Histopathological reporting of resected carcinomas of the oesophagus and gastro-oesophageal junction

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Introduction

In 1999, the Institute of Medicine (IOM) published a report entitled 'To err is human' regarding medical error and its effects on patient's safety in the United States (1). The 287-page report stated that medical errors cause a large number of deaths in American hospitals and that physicians have been rather complacent about iatrogenic injury. The report also formulated measures to reduce future medical errors. The more recent IOM report singles out physicians 'irrational variation' as a major contributor to the 'quality chasm' (2). In 1991 The American Association of Directors of Anatomic and Surgical Pathology (ADASP) produced a list of recommended types of departmental audit (3). More recently the Association of Directors of Anatomic and Surgical Pathology has named several committees to develop recommendations regarding the content of the surgical pathology report for common malignant tumours. A committee of individuals with special interest and expertise wrote the recommendations, and they were reviewed and approved by the council of ADASP and subsequently by the entire membership. These recommendations have been broadly published as series in a number of journals of pathology such as Human Pathology, Virchows Archives, American Journal of Clinical Pathology and Modern Pathology. The overall concept of the recommendations had been divided into the following four major areas :

1. items that provide an informative gross description ;
2. additional diagnostic features that are recommended to be included in every report if possible ;
3. optional features that may be included in the final report ; and
4. a checklist.

The final purpose of these recommendations is to provide an informative report for the clinician. The recommendations, as published, for the reporting of oesophageal carcinomas will be discussed in detail (4-7).

Features to be included in the final report

The following data document the identity and source of the specimen and provide information useful for the pathologic evaluation and subsequent staging of the neoplasm. They are generally accepted as being of prognostic value, required for therapy and/or traditionally expected.

1. *Gross description – macroscopic examination*

1.1. Identifying features of the specimen : labelled with patient name, medical record number, source of specimen, etc.

1.2. How the specimen was received : fresh, in fixative (specify type), unopened, opened, etc., and how designated.

> *It should be noted that after resection the oesophagus undergoes **shrinkage**, which affects the upper margin more than the lower, with the tumour remaining relatively stable in length. Even if the oesophagus is immediately pinned and fixed it shrinks by more than 10%. If pinning and fixation are delayed the oesophagus shrinks by more than 50%, which may account for a discrepancy between surgeons' and pathologists' measurement (8).*
> *Resection specimen are ideally received fresh. They should be carefully examined, and the outer (circumferential) surface painted with Indian **ink** or other marking dye. This is important for the assessment of completeness of excision and measurement of distance of tumour from the circumferential resection margin. The specimen should then be opened longitudinally, pinned to a cork board, and fixed by immersion in a fixative (usually buffered 10% formalin or 10% formalin saline) for 48-72 hours to ensure adequate fixation and facilitate obtaining thin slices.*

1.3. Appropriate overall gross description, including nature of the specimen (segmental oesophagectomy, oesophagogastrectomy, etc.), measurements (including overall length of specimen, length of oesophagus, length of stomach), amount and nature of peri-oesophageal tissue included.

> ***Anatomical hallmarks :** The cervical oesophagus begins at the lower border of the cricoid cartilage and ends at the thoracic inlet (the suprasternal notch), approximately 18 cm from the upper incisor teeth. The intrathoracic oesophagus consists of three parts : the upper portion extends from the thoracic inlet to the level of the tracheal bifurcation, approximately 24 cm*

from the upper incisors, the midthoracic portion is situated between the tracheal bifurcation and the distal oesophagus just above the oesophago-gastric junction. The lower level of this portion is approximately 32 cm from the upper incisor teeth. The lower portion, approximately 8 cm in length, includes the intra-abdominal portion of the oesophagus and the oesophago-gastric junction. The latter is approximately 40 cm from the upper incisor teeth.

1.4. Description of opened specimen including neoplasm (gross appearance, measurements in three dimensions, etc.), and mucosal surface away from neoplasm (evidence of Barrett's oesophagus, other abnormalities), distance of neoplasm from proximal and distal margins.

