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Dataset for the histopathological reporting of oesophageal carcinoma (2nd edition)

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1 INTRODUCTION TO OESOPHAGEAL CANCER DATASET

These proposals for reporting of oesophageal cancers should be implemented for the following reasons:

- prognostic information for the patient[1]
- prognostic information for clinicians
- feedback to the surgeon on the quality of resection and the effects of neoadjuvant therapy[2]
- for efficient audit for individual surgeons and between surgeons and between surgical techniques
- feedback for other specialties, e.g. radiology.

As a guiding principle, the TNM staging system is used.[3] This has the advantage of being widely accepted and familiar, and is adhered to (except for the assessment of lymph node metastases – see below) throughout this document.

The first edition of this document (1998) included little detail regarding dissection techniques, histological interpretation, etc. It was felt that there were a number of equally valid ways in which the same, minimum, data could be extracted. There have since been requests for guidance on such matters and some have been included below. It is stressed that these are for guidance and are not prescriptive. The Association of Clinical Pathologists has produced guidelines for the handling of oesophageal specimens;[4] these address many of the above issues.

This document has been devised to include the data required for adequate reporting of oesophageal specimens containing cancer. Where possible, **core** data that represent a minimum standard for patient management have been distinguished from **non-core** data that form part of a complete report but which do not have a sufficient basis in published evidence. The dataset has been approved by the UK Association of Cancer Registries and panels of specialised and general histopathologists acting on behalf of the College.

2 SPECIMEN RECEIPT AND PREPARATION

Oesophagectomy specimens contract immediately they are removed from the patient. They lose a quarter of their natural length initially and can be as little as a third of that length if fixed without being pinned.[5] Ideally the specimen should be delivered rapidly, to the laboratory. It is recommended that specimens are pinned out, fresh, on cork boards before being fixed. When the specimen is measured, note should be made of whether or not the specimen was pinned.

The stomach should be opened along the gastric resection margin. The oesophagus itself may be pinned out intact. This allows optimum assessment of the whole of the circumferential resection margin by serial horizontal slicing of the oesophagus and does not significantly impair fixation in most tumours. Alternatively, the oesophagus may be opened along its length. This allows detailed assessment of background abnormalities in the rest of the oesophagus. Some pathologists feel that this does not impair assessment of the circumferential resection margin. If this method is used, the outer surface of the oesophagus should be painted before opening.

3 TISSUE SAMPLING

The following blocks of tissue are recommended as a minimum sampling:

- proximal resection margin – block(s) parallel to margin
- distal resection margin – block(s) parallel to margin
- three blocks of tumour to show closest approximation of tumour to circumferential margin and relationship to adjacent mucosa
- sampling of lymph nodes.

There are two approaches to sampling the tumour:

- Blocking out the tumour with horizontal and longitudinal slices is recommended by some.[4] This probably best demonstrates the relationship of the tumour to the surrounding mucosa.
- Others recommend serial horizontal slices of the tumour. This allows more readily understandable photography of specimen slices and correlation with radiological images.

4 CORE DATA

- Maximum tumour diameter
- Siewert tumour type (cardiac tumours only)
- Maximum depth of invasion (anatomical layer)
- Polypoid or other morphology
- Histological type
- Grade of malignancy
- Serosal involvement (gastric, pleural or pericardial)
- Resection margins (proximal, distal and circumferential)
- Vascular invasion
- Lymph node status

5 NON-CORE DATA

- Comment on specimen preparation
- Overall dimensions of specimen
- Presence of Barrett's metaplasia
- Effects of neoadjuvant therapy (if applicable)
- Molecular data (if applicable)

6 GROSS DESCRIPTION

The overall dimensions of the specimen and the lengths of oesophagus and stomach should be recorded. The maximum length of tumour should be recorded. Tumour size influences prognosis.[6, 7] To conform with other datasets, the tumour size and distance to resection margins are based on macroscopic assessment, confirmed or amended on the basis of microscopy.

The macroscopic appearance of the tumour has little contribution to the prognosis, with the exception of polypoid tumours.[8]

The classification of carcinomas involving the gastro-oesophageal junction is difficult. There is no separate TNM system for cardiac cancers. TNM staging systems are different for the oesophagus and stomach. The decision must be made, for each gastro-oesophageal junction cancer, which dataset and which TNM scheme to use. This decision may affect the tumour's T or N stage.

