Introduction to the ICCR; Dataset for Nasopharyngeal and Oropharyngeal Cancers

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on behalf of the ICCR Dataset Authoring Committee

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Lester Thompson

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Diagnostic reports – How and why?

• International accepted standards
  • Diagnosis – WHO/IARC ‘Blue Books’
  • Prognosis – TNM staging (UICC, AJCC)

• In practice, what information does a pathologist need to remember to identify and collate to fulfil expectations of surgeons and oncologists?
  • Increasing complicated
  • National datasets exist – vary in approaches; require time and effort to produce; only published in a minority of countries
Aggregated Pathology Cancer Data

- Data duplication
- Interoperability compromised or precluded

No Data
Incompatible datasets

Need:
Standardised, internationally accessible datasets
• Data Elements:
  • Naming conventions
  • Value lists
  • Units and methods of measurement
- and explanatory text
International Collaboration on Cancer Reporting

Hong Kong College of Pathology
Chinese Anti-Cancer Association
Brazilian Society of Pathology
German Society of Pathology
Austrian Society of Pathology
What does ICCR do?

• The goal of the ICCR is to develop a set of data elements which will form the core of any pathology report on the specific cancer around the world.

• Pathologists may add other elements when implementing or reporting. The intent is not to restrict them from adding in additional items they feel are important/fit local practice.

• Publication of evidence based protocols for the pathology reporting of cancers as structured data
  • Improves clinical practice.
  • Ensures ‘buy in’ from pathologists
  • Quality assurance at this stage underpins everything else
<table>
<thead>
<tr>
<th>2011 – Pilot project</th>
<th>2018</th>
<th>New for 2019-2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Endometrial Prostate Melanoma</td>
<td>Thorax x 4 Skin - melanoma Gynaecological x 3 Urology x 12 Liver CNS Head and Neck x9</td>
<td>Skin – Merkel cell - Melanoma update Endocrine (adrenal, thyroid, parathyroid) Gastrointestinal (liver update, upper and lower GI, pancreas) Breast (x3) Bone and soft tissue (x3)</td>
</tr>
</tbody>
</table>

N.B. Endocrine datasets currently out for consultation

[www.iccr-cancer.org](http://www.iccr-cancer.org)
ICCR Steering Committee

Dataset series champion

Dataset Steering Committee
National organisations + Project management
Key ICCR dataset development points

**Definitions – CORE (REQUIRED) elements**

- Core elements - essential for staging, clinical management, or prognosis of the cancer. Essential = good published evidence.
- The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

**Definitions – NON-CORE (RECOMMENDED) elements**

- Non-core elements - unanimously agreed should be included in the dataset but are not supported by sufficient evidence.
- These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.
Key ICCR dataset development points

**Commentary on data items**

- Commentary is explanatory text, diagrams or tables that clarify the elements used to:
  - defines the way an item should be reported, to ensure clarity and conformity
  - explains why an item is included (e.g. how does the item assist with clinical management or prognosis of the specific cancer)
  - cites published evidence in support of the element
  - states any exceptions or issues

- Commentary provides contextual guidance for the reporting pathologist.
Patient care
Prognosis
Prediction

Head and Neck Cancer Pathology Datasets

WHO Classification of Head and Neck Tumours

TNM Classification of MALIGNANT TUMOURS
Eighth Edition

ICCR

UNION FOR INTERNATIONAL CANCER CONTROL

WILEY Blackwell
• Reporting proforma with hyperlinks
• Explanatory text
ICCR dataset

• Includes
  • all invasive carcinomas of the nasopharynx
  • all invasive carcinomas of the oropharynx including:
    • base of tongue
    • tonsils
    • soft palate
    • posterior wall
    • uvula

• Excludes
  • Lymphomas
  • Sarcomas

• Neck dissections are covered in separate dataset
Carcinomas of the Oropharynx and Nasopharynx

Impact of viral aetiology at both sites

• Changes in diagnostic categorisation of oropharynx related to HPV status
  • Relates to prognosis – different staging
  • Impact on management – evolving

• EBV status in nasopharynx
  • Does not affect staging
  • Impacts on prognosis
  • Impact on management – evolving

• Traditional pathological prognostic features are not relevant in virus-associated carcinomas
  • Grade, depth of invasion, in situ disease
Molecular profile of HPV-associated cancers

