

From Implementing Digital Pathology to IC³R

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Declaration of Interests

- International Agency for Research on Cancer
- World Health Organisation
- Previously at U.K. NHS overseeing implementation of GE Omnyx digital pathology in Coventry
- All opinions expressed are personal, and not those of any of the organisations above.



IARC - An international effort to combat cancer Cancer research for global cancer prevention





IARC and WHO A complementary partnership



Evidence-base





for cancer prevention and control programmes

International Agency for Research on Cancer





Translates the scientific evidence



into guidelines and policies

IARC – an influential publications programme





WHO Classification of Tumours

WHO Classification of Tumours • 5th Edition

Digestive System Tumours

Edited by the WHO Classification of Turnours Editorial Board







World I Organi



Breast Tumours



Edited by the WHO Classification of Tumours Editorial Board





World Health

International Agency for Research on Cancer



2.0: Tumours of the oesophagus: Introduction

This chapter describes benign and malignant oesophageal Bex2.XX ICD-0-4 topgraphical coding to the analytical sites covered in this chapter tumours of epithelial differentiation and The ICD-O-4 topographical coding for th ered in this chapter is presented in Box 1 common benjan lesion, squamous par a dedicated section. Throughout this fit 2.1.2.2: Oesophageal squamous precursor lesions are typically describe from malignant turnours - a change from dysplasia decision to make this change was base expansion of our understanding of the bi cal features of precursor lesions and th practice There are two main types of precursor gus: Barrett dysplasia and squarrous d

A (AG)

R (900)

rell cardiname (BCC)

Definition 10 years or so, we have seen an impo-Squamous dysplasia of the oesophagus is an une towards ablation for the treatment of neoplastic alteration of the oesophageal squamous epi patients with high-grade dysplasia. The without invasion. ally occur in the treatment of low-grad

ICD-O coding 80770/0 Low-grade squamous dysplasia 80770/2 High-grade squamous dysplasia ICD-11 coding

2E92.0 & XH3Y37 Benign neoplasm of oesophagus & (ageal squamous intraepithelial neoplasia (dysplasi orade 2E60.1 & XH9ND8 Carcinoma in situ of oesophagus & (

Ochiai Odze R 40

ageal squarrous intraepithelial neoplasia (dysplar orade

Related terminology

Subtype(s)

Localization Squamous dysplasis can occur anywhere in the oeso and it is likely to follow the distribution of squamous or noma.

Clinical features

Patients at high risk of oesophageal squarrous cell car are usually followed using a combination of Lugol's chr doscopy and narrow-band imaging (1366). With Lugol's low-grade dysplasia appears as an unstained or weakly area; high-grade dysplasia is consistently unstained Features associated with neoplastic disease include last non-flat appearance, positive pink-colour sign, and n ity of distinct iodine-unstained lesions (3702). On name

Fig. 2.XX National age-standardized incidence rales Turnours of the cesophagus



Fig.2.XX Oesophagaal squareous dyspizala. A On kw-magnification or the hort kill wail, 30 cm from the indisce. B On high-magnification endose between them is brightly coloured. © On while-light endoscopy, the leater leaters is meltike the the elekcopicy size _ it is well democratical and unstate

bility (2802).

Macroscopic appearance

escohageel mucosa.

Oesophageal adenocarcinoma shows gastric, intestinal, and mixed (hybrid) lineage, evidenced by a combination of mor-phological and immunohistochemical features (1548,426).



Fig. 2.XX Ossphageal adenocarcinens. A Tabular patters. B Papillary patters. C Mucineus patters. D Signet-ring cell patte

Takubo KT

Full SF

In recent years, past-generation sequencing techniques have The mucosa adjacent to the adenocaroingma may show Be given rise to global projects involving whole-genome sequenc-ing of oesophageal adenocarcinoma (2566). These projects have revealed key gene pathways and mutations involved in tubular, papillary, mucinous, and signet-ring cell patterns. Only pathogenesis (2027,907), identified novel genes (818), and shown that the genomic landscapes of prechemotherapy and therefore, patterns are described rather than subtypes. A mixpostchemotherapy samples of oesophageal adengoarcingma have of these patterns is often seen. The tubular pattern is most re similar (2367). There are currently no clinical applications common. It is characterized by irregular, single or anastomosing for these comprehensive but complex data, but clinically relevant and diagnostically useful prognostic and predictive markmalignant epithelium; neoplastic glands often show variable Allas (TCGA) also suggest that oesophageal adenocarcinoma in mounts of intracellular mucin production and may show dista-tion (1756). The papillary pattern is characterized by papillae. Atlas (TCGA) elso suggest that oscophageal adencoschoma strong/ resembles gastic carcinoma with chromosomal insta-with rare cases showing microgabilary architecture (1182). The mucinous pattern generally shows carcinoma cells floating in



Fig.2.XX Oesophageal adenceatinome. An example in Barrett oesophages with a double layer of muscularis successe.

Turnours of the oesophagus 17

Pathology in the past...

- A microscope
- A good library two volumes should do it...
- What's this ridiculous idea about antibodies?
- Electron microscopy?



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Pathology today

- Microscope
- Dusty bookshelves full of out of date texts (I bought the last one, and the diagnoses haven't changed much...)
- Internet if you're stuck?
- Immunohistochemistry works well...does anyone use electron microscopy anymore?
- Better send off a few sections for molecular pathology
 - I wonder what they do all day?





Pathology of the Future?