A widely used classification of cancers at the cardia divides them into three groups: those arising 1–5 cm above the gastro-oesophageal junction (Type 1), at the junction (Type 2) or 2–5 cm below the junction (Type 3).[9] In this system, the gastro-oesophageal junction is defined as the proximal limit of the gastric rugal folds. This classification is now recommended by the British Society of Gastroenterology.[10] The Siewert type has been included as a core data item in this dataset.

There is some evidence that Type 1 cancers are different from Types 2 and 3 cancers in features such as the pattern of lymph node metastasis.[11, 12] Thus there might be an argument for using the oesophageal dataset for Type 1 tumours, and the gastric dataset for Type 2 and 3 tumours. Other authorities believe that Type 2 tumours should be included with oesophageal cancers.

Recent International Union Against Cancer (UICC) guidance on these matters is contradictory.[13] In the 'frequently asked questions' segment of this publication, it states that all adenocarcinomas of the gastro-oesophageal junction (GOJ) should be classified according to the gastric TNM scheme. In the main text, however, it specifically states that 'if more than 50% of the tumour involves the oesophagus the tumour is classified as oesophageal, if less than 50% as gastric'. It further specifies that tumours exactly at the junction should be classified according to their histology, so squamous cell, small cell and undifferentiated carcinomas would be oesophageal and adenocarcinomas would be gastric. This was effectively the advice from the first edition of this dataset. In the absence of further recommendations from the UICC or a new TNM scheme for cardiac cancers, this advice stands.

This dataset should be used when more than half of the cancer (measured on the mucosal aspect) is above the GOJ. The GOJ is often obvious on the mucosal surface. Sometimes, large tumours obliterate the junction or extensive Barrett's oesophagus can make it difficult to identify the GOJ. In these situations, the junction is probably most easily identified by the highest extent of the peritoneal reflection on the serosal surface. If more than half of the cancer is below the GOJ the Gastric dataset should be used. Thus this dataset should be used for all oesophageal cancers, cardiac cancers of Siewert type 1, and some cardiac cancers of Siewert type 2. This may be subject to revision in the near future.

The size and position of the tumour will allow its location with respect to the GOJ to be determined.

7 MICROSCOPIC FEATURES

Histological type of tumour

The vast majority of these lesions will be adenocarcinomas and squamous carcinomas, with a few adenosquamous lesions and small cell carcinomas. Whilst the type of carcinoma may have little influence on prognosis in the majority of lesions,[14] in very early cancers (T1) it may be better to have an adenocarcinoma – they have less local recurrence and fewer new primary lesions.[15] Irrespective of the prognostic implications, it provides useful validation of the presurgical diagnosis, which may be important in adjuvant therapy decisions.

Tumour differentiation

Opinion is divided upon the prognostic significance of tumour differentiation. In some studies, it was prognostically significant for squamous carcinomas,[16] adenocarcinomas[17] or both.[14, 18] However, in one large study it was not significant.[1] As it is usually easy to assess and may be important prognostically, it is therefore included in the core dataset. The World Health Organization (WHO) classification in the series, *International Histological Classification of Tumours*,[19] specifies that 'when a tumour shows different grades of differentiation the higher grade should determine the final categorisation'. The

newer classification from WHO does not specify how to classify different grades of differentiation in the same tumour.[20] In conformity with other datasets, differentiation is assessed as being that of the highest grade in the tumour.

Dysplasia

Occasionally an oesophageal resection will be performed upon a patient who has had multiple biopsies showing high-grade dysplasia, usually in the context of Barrett's oesophagus. These patients usually have invasive adenocarcinoma in the resection specimen, but occasionally a resection will show only high-grade dysplasia.

Depth of invasion

The depth of invasion is assessed according to the TNM staging system and is one of the most consistent predictors of prognosis.[1, 14, 17, 21–23] It is often the only independent prognostic indicator on multivariate analysis.[1, 14, 17] Some authors have attempted to go further and distinguish mucosal and submucosal invasion.[17, 24] Whilst this may predict the likelihood of lymph node metastases,[25, 26] it is not an independent prognostic factor in patients who do not have nodal metastases.[24] Distinguishing intramucosal carcinoma from submucosal carcinoma is thus more important in endoscopic mucosal resection specimens than in oesophagectomy specimens.