- High risk HPV types (HPV-16/18)
- E6 and E7 viral proteins inactivate p53 and pRb
- Removal of negative feedback by pRb allows overexpression of p16
- Compared with smoking and alcohol-associated cancers
  - Less aneuploidy, fewer oncogene abnormalities, fewer p53 mutations
  - More frequent 3q amplification and 16q loss
### WHO classification of tumours of the oropharynx (base of tongue, tonsils, adenoids)

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>8085/3*</td>
</tr>
<tr>
<td>Squamous cell carcinoma, HPV-positive</td>
<td>8086/3*</td>
</tr>
<tr>
<td>Salivary gland tumours</td>
<td></td>
</tr>
<tr>
<td>Pleomorphic adenoma</td>
<td>8940/0</td>
</tr>
<tr>
<td>Adenoid cystic carcinoma</td>
<td>8200/3</td>
</tr>
<tr>
<td>Polymorphous adenocarcinoma</td>
<td>8525/3</td>
</tr>
<tr>
<td>Haematolymphoid tumours</td>
<td></td>
</tr>
<tr>
<td>Hodgkin lymphoma, nodular lymphocyte predominant</td>
<td>9665/9</td>
</tr>
<tr>
<td>Classical Hodgkin lymphoma</td>
<td></td>
</tr>
<tr>
<td>Nodular sclerosis classical Hodgkin lymphoma</td>
<td>9663/3</td>
</tr>
<tr>
<td>Mixed cellularity classical Hodgkin lymphoma</td>
<td>9652/3</td>
</tr>
</tbody>
</table>

Morphology alone not sufficient p16 immunocytochemistry acceptable HPV associated DNA or RNA ideal

### WHO Classification 4th Edition

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte-rich classical Hodgkin lymphoma</td>
<td>9651/3</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>9655/3</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>9687/3</td>
</tr>
<tr>
<td>Malignant lymphoma</td>
<td>9690/3</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>9673/3</td>
</tr>
<tr>
<td>T-lymphoblastic leukaemia/lymphoma</td>
<td>9837/3</td>
</tr>
<tr>
<td>Follicular dendritic cell sarcoma</td>
<td>9758/3</td>
</tr>
</tbody>
</table>

Resource-poor countries - Strict classification rules so if p16 not available then HPV negative BUT Can use clinical judgement for management

HPV-positive carcinoma

HPV-negative carcinoma
Morphology of Oropharyngeal HPV-associated Carcinomas

Varied terminology

- Non-keratinising
- Basaloid
- Poorly-differentiated
HPV-associated oropharyngeal carcinoma has a distinctive phenotype

- Arises from reticulated epithelium of tonsillar crypts
- Non-keratinising SCC
  - May show focal maturation (eosinophilia, keratin whorls)
  - Not “poorly differentiated” – fewer genetic changes, better prognosis
- However,
  - Not all non-keratinising SCC are HPV related
  - Some keratinising SCC are HPV related
  - Some basaloid squamous carcinomas are HPV-positive (non-HPV basaloid SCC are more aggressive)
  - Some small cell carcinomas are HPV positive (aggressive)
‘Typical’ non-keratinising HPV associated carcinoma
HPV-associated papillary squamous cell carcinoma
HPV-associated carcinoma – adenoid cystic like
HPV associated small cell carcinoma

CK5/6

synaptophysin
Nasopharyngeal carcinoma

• Morphological subtypes are not important prognostically
• EBV immunocytochemistry is unreliable
• EBV encoded RNA (EBER) in situ hybridisation is standard practice
<table>
<thead>
<tr>
<th>Core elements (required)</th>
<th>Non-core elements (suggested)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant therapy</td>
<td></td>
</tr>
<tr>
<td>Operative procedure</td>
<td>Depth of invasion</td>
</tr>
<tr>
<td>Specimens submitted</td>
<td>Coexistent pathology</td>
</tr>
<tr>
<td>Tumour site</td>
<td></td>
</tr>
<tr>
<td>Tumour dimensions</td>
<td></td>
</tr>
<tr>
<td>Histological tumour type</td>
<td></td>
</tr>
<tr>
<td>Tumour grade (virus negative)</td>
<td></td>
</tr>
<tr>
<td>Margin status (invasive)</td>
<td></td>
</tr>
<tr>
<td>Ancillary studies (viral status)</td>
<td></td>
</tr>
<tr>
<td>Pathological staging</td>
<td>Oropharynx only – perineural and lymphatic invasion (core data)</td>
</tr>
</tbody>
</table>

Where is the tumour? What is the type of tumour? How is it likely to behave? Options for treatment?