- Digital pathology with computer assisted diagnosis.
- Immunohistochemistry and Image Analysis.
- Next-generation sequencing of panels of gene, exome or WGS (complementary diagnostics).
- Proteins, RNA, Metabolome.
- Integrated reporting LIMS or EPR?
- Predictive measurements to underpin treatment.
- Continuous education...books?



Digital Pathology: Intuitive, Easy To Use, Automatic





















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Validation study

- Double reporting by same pathologist
- Glass first digital second
- Minimum 3 week 'washout' period
- 3,034 cases 10,138 scanned slides (2.22 terabytes) giving 80% power at α = 0.05
- Omnyx funded
- Results showed <2.4% discrepancies (72)

Snead DR *et al.* Validation of digital pathology imaging for primary histopathological diagnosis. *Histopathology* 2015 Sep 26. doi: 10.1111/his.12879.





Tools becoming available

- Image analysis tools developed from 1980s to present day.
- Slide scanning technology available!
- Storage now simple and low cost
- Machine learning/AI technologies



Siriniukunwattana K, et al. IEEE Transactions 2016.

Detected epithelial, inflammatory and fibroblast nuclei are represented as red, green, and yellow dots,





The problem of artefacts...

Or why you still need the pathologist!



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Trahearn N, Tsang YW, Cree IA, Snead D, Epstein D, Rajpoot N. Simultaneous automatic scoring and co-registration of hormone receptors in tumor areas in whole slide images of breast cancer tissue slides. Cytometry A. 2017; 91(6): 585-594.

Measuring cellular interaction



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Sirinukunwattana K, Snead D, Epstein D, Aftab Z, Mujeeb I, Tsang YW, Cree I, Rajpoot N. Novel digital signatures of tissue phenotypes for predicting distant metastasis in colorectal cancer. Sci Rep. 2018 Sep 12;8(1):13692.

Why go digital?

- Economic reasons
 - Increase efficiency of pathologists
 - Reduce turn around time to report cases
 - Improved review of cases including MDT review
- Quality advantages
 - Reduced error rate
 - Increased sub-specialisation
 - IHC scoring and indexing
 - Tumour grading / dysplasia grading
 - Cancer finder AI methodology in practice



Economic argument

- 12-13% (claimed) efficiency gain at pathologist level
- Saving on retrieval of archived slides
- Merger of departments saving pathologist numbers
- Reduced turn around time changes patient pathways
 - reducing visits and in-patient time
 - better more efficient use of resources
- Facilitates review improving diagnostic accuracy



Pathologist T&M Study Results Breakdown of Time Working Cases





Pathologist T&M Study Results Breakdown of Workflow Opportunities

Workflow Opportunities





The International Collaboration for Cancer Classification and Research (IC³R)

IC³R will provide a forum for encouraging high quality research, and for coordinating evidence generation, synthesis, and evaluation, for tumour classification. Member institutions include universities, research centres and other interested parties, that will assign representatives to discuss and coordinate international efforts for the provision of high level, up-to-date evidence and the promotion of universal standards to underpin the WHO Classification of Tumours.



collaboration for cancer classification



IC³R Framework





Dichotomising continuous variables



Doug Altman, 1948 - 2018



http://www.equator-network.org

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STATISTICS IN MEDICINE Statist. Med. 2006; 25:127-141 Published online 11 October 2005 in Wiley InterScience (www.interscience.wiley.com), DOI: 10.1002/sim.2331

Dichotomizing continuous predictors in multiple regression: a bad idea

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Practice

Statistics Notes

The cost of dichotomising continuous variables

Douglas G Altman, Patrick Royston

Measurements of continuous variables are made in all branches of medicine, aiding in the diagnosis and treatment of patients. In clinical practice it is helpful to label individuals as having or not having an attribute, such as being "hypertensive" or "obese" or having "high cholesterol," depending on the value of a continuous variable

MRC Clinical Trials Categorisation of continuous variables is also common in clinical research, but here such simplicity is gained at some cost. Though grouping may help data presentation, notably in tables, categorisation is unnecessary for statistical analysis and it has some serious Correspondence to: drawbacks. Here we consider the impact of converting continuous data to two groups (dichotomising), as this is the most common approach in clinical research.1

BMJ 2000:532:1080 What are the perceived advantages of forcing all individuals into two groups? A common argument is that it greatly simplifies the statistical analysis and leads

preferable to performing several analyses and choosing that which gives the most convincing result. Use of this so called "optimal" cutpoint (usually that giving the minimum P value) runs a high risk of a spuriously significant result; the difference in the outcome variable between the groups will be overestimated. perhaps considerably; and the confidence interval will be too narrow. This strategy should never be used.97

When regression is being used to adjust for the effect of a confounding variable, dichotomisation will run the risk that a substantial part of the confounding remains.47 Dichotomisation is not much used in epidemiological studies, where the use of several categories is preferred. Using multiple categories (to create an "ordinal" variable) is generally preferable to dichotomising. With four or five groups the loss of information can be quite small, but there are complexities in analysis.

Instead of categorising continuous variables, we pre-

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Systematic review process and tools



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Source: Adapted from Cochrane Infographics: The Concept of a Systematic Review. Available at https://cccrg.cochrane.org/infographics

Conclusions

- Digital pathology is ready for clinical use and of proven benefit.
- It will produce data to show which diagnostic criteria are robust and reproducible.
- Evidence, rather than opinion, is required for translation: including comparative validation studies in multiple centres.
- Study design is key to success.
- Health economic arguments need to be won with data...
- Consensus is not enough we need systematic reviews and high quality studies to underpin guidance.
- Some implementation can occur through the WHO Classification of Tumours.



Thank you!