*According to recommendations of the International Union against cancer (UICC) : If the lesion arises in the **gastro-oesophageal junction region** and involves both the oesophagus and stomach, it should be classified as an oesophageal carcinoma if the epicenter of the lesion is in the oesophagus, as a gastric carcinoma if the epicenter is in the stomach, and as a gastro-oesophageal junction primary if the epicenter coincides with the oesophagogastric junction. For this purpose, the gastro-oesophageal junction is defined as the junction between the tubular oesophagus and the saccular stomach. Furthermore, according to these advices a tumor situated on the gastro-oesophageal junction is likely to be of oesophageal origin when the neoplastic lesion is associated with a Barrett's oesophagus of the specialized or intestinal type (9). Alternatively extensive Barrett's oesophagus can make it difficult to identify the gastro-oesophageal junction. In these cases the junction is probably most easily identified by the highest extent of the peritoneal reflection on the serosal surface of the stomach (10).*
*The **macroscopic appearance** of the tumour has little contribution to the prognosis, with the exception of polypoid tumours (11).*

1.5. Description of any additional structures included (stomach, pericardium, etc.)

1.6. If margins are inked (proximal, distal, radial) (with different colours), provide code.

1.7. Paraffin block key (ideally at end rather than incorporated into narrative).

*In contrast to the publications of the Association of Directors of Anatomic and Surgical Pathology the Best Practice N° 155 of the ACP gives an extensive description of the prelevation of **representative blocks** from the tumour (12). Tumour should be adequately sampled ; this is important for the assessment of the various prognostic features. It is recommended that the whole tumour is serially sectioned with a sharp knife. First, the bulk of the tumour should be sectioned transversely, to allow assessment of the circumferential resection margin, then the proximal and distal extremities are sectioned longitudinally to allow demonstration of the transition between the tumour and adjacent non-neoplastic mucosa. Sections should be examined to assess maximum depth of infiltration. As a minimum, four blocks should be taken from the tumour, two to include maximum circumferential infiltration and two to include the transition. Sections should also be taken to include the proximal and distal section margins, the gastro-oesophageal junction and any abnormal background mucosa.*
*If no obvious tumour is seen on macroscopic examination of oesophagectomy specimens carried out following a diagnosis of high grade dysplasia or in situ carcinoma of the squamous type the demonstration of the lesion may be facilitated by the application of **Lugol's solution** to the oesophageal mucosa at a concentration of 1% for one or two minutes. Normal squamous epithelium stains dark brown while severe dysplasia/in situ carcinoma shows no colour change. In any case when no obvious tumour is seen at macroscopy representative blocks will be embedded, if these fail to show malignancy, further blocks should be taken.*

2. *Diagnostic information – i.e. microscopic examination*

The continuing objective of the UICC is to achieve consensus in the classification of anatomical extent of cancer. The TNM system is internationally widely accepted and will therefore be referred to.
*In oesophageal malignancy, the histopathology report should incorporate all data that are regarded as having prognostic significance. Residual disease at surgery (R2), depth of invasion of the primary tumour (pT), and lymph node status (pN) are the most important, independent prognostic indicators, while other histopathological variables such as tumour histological type, tumour grade, vascular invasion, and even status of microscopic resection margins, appear to lose their prognostic significance in **multivariate analysis** (13-26). However, it is recommended that detailed histopathological data should be recorded.*

2.1. Topography. The type of specimen should be specified : oesophagus, oesophagus and proximal stomach, etc.

2.2. Procedure. The type of surgical procedure should be stated : total or segmental oesophagectomy, oesophago-gastrectomy ; as well as how the procedure was carried out, if known (transhiatal or transthoracic).

2.3. Histologic type of neoplasm. Use of the World Health Organization (WHO) classification is recommended (27).

- Squamous cell carcinoma (including pseudosarcomatous)
- Adenocarcinoma
- Adenoid cystic carcinoma (basaloid squamous)
- Mucoepidermoid carcinoma
- Adenosquamous carcinoma
- Undifferentiated carcinoma
- Other

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 the lesions, in very early cancers it may be better to have an adenocarcinoma – they have less local recurrence and fewer new primary lesions (17,18). Irrespective of the prognostic implications it provides useful validation of the presurgical diagnosis which may be important in adjuvant therapy decisions.

2.4. Histologic grade of neoplasm. Use of the American Joint Committee on Cancer grading system is recommended.

- Grade cannot be assessed (GX)
- Well differentiated (G1)
- Moderately differentiated (G2)
- Poorly differentiated (G3)
- Undifferentiated (G4)

Opinion is divided upon the prognostic significance of tumour differentiation. Some studies have demonstrated significance in squamous carcinomas, adenocarcinomas or in both, however a large study failed to confirm these findings (14,15,17,19).
The ACP states that the grade should be recorded according to the ***predominant*** *area as well differentiated, moderately differentiated, or poorly differentiated (12). Degree of differentiation has also been included in the minimum data set of the Royal College of Pathologists (10).*

2.5. Extent of invasion of neoplasm in the oesophagus, utilizing TNM system.

- None (Tis) (although Tis refers to carcinoma-in-situ, the authors prefer the term high-grade dysplasia for this lesion)
- Limited to lamina propria (intramucosal carcinoma) (T1a)
- Into submucosa (T1b)
- Into muscularis propria (T2)
- Into adventitia (T3)
- Into adjacent structures (T4)