- Provide context for interpretation of other data
- Indicate potential limitations of some data items if only limited biopsy material is present
Tumour site

If neck dissection submitted, use separate dataset to record information
Tumour dimensions

Macroscopic size, confirmed or amended after microscopy
Tumour
Histological Type
Grade (if appropriate)

Tumours which are not graded

Nasopharyngeal carcinoma
HPV (p16) associated carcinomas
Post-therapy
Margin status

- Involved margin = ‘cut through’
- Difficult when laser resection due to thermal artefact
- If separate marginal biopsies present, record distance to margin in main specimen and status (+/-) in biopsies
- HPV-associated carcinomas – cannot distinguish invasive from in situ disease
Ancillary studies
- virus testing

ANCILLARY STUDIES

Viral testing/Viral tumour markers

OROPHARYNX
- Not performed/unknown
- Performed (select all that apply)
  - p16 Immunohistochemistry
    - Positive
      - >70% nuclear and cytoplasmic staining of at least moderate to strong intensity
      - Other criterion used, specify
    - Negative
      - Criteria used to determine results, specify

High risk HPV specific testing
- DNA PCR
  - Not identified
  - Present
- DNA in situ hybridization
  - Not identified
  - Present
- E6/E7 mRNA in situ hybridization
  - Not identified
  - Present
- E6/E7 mRNA RT-PCR
  - Not identified
  - Present
Oropharynx - Pathological Staging – UICC TNM v8

TNM Descriptors (only if applicable) (select all that apply)

☐ m - multiple primary tumours
☐ r - recurrent
☐ y - post-therapy

Primary tumour (pT)****

p16 Positive oropharynx

☐ T0 No evidence of primary tumour, but p16 positive cervical node(s) involved
☐ T1 Tumour 2 cm or less in greatest dimension
☐ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
☐ T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
☐ T4 Tumour invades any of the following: larynx^^, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible^^, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

p16 Negative oropharynx

☐ Tis Carcinoma in situ
☐ T1 Tumour 2 cm or less in greatest dimension
☐ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
☐ T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
☐ T4a Moderately advanced local disease
Tumour invades any of the following: larynx^^, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, or mandible
☐ T4b Very advanced local disease
Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery
Nasopharynx - Pathological Staging – UICC TNM v8

Not applicable in most cases as patients treated with primary chemoradiotherapy

Nasopharynx

- **T0** No evidence of primary tumour, but EBV-positive cervical node(s) involved
- **T1** Tumour confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement
- **T2** Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles
- **T3** Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses
- **T4** Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or infiltration beyond the lateral surface of the lateral pterygoid muscle
Oropharyngeal carcinomas
Impact of HPV status on prognosis

• HPV+ oropharyngeal carcinomas have a relatively good prognosis regardless of treatment

• Cancers are not inherently more sensitive for radiotherapy or cisplatin; these treatments result in a more intense immune response in HPV+ cancers

• HPV and smoking
  • Patients with HPV+ carcinoma and who were smokers tend to have intermediate prognosis
  • ?HPV improves outcome of smoking induced cancers
  • ?smoking reduce immune response to HPV-induced cancers
Oropharyngeal carcinomas
Impact of HPV status on management

• Stratification of patients by HPV status is a useful guide to prognosis using standard therapies
• Extranodal extension – may be of less importance in HPV-related carcinomas – needs confirmation
• HPV+ SCC with small cell component – highly malignant
• Should HPV status be used to modify treatment?
  • Results of clinical trials are awaited
  • ? Should we treat advanced disease more aggressively if know prognosis is better
  • ? Should de-escalate treatment to reduce side effects
HPV-assessment in clinical practice – potential impact

Suitable for Surgery?

Operable
- Open Surgery / Free Flap
- Trans-Oral Laser Resection

Inoperable or poor function predicted
- Chemoradiotherapy / Radiotherapy / IMRT
- Palliation

HPV