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Chapter 1 - Introduction

Cancer is one of the major health hazards in the world. In contrast to the situation a few decades ago, the majority of the global cancer burden now occurs in medium- and low-income countries. Assuming an annual increase in cancer incidence and mortality of 1%, by 2030 there could be 26.4 million new patients with cancer, 17.1 million annual cancer deaths, and 80 million people alive with cancer within five years of diagnosis.

The worldwide economic toll of cancer diagnosis and treatment is also important. It has been estimated that global cancer care in 2009 cost \$ 286 billion while the projected global cost in 2030 is \$458 billion. In 2011 the total estimated direct medical costs in the United States of America (USA) were \$88.7 billion according to the Agency for Healthcare research and Quality. If costs of care increase annually by 2% in the initial and last year of cancer care, the total cost in 2020 is projected to be \$174 billion. In the 27 countries of the European Union, the cancer cost was estimated to be €126 billion in 2009 and is estimated to increase further due to the demographic shift.

The costs of health care in relation to cancer have been increasing rapidly due to the introduction of new diagnostic techniques and treatments, requiring additional resources for these areas. Consequently, it is important that the available funding is used in an optimal way to ensure the continuity of adequate cancer diagnosis and treatment.

Diagnosis should identify the presence of cancer, mostly by pathological or cytological examination, and the extent of the disease by staging. Several staging examinations are available, but only those that are relevant should be employed. New techniques should be evaluated in randomised clinical trials before they enter daily clinical practice.

Results from pathology and staging examinations, together with patient-related factors, can determine the prognosis of patients with cancer. Combined with society-related factors, these examination results play an important role in determining optimal treatment strategies.

Several predictive factors that can indicate response to a specific treatment have been determined and can be used to direct treatment choices. When opting for a specific treatment, adequate treatment evaluation and prevention of acute and late toxicity should be taken into account to preserve the quality of life of cancer survivors.

Revalidation and reintegration in society should be envisaged after diagnosis and treatment of cancer.

This handbook describes and discusses cancer diagnosis and treatment evaluation.

Further Reading

- <http://cancerprogressreport.org/Pages/GetACopy.aspx>
- <http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer>
- <http://costprojections.cancer.gov/>

- Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol.* 2013 Nov;14(12):1165-74. doi: 10.1016/S1470-2045(13)70442-X. Epub 2013 Oct 14.

Chapter 2 - Pathology

Introduction

What is Pathology?

Pathology is the study of structural and functional abnormalities that are expressed as diseases of cells, organs, or organ systems. Clinical pathology applies the knowledge of such studies for the diagnosis of disease in an individual patient. A pathological diagnosis is generally based on the integration of clinical, macroscopic, (sub) microscopic, and in some cases genetic findings. Histopathology is the study of tissues from patients, whereas cytopathology is the study of cells that are retrieved by either fine-needle aspiration (FNA) or by brushing or scraping of cells off a surface within the body. Spontaneously shed cells in body fluids like urine can also be examined.

Histopathology

The histopathological examination of tissue biopsies or resection specimens from patients forms the cornerstone of cancer diagnosis. There are national guidelines and standardised protocols for the pathological analysis of the most frequent tumour types. A large number of histochemical stainings can be performed in addition to the routinely performed haematoxylin-eosin (H&E) staining. An important recent development in histology is rapid tissue processing, enabling fast, one-day or one-hour diagnosis. For cancer diagnosis, immunohistochemistry and molecular pathology are commonly used for detailed classification and characterisation of tumours.

Cytopathology

Compared to a biopsy, an important advantage of cytology is that it is less invasive. The widest application of cytopathology is in early detection in the context of cancer of the uterine cervix. Cytopathology is also useful for detection of cancer in the bladder, lung, and endometrium. In addition, cytopathology is, in some tumour types, the most feasible technique for detecting tumour recurrence, for instance in the urinary tract. With FNA virtually every organ is accessible. Under negative pressure, cells can be aspirated from a target organ or lesion. FNA can be performed under radiographic or ultrasound guidance.

Most cytological specimens are stained by either Giemsa or by the Papanicolaou technique. Smears and possibly cell-blocks are prepared from the aspirated cells. The latter has the advantage in that immunostaining can be performed.

Advantages of cytopathology, in comparison to histology, are that it produces less tissue damage, a larger sampling surface is available, and tissues difficult to reach for a histological biopsy can be evaluated. In addition a rapid diagnosis is possible, there is less discomfort for the patient, and it increases the detection rate of malignancy when combined with biopsies (for instance in lung cancer).

Disadvantages are the limited possibility for detailed classification and the inability to differentiate in situ cancer from invasive cancer, for instance in the breast and urinary bladder.