Serosal involvement

Some tumours may involve the pleura or pericardium. Many distal oesophageal carcinomas will involve the proximal stomach. At these sites, there is no circumferential margin but there is a serosal surface. Whilst there is no evidence to confirm or refute serosal involvement as an important prognostic indicator in oesophageal carcinoma, it is undoubtedly so in the stomach[27] and for this reason it is included in the dataset. Indeed in one study,[28] 25.6% of patients dying of oesophageal carcinoma had serosal carcinomatosis. The different types of serosal surface (pleura, pericardium and peritoneum) are not distinguished in this dataset.

Proximal and distal margins

The proximal (upper) and distal (lower) resection margins of the oesophagus require histological exclusion of involvement. There is good evidence that involved proximal margins increase the likelihood of recurrence[16, 17, 29, 30] but less evidence for distal margins.[17,31] The proximal margin of the oesophagus should always be sampled, no matter what the distance from the tumour, because of the risk of discontinuous foci of carcinoma in the proximal oesophagus.[32] There are recommendations for clearance of tumour from proximal and distal margins, but this may vary depending upon the type of tumour.[30, 31] In conformity with other datasets, the distances are measured macroscopically.

Circumferential resection margin (CRM)

Before Sagar *et al* published their study of CRM involvement in the oesophagus,[33] few studies even mentioned this as a possible parameter.[2, 16] Sagar's retrospective study and a follow-up prospective study[34] showed CRM involvement to be a predictor of poor prognosis, especially in patients with no or few involved lymph nodes. Longer follow up on still more patients rather confusingly found CRM status to be only significant on univariate analysis.[35] However, as R status was included in the factors investigated and R status (presumably) included CRM status, this is perhaps not surprising. R status was an independently significant factor. (R0 resection is a fully resected tumour with no involvement of any margins; R1 resection is macroscopically a clear resection but which proves on histological examination to have positive margins; R2 resection is one in which margin involvement is obvious macroscopically, either to the surgeon or pathologist). Another study to have looked at this parameter concluded that it has no prognostic significance on multivariate or even univariate analysis.[18]

It is perhaps not surprising that CRM involvement is not significant in patients with very early (T1 or T2) tumours or advanced (T4 or those with large numbers of nodal metastases) tumours. However, when T3 tumours with fewer than 25% of nodes involved are investigated, CRM status is again shown to be of major prognostic significance.[36] The same authors who produced the negative study mentioned above were unable to show any significance to margin involvement in their node negative

cancers.[37] Improved margin clearance is related to improved survival following neoadjuvant treatment.[38]

Some authors have suggested that CRM status should not be included in the dataset.[18] However, CRM status also provides surgical and radiological feedback and may be a useful audit tool. Whilst opinion is still mixed on the prognostic significance of this parameter, it is suggested that it remain as a **core data** item in the dataset. It is said to be involved if carcinoma is identified microscopically within 1 mm of the CRM

Some surgeons prefer to remove lymph nodes from an oesophagus before sending the specimen to the laboratory. The circumferential resection margin cannot be assessed in this situation and the margin should be recorded as 'not assessable'.

Vascular invasion

Vascular invasion is an effective prognostic indicator. Different studies have detected involvement in different ways, some using special stains, some specifying venous over lymphatic invasion and some with no details on how it was identified. Many showed a significant effect on univariate analysis[1, 16, 17, 21, 39] and, in two studies,[17, 35] it was as independently prognostic as depth of invasion on multivariate analysis. Lymphatic invasion has specifically been shown to indicate a poor prognosis.[40, 41] There is no separate data comparing intra- and extramural vascular invasion. It is recommended that invasion of any vascular space is recorded.

Perineural invasion

There is less evidence for perineural invasion as a prognostic indicator. In one study,[17] the only significance here was lost on multivariate analysis. However, in another study,[42] neural invasion was an important prognostic factor.

Lymph node stage and numbers of involved nodes

All studies in which crude lymph node status is assessed show it to be a significant indicator of prognosis.[1, 14, 16–18, 21, 22, 39] In many of those papers, it was the most significant prognostic indicator.

The TNM staging system indicates only whether or not lymph nodes are involved, with no sub-classification into N2 or N3, unlike the system used in the stomach. However, when assessed, a large number of involved nodes is usually,[1, 6, 14, 21, 35] although not always,[17] a significant factor. The ratio of involved to uninvolved nodes is also important.[12, 35] This reinforces the importance of documenting not only the number of involved nodes, but also the total numbers examined.

There is little information upon the significance of the location of involved lymph nodes, and few papers on features such as extracapsular invasion.[43] In the absence of more evidence, these features are not included in the dataset.

