost-effective	Cells of interest may be enriched by microdissection	DNA extraction possible	May be diluted by normal cells	Cells of interest may be enriched by microdissection	Partial cells in sections	Avoids cross-linkage of formalin fixation	May be affected by alcohol fixation (e.g. PR)
Whole cells		Whole cells			Sections	Whole cells	

FISH, fluorescence in situ hybridization; FN, false negative; ICC, immunocytochemistry; PR, progesterone receptors.

Source: Jain D, Mathur SR, Iyer VK. Cell blocks in cytopathology: a review of preparative methods, utility in diagnosis and role in ancillary studies. *Cytopathology*. 2014 Dec; 25(6): 356–71.

Cytology Report

CPA Accredited Laboratory

Department of Histopathology
University College London Medical School
Rockefeller Building, University St, London WC1E 6JJ

Lab No.: NG00-0404 Hospital No.: 0000000
Name : XXXXX,YYYYYY Age/Sex : 18Y M
Cons/GP : Doctor X Ward : Maxillofacial Unit,

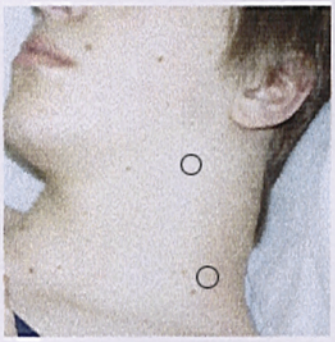
SPECIMEN : Neck Fine needle aspirate

EXAMINED BY: DR T HATTER

SPECIMEN OBTAINED BY: DR G KOCJAN

CLINICAL DATA:
Swelling left neck and post auricular region.
Fluctuant below angle mandible.

MATERIAL RECEIVED:
Nineteen slides from FNA 2 different sites in the left neck (see illustration).



MICROSCOPIC DESCRIPTION:
Smears show numerous single and small aggregates of cells. The cells have large oval nuclei with fine chromatin pattern, indistinct nucleoli, and scanty basophilic cytoplasm with prominent vacuolation.

Immunocytochemistry: LCA and CD20 positive. Tdt, desmin, SMA, myoglobin, MYC2 negative.

CYTOLOGICAL DIAGNOSIS:
FNA left neck. High grade B cell non Hodgkin's lymphoma (? Burkitt's). Biopsy is advised.

SNOMED : TY0600;M095903

Signed : Pathologist : DR G KOCJAN

Date : 14/02/2000

UCL HOSPITALS

PATHOLOGY DIRECTORATE

Figure 1.8 Cytopathology report should contain patient's details, clinical history, number and position of the site(s) sampled (preferably illustrated by a photograph or a diagram), indicate the name of the aspirator, date of sample, number of slides made and/or other material obtained, microscopic description, special techniques used, cytological diagnosis, diagnostic code, pathologist's signature and date. This report is just an example for illustration. Today we would use flow cytometry and cell block immunocytochemistry to confirm and specify the diagnosis of lymphoma on FNAC.

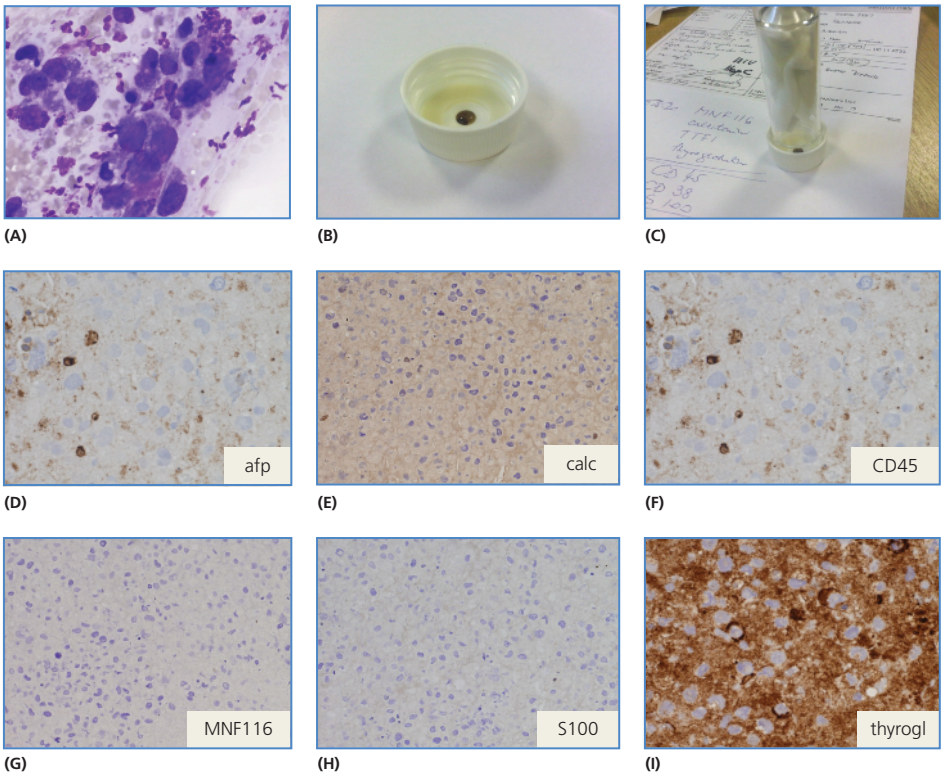


Figure 1.9 Images demonstrating the main steps in the preparation of a vapour fixed cell block. (A) The FNAC material from the thyroid is stained with May Grunwald Giemsa (MGG) and shows undifferentiated tumour cells. (B) The material is expelled from the needle into the well of the lid in a universal container. (C) It is left inverted for at least 6 h to allow the formalin vapours to fix it until solid after which it is handled as a histological sample. (D) afp negative, (E) calcitonin negative, (F) CD45 negative, (G) MNF 116 negative, (H) S100 negative and (I) Thyroglobulin positive. The conclusion was that this is anaplastic carcinoma arising from the thyroid.

Figure 1.10 Cytology education and training. Most interesting cases are discussed weekly at the multiheaded microscope; once a year, a traditional Christmas quiz, in addition to the seasonal jollity, provides a reminder of the most difficult cases.

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