Immunohistochemistry

Immunohistochemistry (IHC) aims to detect tissue or cell-specific antigens by applying labelled antibodies that can be visualised by light or fluorescence microscopy. In the past 20 years this field has developed rapidly and has become of great importance in daily practise, especially when this method became widely available for formalin-fixed paraffin embedded tissue.

IHC has an important application in diagnosis of tumours by establishing the line of differentiation in poorly differentiated tumours. Most pathologists use a stepwise approach, first using a panel of generic markers containing cytokeratins (for epithelial differentiation), melanocytic markers, CD45 (leukocyte common antigen for hematopoietic differentiation), and vimentin (for mesenchymal differentiation). More specific antibodies can be chosen for a second step based on the initial findings.

It is important to pay careful attention to positive and negative controls in each immunostaining. In this respect, internal controls within the specimen itself are more reliable than external controls even if placed on the same glass slide since the results of immunostaining are largely dependent on tissue fixation and processing.

IHC can indicate the site of origin for a metastasis from an unknown primary cancer. For instance, the transcription factor TTF1 is expressed in normal cells of the lung and thyroid, but also in tumours derived from these organs.

In addition to tumour diagnosis and classification, IHC is also important for prognostication and prediction of therapy response. With the availability of targeted therapies, determination of the presence of a protein by IHC in the patient's tumour can determine the subsequent treatment. Examples are oestrogen receptor status and, more recently, Her2-neu expression in breast cancer.

Molecular Pathology

Assessing DNA and/or RNA (changes) in tumour tissue, generally referred to as diagnostic molecular pathology, is rapidly becoming indispensable. Several methods are available, which can be divided into those that use tissue slides (in situ hybridisation) and those that use extracted nucleic acids.

In situ hybridisation is nowadays commonly used to detect specific gene amplifications, like Her2-neu in breast cancer, or chromosomal translocations, like the t(8;14) in Burkitt lymphoma.

Extracted nucleic acids can be used to detect specific, known genetic alterations, like the *HRAS* mutation in desmoplastic dermal Spitzoid melanocytic tumours, or for a general overview of the genomic alterations in a tumour (comparative genomic hybridisation array and whole exome or genome sequencing) or the RNA expression profile (expression array). The latter techniques are currently mainly used for research purposes but some are available for individual patients, especially dedicated prognostic expression arrays for breast cancer (Oncotype DX and MammaPrint).

Aims in Diagnosis and Treatment

Clinical pathology aims to diagnose and classify a patient's disease based on the analysis of cells or tissues. The first aim for a pathologist when assessing a biopsy from a lesion is to assess whether the lesion is reactive (inflammatory) or neoplastic. If it is neoplastic, the distinction between benign and malignant needs to be made.

Next, the line of differentiation must be established with accurate subtyping in order to guide treatment. In many cases standard H&E stained tissue slides suffice (as in the case of "standard" squamous cell carcinoma or adenocarcinoma). However, about 20% of cases require additional techniques (Fig. 2.1). Additional molecular testing or protein expression can be performed in specific tumour types when relevant for diagnosis or targeted treatment (for instance, mutational analysis in gastrointestinal stroma cell tumours).

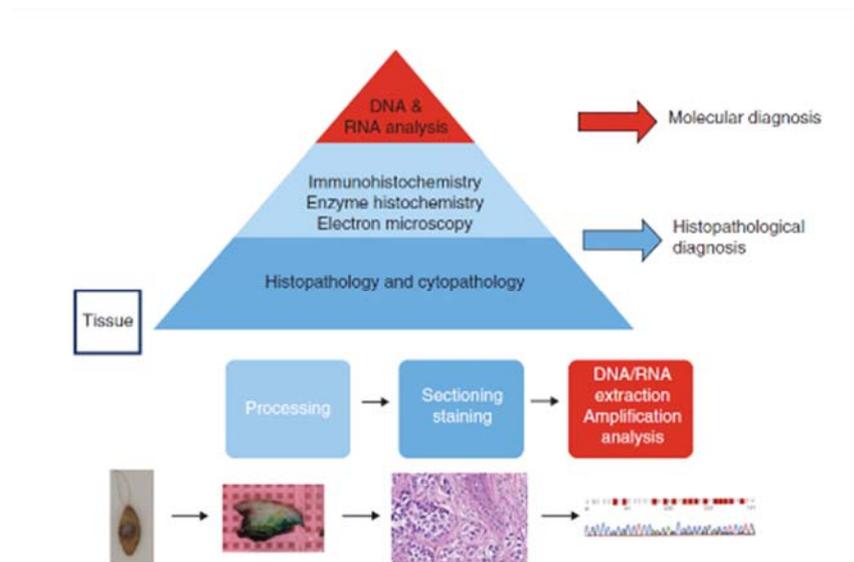


Figure 2.1 The pyramid illustrates that most histopathological diagnoses can be made on standard H&E-stained histological tissue slides or by either Giemsa or Papanicolaou staining of a cytological specimen. However, about 20% of cases require additional techniques, mostly immunohistochemistry, and occasionally electron microscopy. In specific tumour types additional molecular testing or protein expression can be performed when relevant for diagnosis, prognosis, or targeted treatment. The lower panel illustrates the processing of tissues in a pathology lab from the macroscopic to the microscopic level, and sometimes sub-microscopic level with molecular analysis.