The original TNM classification also includes :TX – primary tumour cannot be assessed, ***T0*** *no evidence of primary tumour.*
In the publications of the Association of Directors of Anatomic and Surgical Pathology the distinction is made between tumours confined to the mucosa – ***T1a*** *– and those involving the submucosa –* ***T1b*** *–, a distinction that has been shown to be of considerable prognostic significance. Several studies have demonstrated that oesophageal tumours which are confined to the epithelial lining (in situ carcinomas) are always curable, and invasive tumours that are confined to the mucosa are nearly always curable. However, submucosal cancer has been shown to be a relatively advanced disease which is associated with a significant risk of vascular invasion and lymph node metastasis. Lymph node metastasis has been reported to occur in 30-50% of squamous tumours involving the submucosa, this figure is similar to that for advanced cancer (17). In view of these findings, it is recommended that if the term* ***'superficial carcinoma'*** *is to be used in histopathology reporting, it should be qualified by the depth of invasion. However, the distinction between mucosal and submucosal extension was not included in the Minimum data set of the Royal College of Pathology because of insufficient evidence (10). Neither has it been included in the latest edition of the TNM classification (13). Many distal oesophageal carcinomas will involve the proximal stomach. At this site 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 and for this reason it is included in the Minimum data set of the Royal College of Pathologists (10).*
In specimens resected ***following radiation or chemotherapy****, or both, a comment should be made about whether or not viable-appearing neoplastic tissue remains. If none is identifiable, a comment regarding the extent of the radiation/chemotherapy-induced injury should be made, i.e., its depth of extension into the oesophageal wall as an indication of the probable depth of invasion of the neoplasm.*

2.6. Mucosal abnormalities away from carcinoma.

- Squamous epithelial dysplasia
- Presence of Barrett's metaplastic epithelium
- Dysplasia in Barrett's metaplastic epithelium
- Other.

2.7. Surgical margins.

- Status of proximal and distal surgical margins.
- Status of radial (adventitial) margin.
- If Barret's oesophagus, nature of the mucosa at proximal margin (squamous vs. Barrett's ; if Barrett's comment on presence or absence of dysplasia).
- If distal margin is stomach, comment on any gastric abnormalities (Helicobacter pylori gastritis, etc.)

Carcinoma involving the circumferential, proximal, or distal resection margins and clearance ***(in mm)***

should be documented. The status of resection margins has been shown in univariate analysis to be an important prognostic factor (1,20-22). Presence of carcinoma at less than 1 or 2 mm, depending on the authors, from the circumferential margin is considered to be the criterion for margin involvement (22,23). This feature has been included with a margin of 1 mm in the Minimum data set of the Royal College (10).

2.8. Lymph nodes : report total number of nodes/number containing metastatic carcinoma.

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

***Regional lymph nodes** : For an adequate staging of pN a mediastinal lymphadenectomy specimen should include **6** or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, the lymph nodes should be classified as pN0 according to the latest edition of the TNM classification (13). In contrast the previous edition indicated that pNX should be used (28). The working party for gastrointestinal cancer favours the use of pNX from point of view of quality. The respective regional lymph nodes are : Cervical oesophagus : scalene, internal jugular, upper cervical, peri-oesophageal, supraclavicular, cervical NOS for the intrathoracic oesophagus : tracheo-bronchial, superior mediastinal, peritracheal, carinal, hilar (pulmonar roots), peri-oesophageal, perigastric, paracardial, mediastinal NOS. Involvement of more distant nodes (e.g. cervical or celiac axis nodes) is considered distant metastasis for intrathoracic lesions. The **site** of regional lymph node involved by tumour may be useful to document, though there is evidence to suggest that this may not be of prognostic significance (17). In daily practise, it is however wise to embed lymph nodes retrieved along the oesophagus and the stomach in separate blocks, since depending on the primary site of the tumour involvement may be considered as regional lymph node metastasis or distant metastasis. In oesophageal cancer there is no evidence to perform **additional** techniques to investigate lymph node status as serial sectioning or immunohistochemical stains with antibodies directed against cytokeratins. Only one study has identified micrometastases in the lymph nodes around the oesophagus using Ber-EP4 (24). The authors found that this finding worsened prognosis in patients who were conventionally node negative. **Extracapsular extension** or infiltration of perinodal fibrofatty tissue by tumour has been suggested to be an important prognostic factor in patients with curative resection (25).*

2.9. Distant metastasis

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

Further specification of the presence of distant metastasis (M1a and M1b) depends on the localisation of the primary tumour in the oesophagus.

