How the WHO Blue Books are handling hereditary cancer syndromes

International Agency for Research on Cancer Lyon, France

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2.0: Tumours of the oesophagus: Introduction

2.1.2.2: Oesophageal squamous dysplasia

Definition: Oesophageal dysplasia of the oesophagus is a premalignant histologic abnormality of the oesophageal squamous epithelium without invasion.

ICD-O coding:

- 8270/3: Oesophageal squamous dysplasia
- 8272/3: High-grade squamous dysplasia

Etiology:
- Tobacco and alcohol consumption
- Chronic irritation and inflammation

Molecular pathology:
- Alterations in p53, p16, and Ki-67
- Increased expression of cyclins and cyclin-dependent kinases

Clinical features:
- Asymptomatic or may present with dysphagia
- Endoscopic examination is the primary diagnostic tool

Prognosis:
- Depends on the grade of dysplasia

Therapy:
- Observation
- Endoscopic resection

References:
WHO Classification of Tumours ONLINE

Now available at: tumourclassification.iarc.who.int

Access to the following books:

5th edition
- Digestive Tumours
- Breast Tumours

4th edition
- Skin Tumours
- Eye Tumours
- Endocrine Tumours
- Head and Neck Tumours

Special launch rate of 100 Euros

More details from the IARC team – Booth A14, 2nd level, Agora 2 Hall
9am to 5.15pm, from Sunday 8 to Tuesday 10 September
The 5th Series WHO Classification of Tumours

- Digestive System Tumours
- Breast Tumours
- Soft Tissue and Bone Tumours
- Female Genital Tumours
- Thoracic Tumours
- Urinary and Male Genital Tumours
- Central Nervous System Tumours
- Head and Neck Tumours

- Endocrine Tumours
- Haematolymphoid Tumours
- Skin and Adnexa Tumours
- Eye and Orbit Tumours
- Paediatric Tumours
- Neuroendocrine Tumours
- Hereditary Tumours

http://whobluebooks.iarc.fr
WHO Classification of Tumours 5th Edition: Digestive System tumours
2nd Editorial Board meeting, 3-5 July 2018, IARC, Lyon, FRANCE
WHO Blue Books Faculty

Users

Subscribers

Authors

Editorial Board

WCT Blue Books team

- 300,000 (estimate)
- 60,000 – mainly pathologists
- 1,800 (150 per book)
- 20 standing + 144 expert

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5th Series Changes

- Increased speed of production by improved process management.
- Evidence not eminence...author selection by informed bibliometrics.
- Editorial board formed with standing and expert members to decide classification, based on evidence – including systematic reviews.
- Quality – HGVS for genomic notation, SI units (mm$^2$ not HPF).
- Epidemiology – from GICR epidemiologists.
- Etiology, pathogenesis – incorporate new information - e.g. metabolites, genetic predisposition.
- Harmonise topics across series – e.g. NEN, Lymph, ST&B.
- Website launched, but there are still books, and they are still blue!
Systematic review process and tools

- Review question format and structure
- Reference management software
- Data extraction form
- Appropriate method for data synthesis
- Database and search tools
- Results reporting: PRISMA flow diagram
- GRADE Summary of Findings table
- Forest plot

Source: Adapted from Cochrane Infographics: The Concept of a Systematic Review. Available at https://ccrg.cochrane.org/infographics
The multi-dimensional nature of cancer classification

- Tumour Type
  - ICD-O and ICD11 Codes
  - Variants
  - Epidemiology
  - Etiology
  - Genetics
  - Pathogenesis
- Clinical features and Radiology
- Synonyms
- Localization
- Cytology
- Staging (TNM)
- Molecular pathology (DNA, RNA, Protein)
- Prognosis and Prediction
- Histopathology

International Agency for Research on Cancer
World Health Organization
The multi-dimensional nature of cancer classification

- Genetics
  - Gene 1
  - Gene 2
  - Gene 3

- Tumour Type
  - Category
  - Family
  - Type
  - Sub-type

- Definition
  - Text

- Codes
  - ICDO
  - ICD11

- Histology
  - Macroscopic appearance
  - H&E appearance
  - Immune response & Microenvironment
  - Vascularity
  - Invasion (e.g. PNI)
  - Immunohistochemistry
  - Differential diagnosis
  - Diagnostic criteria – essential and desirable

- Epidemiology
  - Incidence
  - Causes
  - Predisposition

- Sub-types
  - List

- Synonyms
  - Text

- Pathogenesis
  - Text

- Molecular Pathology
  - Somatic genetics
  - Gene expression
  - Protein expression
  - Tumour markers