The search for involved lymph nodes has been refined in some sites by the use of immunohistochemistry and serial sections to detect 'micrometastases'. Some studies indicate this provides important prognostic information. Such techniques have demonstrated micrometastases in some patients identified as being node negative using conventional histology.[44–46] Some authors claim this is prognostically significant, [47–49] whilst other deny the significance.[44, 46, 50] Immunohistochemistry is not recommended in the routine search for lymph node metastases. Other techniques, such as rtPCR[51] are obviously beyond the scope of a dataset.

Some confusion has arisen over the classification of lymph nodes in the new (6th edition) version of TNM.[3] In this edition, a tumour nodule in the connective tissue is classified as a regional lymph node metastasis if it has the form and smooth contour of a lymph node. A tumour nodule with an irregular contour is classified in the pT category. Prior to this change, a tumour nodule was classified as a regional lymph node metastasis if it was larger than 3 mm in diameter, irrespective of its shape.

In a further departure from previous practice, very small deposits in lymph nodes are classified as 'isolated tumour cells'. These are defined as clusters of cells not more than 0.2 mm in greatest dimension. The classification indicates that such small deposits should be ignored for the purpose of counting lymph node metastases. The presence of isolated tumour cells as the only lymph node metastasis may be indicated as N0(i+) in TNM 6th edition.

Until these changes reach wide acceptance and are validated by some supporting evidence, it is proposed that the dataset should adhere to previous practice. Thus deposits greater than 3 mm in size and small deposits in lymph nodes identified on routine microscopy (irrespective of size) are counted as lymph node metastases. A separate area on the form is available as 'non core' data for those who wish to record TNM stage in the 6th edition format.

See appendix A for details of which lymph node metastases should be included in the N stage and which in the M stage.

Barrett's metaplasia

Some studies indicate a positive prognostic effect of the presence of Barrett's metaplasia in the adjacent oesophagus.[52] Whilst this may identify less advanced tumours, many of these patients may have been screened for Barrett's and documentation of its presence is useful for audit. It is included as a non-core data item.

Other markers

Many other markers of prognosis have been investigated, including ploidy[16, 23, 53], angiogenesis,[54] CD44[55] and EGFR.[56] Many show some prognostic significance, but without confirmatory evidence in larger studies the use of such special techniques is not justified in a core dataset.

Neoadjuvant treatment

Neoadjuvant treatment is increasingly being used in oesophageal carcinoma. Consequently, oesophageal resection specimens will increasingly show the effects of such treatment. Mucin lakes or collections of keratin are often taken to identify areas where tumour has been ablated by chemotherapy or radiotherapy. These structures will often contain no identifiable tumour cells (it may be necessary to confirm this by a cytokeratin immunohistochemical stain). For the purposes of this dataset, tumour is only assumed to be present in lymph nodes and resection margins when viable (i.e. non apoptotic) tumour cells are seen.[57] This approach is now supported by one small study of mucin lakes in post-treatment specimens.[58]

A number of schemes have been suggested for the classification of response to chemotherapy, [2, 59] but none has been universally accepted and these are most likely to be used in a research setting. A specimen in which no tumour is identified following neoadjuvant treatment is staged as ypT0N0.

8 DATASET FOR AN INITIAL BIOPSY DIAGNOSIS OF OESOPHAGEAL CARCINOMA

An initial biopsy report should identify the type of carcinoma: squamous cell or adenocarcinoma. The presence of overlying squamous cell dysplasia, glandular dysplasia or Barrett's metaplasia will also provide support for a primary oesophageal origin and so should also be included if present. The depth of invasion may also be useful information. Submucosal invasion (as opposed to intra-mucosal invasion only) is a prognostic indicator of nodal metastases.[17] This would be of little use in a resection specimen where the nodes are available for dissection and thus the TNM classification of depth of invasion (which does not differentiate between mucosal and submucosal invasion) is used for resection specimens. However, it may be helpful for the clinicians to know if submucosal invasion is identifiable in a biopsy specimen and thus the presence or absence of submucosal tissue, and its involvement should be included in biopsy reports.

There is evidence that some types of adenocarcinoma, such as mucinous or signet ring cell types (assessed in post-therapy and pre-treatment specimens),[60] may respond better to chemotherapy, but there is insufficient evidence to require subclassification of adenocarcinomas as a core data item.