Screening and Prevention

The role of pathology herein is mainly to define and diagnose precursor lesions that can be treated before they evolve into cancer. Examples are the early detection of cervical cancer (by cytopathology) and regular histopathological evaluation of endoscopic biopsies in patients with longstanding Barrett's oesophagus or inflammatory bowel disease to detect the development of dysplasia or cancer.

Establishment of the Nature of a Tumour

Classification of tumours is based on the cell of origin approach. Squamous cell carcinoma is derived from squamous cells, leiomyosarcoma from smooth muscle. Especially in lymphoma and sarcoma there are many different types of cells and thus many different types of tumours.

Most pathologists use the following stepwise approach in classifying a malignant tumour.

1. **Histology or cytology.** In 80-90% of all tumours, a tumour can be diagnosed based on these alone because of characteristic morphology and architecture.
2. **Immunohistochemistry.** In 10-20% of tumours additional immunohistochemistry is required to establish or confirm the line of differentiation, for establishing the primary site in case of a metastasis from an unknown primary, or for prognostication.
3. **Molecular pathology.**
 - **Clonality assays.** Clonality testing is performed in selected cases that are suspected for malignant lymphoma using the gene rearrangement pattern of antigen receptors.
 - **Molecular genetics.** Techniques such as polymerase chain reaction (PCR), reverse transcriptase (RT)-PCR, Southern blot, and fluorescence in situ hybridisation (FISH) can be used to detect chromosomal translocations, deletions, inversions, and numerical chromosomal abnormalities. For instance, the fusion gene BCR-ABL/(t(9;22)(q34;q11.2) in chronic myeloid leukaemia patients can be detected and quantified in blood of affected patients by real-time PCR. It helps to establish the diagnosis, but it can also be used to monitor the effect of targeted therapy with imatinib. The translocation can also be detected with FISH.
 - An example of the diagnostic application of mutation detection is the demonstration of a clonal relation between two tumours in one patient for instance by comparison of TP53 and CDKN2A mutations, in synchronous or metachronous melanoma or squamous cell carcinoma. Since tumours are of clonal origin and mutations in these genes are frequently unique in each tumour, this type of mutation detection is helpful in discriminating a second primary tumour from a metastatic tumour.

There are several examples where molecular approaches have led to subclassification of cancer. Well known examples are the distinction of germinal centre and activated B-cell types of diffuse large B-cell lymphoma, the basal and luminal types of breast cancer and most recently the subtyping of colon cancer into four types. All these examples are based on expression arrays, which is a technique that is not widely available. It can be expected that immunohistochemistry or other tools will be developed so that this subtyping can be generally applied.

Next-generation sequencing, also called massive parallel sequencing, has now entered routine practise. This means that much more information on the genetic make-up of a tumour is becoming available and is already being used for treatment choices, like the BRCA1/2 mutations indicating benefit from PARP inhibition in ovarian cancer or RAS mutations indicative of resistance for EGFR targeting in colorectal cancer.

Grading and Staging

Tumours are graded and staged according to schemes and protocols to predict prognosis and to guide treatment selection.

Grading is rather subjective and variably related to outcome. Grading is based upon histological resemblance of a tumour to the tissue of origin, and it takes into account the amount of anaplasia and proliferation rate. Most tumour types are divided into three grades of increasing malignancy. Well-differentiated tumours resemble their benign counterparts, whereas poorly differentiated tumours bear little resemblance to them. Moderately differentiated tumours are all those in between.

Staging is much more objective and is aimed at assessing the extent of local and possible regional or distant tumour spread. Staging is independent of grading. The most commonly used criteria for staging are tumour size, local tumour extension, regional/lymph node metastases, and distant lymph node or haematogenous metastases. These are codified in an international TNM (tumour, node, metastases) cancer staging system.

Recognition and Establishment of Aetiology: Detection and Testing in Hereditary Cancer Syndromes

In hereditary cancer syndromes mutations in disease-causing genes are transmitted in the germ-line of the family pedigree. In many familial cancer syndromes only one gene is responsible for one hereditary cancer, as in the case with the APC gene in familial adenomatous polyposis. However, sometimes mutations in multiple genes cause one hereditary syndrome, such as mismatch repair genes in Lynch syndrome. In addition to highly penetrant dominant genes also a variety of polymorphisms may contribute to cancer predisposition.