- Localisation
  - Site(s)

- Clinical
  - Radiology
  - Signs
  - Symptoms
  - Appearance

- Prognosis and Prediction
  - Tests
  - Results
  - Interpretation

- Staging
  - Tumour
  - Node
  - Metastasis

- Cytology
  - Appearance
  - Cellularity

- International Agency for Research on Cancer
  - World Health Organization
WHO BB Layout (5th Series) DRAFT

- Definition
- ICD-O and ICD11 Codes
- Related Terminology (Synonyms)
- Subtypes
- Localization
- Clinical features and Radiology
- Epidemiology
- Etiology
  - Causes
  - Predisposing factors (Genetics)
- Pathogenesis
- Macroscopic appearance
- Histopathology
  - H&E appearance
  - Immune response & Microenvironment
  - Vascularity
  - Invasion (e.g. PNI)
  - Immunohistochemistry
  - Differential diagnosis
- Cytology
- Molecular pathology
  - Somatic genetics
  - Gene expression
  - Protein expression
  - Tumour markers
- Diagnostic criteria – essential and desirable
- Staging (UICC TNM)
- Prognosis and Prediction
  - Prognostic factors
  - Predictive biomarkers
- Links to other resources
  - ICCR reporting guidance
  - TNM (UICC)
Classification of hereditary tumour syndromes (HTS)

• HTS classification is complex...
• Options include:
  • Mechanism
  • Gene
  • Clinical syndrome – often with an eponymous name
• These are often used interchangeably in current practice.
• Current volumes of the WHO Blue Books list HTS in a separate chapter at the end of each volume, without any attempt to classify them.
CAROLI LINNAEI

ETATIS DE STELLA POLARI,
ARCHAEO REGIV, MED. & BOTAN. PROFESS. UPIAL.;
ACAD. UPIAL, HOLMII, PETROPOL. BEROL. IMPII.
LORD. MONACI. TOLO, FLOREN. SOCI.

SYSTEMA

NATURÆ

PER

REGNA TRIA NATURÆ,
SECUNDUM

CLASSES, ORDINES,

GENERA, SPECIES,

CUM

CHARACTERIBUS, DIFFERENTIIS,
SYNONYMIS, LOCIS.

TOMUS I.

EDITIO DECIMA, REFORMATA.

HOLMÆ,

IMPENIS DIRECT. LAURENTII SALVI,

1773.

Carl Linnaeus (1707 – 1778)
Classification terms

- **Site**, e.g. Stomach
- **Category**, e.g. Epithelial neoplasms
- **Family** (Class), e.g. Adenomas and other premalignant neoplastic lesions
- **Type**, e.g. Adenoma
- **Sub-Type** (Variant), e.g. Pyloric-gland type

Stage and Grade are dealt with separately....
Heirarchy for HTS?

- Hierarchical systems ideally have multiple options under each level.
- In some cases, there can be fairly fairly direct 1:1 correlations between molecular pathways, syndromes and genes,
- Inevitably, there are a some syndromes that involve the same genes, but have different names or expressions of the disease depending on the DNA alteration present or the ability to affect multiple pathways.
Proposed Classification of HTS – Option A

1. *Category* = mechanism/pathway e.g. mismatch repair, HRD, etc (c.f. Hanahan & Weinberg, 2011)
2. *Family* = gene e.g. APC, TP53, etc
3. *Type* = syndrome name, e.g. GAPPS, FAP or other as used in practice as a diagnostic entity
4. *Subtype* = behaviour/severity based which may include location or type of mutation within a single syndrome
Proposed Classification of HTS – Option B

A. Category = mechanistic pathway e.g. DNA mismatch repair
B. Syndrome = syndrome name, e.g. Lynch, etc
C. Type = gene e.g. MLH1, MSH2, MSH6, PMS2, etc
D. Subtype = behaviour/severity based which may include location or type of mutation within a gene/single syndrome that correlates with phenotypic effects (aim for genotype – phenotype correlations in this concept)
Choice?

- The difference between these options is whether syndrome names are regarded as families, with types identified by gene affected, or *vice versa.*
Conclusion

- There is a need for all cancer diagnosticians to contribute to research, to gather the evidence our patients need, and to evaluate that evidence for use in their practice.
- Our diagnoses underpin the management of individual patients, cancer research, and epidemiology.
- There is a need for a classification to systematize the relationship between mechanisms, genes, and syndromes for hereditary cancers.
- Implementation is feasible through the WHO Blue Books, which provide the international standards for diagnosis.
Thank you!