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APPENDIX A TNM CLASSIFICATION OF MALIGNANT TUMOURS

PT Primary tumour

pTX Primary tumour cannot be assessed.
pT0 No evidence of primary tumour.
pTis Carcinoma *in situ*
pT1 Tumour invades lamina propria or submucosa
pT2 Tumour invades muscularis propria
pT3 Tumour invades adventitia
pT4 Tumour invades adjacent structures

pN Regional lymph nodes

pNX Regional lymph nodes cannot be assessed.
pN0 No regional lymph node metastasis
pN1 Regional lymph node metastasis

M Distant metastasis

MX Distant metastasis cannot be assessed.
M0 No distant metastasis.
M1 Distant metastasis

For tumours of lower thoracic oesophagus:
M1a Metastasis in coeliac lymph nodes
M1b Other distant metastasis

For tumours of upper thoracic oesophagus:
M1a Metastasis in cervical lymph nodes
M1b Other distant metastasis

For tumours of mid-thoracic oesophagus:
M1a Not applicable
M1b Non-regional lymph node or other distant metastasis

APPENDIX B SITES AND SUBSITES FOR DESCRIPTION AND THEIR ASSOCIATED SNOMED 'T' CODES

T-56000 Oesophagus

T-56010 Oesophageal mucosa

APPENDIX C COMMON SNOMED 'M' CODES USED IN OESOPHAGEAL NEOPLASIA

Note: This is not a comprehensive list of all malignancies and other codes should be used as necessary.

M-73000 Metaplasia

M-80413 Small cell carcinoma

M-80772 Squamous intraepithelial neoplasia grade 3

M-80703 Squamous carcinoma

M-80833 Basaloid squamous cell carcinoma

M-80743 Spindle cell squamous carcinoma

M-81482 Glandular intraepithelial neoplasia grade 3

M-81403 Adenocarcinoma

M-85603 Adenosquamous carcinoma

M-80203 Undifferentiated carcinoma

M-89361 Gastrointestinal stromal tumour

M-87203 Malignant melanoma

APPENDIX D

NATIONAL DATASET FOR

OESOPHAGEAL CARCINOMA HISTOPATHOLOGY REPORTS

Surname ..... Forenames ..... Date of birth .....

Hospital ..... Hospital no ..... NHS no .....

Date of receipt ..... Date of reporting ..... Report no .....

Pathologist ..... Surgeon ..... Sex .....

Shaded data items = 'non core' data

GROSS DESCRIPTION

Maximum length of specimen: ..... mm
Length of oesophagus: ..... mm
Length of stomach:..... mm
Length of tumour..... mm
Width of tumour: ..... mm

Tumour edge to nearest distal margin: ..... mm
Tumour edge to nearest proximal margin: ..... mm
Type of tumour ☐ Polypoid ☐ Other ☐ Pinned ☐ Not pinned
Siewert tumour type (cardiac cancers only) ☐ 1 ☐ 2

HISTOLOGY

Type of tumour

☐ Squamous ☐ Adenocarcinoma
☐ Other (specify) .....
Differentiation by worst area:
☐ Well ☐ Moderately ☐ Poorly differentiated

Depth of invasion

☐ Tis high-grade dysplasia
☐ T1 invasion of lamina propria/submucosa
☐ T2 invasion of muscularis propria
☐ T3 invasion beyond muscularis propria
☐ T4 invasion of adjacent structures
☐ Yes ☐ No – serosal involvement:

Proximal margin

☐ Normal ☐ Dysplasia ☐ Carcinoma ☐ Barrett's

Distal margin

☐ Normal ☐ Dysplasia ☐ Carcinoma

Circumferential margin

Involvement (<1 mm): ☐ Yes ☐ No ☐ N/A
(If no: distance of carcinoma to nearest circumferential margin ..... mm)

Other features

Vascular invasion ☐ Yes ☐ No
Barrett's metaplasia adjacent to tumour ☐ Yes ☐ No

Lymph nodes

Number examined…..……. Number positive…….
(N0 if no nodes positive, otherwise N1)

Distant metastases

Coeliac axis node positive ☐ Yes ☐ No
(M1a if lower thoracic carcinoma, otherwise M1b)
Cervical node positive ☐ Yes ☐ No
(M1a if upper thoracic carcinoma, otherwise M1b)
Other distant metastasis (M1b) ☐ Yes ☐ No

COMMENTS

PATHOLOGICAL STAGING

Complete resection ☐ Yes(R0) ☐ No(R1 or R2) (y) pT…… pN…… pM……. TNM 5th edition

(y) pT…… pN……(i +/-) pM……. TNM 6th edition

Signature …….. Date …../……/….. SNOMED codes T …….. / M ……