Pathologists have an important role in detection and testing of these cancer syndromes. Pathologists often have access to automated patient databases containing each patient's medical history so they are able to signal the presence of risk for a cancer syndrome, for instance, in a patient with colorectal cancer who also has a history of another Lynch syndrome-related tumour. Subsequently, analysis of microsatellite instability (MSI) in cancer tissue of the patient enables the pathologist to screen for defects in the mismatch repair system. Genetic testing can subsequently be offered to MSI-high patients. The molecular techniques and applications currently available for diagnosing different categories of the most common familial tumours are described by Tomita et al. (Table 2.1). However, further development is ongoing and the most recent data can be found at:

<http://www.cancer.gov/cancertopics/factsheet/Risk/genetic-testing>

Table 2.1 Cancer syndromes and associated genes

Cancer Syndromes	Associated Genes
Familial adenomatous polyposis	<i>APC</i>
Multiple endocrine neoplasia 2a, 2b	<i>RET</i>
Retinoblastoma	<i>RB1</i>
Von Hippel-Lindau syndrome	<i>VHL</i>
Lynch syndrome (hereditary <i>hMSH2</i> , <i>hMLH1</i> , nonpolyposis colorectal cancer)	<i>hPMS1</i> , <i>hPMS2</i>
Hereditary breast ovarian syndrome	<i>BRCA1</i> , <i>BRCA2</i>
Li-Fraumeni syndrome	<i>p53</i>
Familial malignant melanoma	<i>p16</i> , <i>CDK4</i>
Ataxia telangiectasia	<i>ATM</i>

Source: Tomita N, Oto M. Molecular genetic diagnosis of familial tumors. *Int J Clin Oncol*. 2004; 9: 246-56. Review.

Clinical Implications and Use

Pathologists have become important sparring partners of clinicians in multidisciplinary meetings, and their findings are of great importance in determining patients' treatment and outcome. In some fields of pathology, like dermatopathology and bone and soft tissue pathology, clinicopathological correlation is of the utmost importance for reaching the right diagnosis. Pathologists must keep up with the latest developments in their field by adequate postgraduate training and panel meetings.

Review

Pathologists are in the unique position that their diagnosis is based on tissue slides that are stored and thus can be reviewed later and that their diagnosis can be shared with colleagues. For several areas in pathology it is common to discuss cases with a panel of expert pathologists. Pathology is increasingly becoming a field with sub-specialisation, and therefore expert consultation is a relatively cheap and easy method for quality improvement in unusual or difficult cases.

Future Perspectives: Pathology in the “Omics” Era and the Era of Targeted Therapy

At present the enormous amount of information that is generated by novel proteomic and genomic applications is too large to be meaningfully analysed. Translating this plethora of information into clinically useful applications is an important task for pathologists. The development of information technology, with digitisation of slides, archivation, optimisation, and possible quantification of high-throughput testing methods are expected to be of great benefit to patients, clinicians, and pathologists.

Meanwhile, the development of targeted therapies places the pathologist in a situation in which expression of specific proteins or the presence of specific gene alterations is requested by the

clinician in order to install specific therapy. Increasingly, next generation approaches are included in the diagnostic process. Finally, promising results are being seen in the detection of genetic alterations in tumours reflected by circulating tumour DNA in the blood.

Further Reading

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Chapter 3 - Role of Circulating Biomarkers in Oncology

Introduction

Biomarkers are playing an increasingly important role in the detection and management of patients with cancer. Indeed, measurement of specific biomarkers is now mandatory for the optimum management of patients with several different types of malignancy (Table 3.1). The aim of this article is to review the clinical utility of the most widely used circulating biomarkers in the management of patients with cancer. In addition, we briefly discuss some promising circulating biomarkers which may enter clinical use in the near future.

Table 3.1 Examples of the most useful tumour biomarkers currently available

Cancer type	Marker(s)	Main use(s)
Colorectal	CEA	Prognosis, postoperative surveillance, monitoring therapy
	^a KRAS/NRAS	Predicting response to anti-EGFR antibodies (cetuximab, panitumumab)
	^b FOBT	Screening
	MSI	Prognosis
Germ cell	AFP, HCG, LDH	Prognosis, postoperative surveillance, monitoring therapy
Trophoblastic	HCG	Prognosis, postoperative surveillance, monitoring therapy
Ovarian	CA 125	Monitoring therapy, differential diagnosis of benign and malignant masses in postmenopausal women
Prostate	PSA	Screening, prognosis, postoperative surveillance, monitoring therapy