- 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.

3. *Other histological variables not included in the recommendations of the Association of Directors of Anatomic Surgical Pathology :*

3.1. ***Vascular invasion** is an effective prognostic marker. Different studies showed a significant effect on univariate analysis (15,17,19,26,29). In one study it appeared to be an independent prognostic factor as depth of invasion on multivariate analysis. There are no separate data comparing intra- and extramural vascular invasion in oesophageal cancer. Vascular invasion was also included in the Minimum data set and the ACP guidelines (10).*

3.2. *There is little evidence for **perineural invasion** as a prognostic indicator (15).*

3.3. ***Other histological variables** that may be recorded but appear to be of little independent prognostic significance include : pattern of advancing margin (pushing or infiltrating), lymphocytic reaction, and intramural metastasis (30).*

3.4. *Other **markers of prognosis** have been investigated, including ploidy, angiogenesis, CD44 and EGFR (16,19,31-34). Many show some prognostic significance but without confirmatory evidence in larger studies the use of these special techniques is not advocated in routine. Overall, genetic abnormalities, flow cytometric analysis and growth factors and receptors have thus not gained acceptance.*

3.5. *As TNM is the most widely used prognostic indicator, it is recommended by the ACP that the histopathology report should include a conclusion that incorporates the **pTNM staging system**. Additionally, the use of a proforma for uniformity in reporting, which is important for accurate comparison of results of treatments at different centres, is also recommended.*

4. *Checklist*

The original ADASP publication includes a diagnostic checklist recapitulating all items described above. The ACP guidelines recommend the use of a proforma for uniformity in reporting, which is important for accurate comparison of results of treatments at different centres. (12) The checklist in addendum has been adapted according to the comments formulated in this article. It has been designed for histopathological reporting of resected carcinomas of the oesophagus and gastro-oesophageal junction (cfr. Comment 1.4.).

Conclusions

The purpose of the recommendations of the ADASP is to provide an informative report for the clinician. The authors indicate that the recommendations are intended as suggestions and adherence to them is completely voluntary. Furthermore, the recommendations are intended as an educational resource rather than a mandate. Based on other guidelines as those formulated by the Royal College of Pathologists and the ACP on the one hand and the evolving literature data on the other hand it is obvious that some discussion will remain.

Acknowledgement

The Belgian Club for Digestive Pathology mandated a working party for GI cancer in order to prepare National guidelines for pathological examination and reporting of GI cancer. Working party : Bogers J.P. (UIAntwerpen), Cuvelier C. (UZGent), Demetter P. (UZGent), Ectors N. (UZLeuven), Geboes K. (UZLeuven), Jouret A. (CHR Tournai), Nagy N. (ULB Erasme), Sempoux C. (UCLouvain).

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Checklist - pathological report
operation specimen for carcinoma of the oesophagus and gastro-oesophageal junction

Patient's name :	Pathologist :
Date of birth :	Hospital/Laboratory :
Medical record number :	Specimen number :
Pre-operative treatment :	Date of reception :

Type of intervention

Laryngo-oesophagectomy :	Oesophagectomy :	Oesophago-gastrectomy :

Macroscopic examination

Received	fresh	fixed	opened	closed
Tumour localisation	upper thoracic oesophagus		mid-thoracic oesophagus	
	lower thoracic oesophagus		gastro-oesophageal junction	
Gross appearance	protruding	ulcerating	infiltrating	flat
Tumour perforation ?		Barrett oesophagus ?		
Other structures ?		Associated lesions ?		
Length of specimen	overall	oesophagus	stomach	
Tumour distance	from proximal section margin	from gastro-oesophageal junction	from distal section margin	
Tumour dimensions	length	width	thickness	

Microscopic examination

Histologic type	adenocarcinoma	squamous cell carcinoma	other	
Histologic grade	well (G1)	moderate (G2)	poor (G3)	undifferentiated(G4)
Depth of invasion	Primary tumour cannot be assessed			TX
	No evidence of primary tumour			T0
	Carcinoma in situ (high grade dysplasia) (intraepithelial carcinoma)			Tis
	Limited to lamina propria (intramucosal carcinoma)			T1a
	Into submucosa			T1b
	Into muscularis propria			T2
	Into adventitia			T3
	Into adjacent structures			T4
Section margin	proximal	free	involved	
	distal	free	involved	
	Radial, circumferential (lateral)	Distance in mm :		
Regional lymph nodes	number examined	number invaded		
Distant metastasis	lymph node	other		

pTNM staging

TX	T0	Tis	T1a	T1b	T2	T3	T4
NX	N0	N1	MX	M1			