yorkshire cancer research

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TNM8 and RCPath 2017: Updates and controversies

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TNM staging

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UICC editions:

- *UICC TNM pocket book, "the Livre de Poche* (1st ed.). 1968.
- *UICC TNM pocket book, "the Livre de Poche* (2nd ed.). 1974.
- *UICC TNM Classification* (3rd ed.). 1982.
- *UICC TNM Classification* (4th ed.). 1987.
- *UICC TNM Classification* (5th ed.). 1997.
- *UICC TNM Classification* (6th ed.). 2002. Went into effect 2003.
- *UICC TNM Classification* (7th ed.). 2009. Went into effect 2010.
- *UICC TNM Classification* (8th ed.). 2016. Went into effect 2017.

AJCC editions:

- *AJCC Cancer Staging Manual* (1st ed.). 1977. Went into effect 1978.
- *AJCC Cancer Staging Manual* (2nd ed.). 1983. ISBN 0397505949. Went into effect 1984.
- *AJCC Cancer Staging Manual* (3rd ed.). 1988. ISBN 0397509162. Went into effect 1989.
- *AJCC Cancer Staging Manual* (4th ed.). 1992. ISBN 0397512643. Went into effect 1993.
- *AJCC Cancer Staging Manual* (5th ed.). 1997. ISBN 0397584148. Went into effect 1998.
- *AJCC Cancer Staging Manual* (6th ed.). 2002. ISBN 0387952713. Went into effect 2003.
- *AJCC Cancer Staging Manual* (7th ed.). 2009. ISBN 0387884408. Went into effect 2010.
- *AJCC Cancer Staging Manual* (8th ed.). 2016. ISBN 3319406175. Delayed to go into effect 2018.

Short on detail

The Royal College of Pathologists
Pathology: the science behind the cure

Inclusive of the small number of differences
UICC but consistent with AJCC
Sometime changes in advance where UK practice sets the standards
Consistent with other UK guidelines e.g. NHS BCSP

Lots of detail

4th RCPath dataset

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The Royal College of Pathologists
Pathology: the science behind the cure

Draft Oct 2017
Live Dec 2017

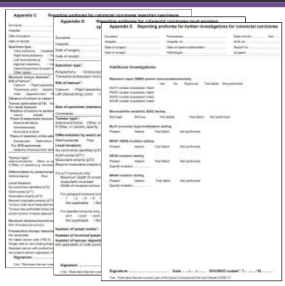
Standards and datasets for reporting cancers

Dataset for histopathological reporting of colorectal cancer

December 2017

Authors: Dr Maurice B Loughrey, Royal Victoria Hospital, Belfast H&SC Trust and Queen's University Belfast, UK
Professor Philip Quirke, Leeds Teaching Hospitals NHS Trust and Leeds University, UK
Professor Neil A Shepherd, Gloucestershire Cellular Pathology Laboratory, Cheltenham, UK

Unique document number	G049
Document name	Dataset for histopathological reporting of colorectal cancer
Version number	4
Produced by	Dr Maurice B Loughrey, Professor Philip Quirke and Professor Neil A Shepherd, on behalf of the College's Cancer Services Working Group. All three authors are senior gastrointestinal pathologists, co-authors of multiple guidelines relating to gastrointestinal diseases and leads in the UK bowel cancer screening programmes.
Date active	October 2017 (to be implemented from 1 January 2018)
Date for review	October 2020
Comments	This edition will replace the 3rd edition of the Dataset for Colorectal Cancer Histopathology Reports, published in 2014. The recommendations of TNM 8 (UICC) are followed in this revision. In accordance with the College's pre-publications policy, this document was on The Royal College of Pathologists' website for consultation from 12 October to 9 November 2017. Responses and authors' comments will be available to view on request. Dr Lorna Williamson Director of Publishing and Engagement



4th RCPath dataset – version 2

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The Royal College of Pathologists
Pathology: the science behind the cure

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December 2017

The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for histopathological reporting of colorectal cancer

September 2018

Revised so that tumour deposits will be recorded in all cases

Summary of changes

- Sample at least five blocks from the tumour (not listed at the front!)
- TNM8 has been adopted with refinements to pT, pN and pM
- Dukes' staging dropped as it is not compatible with TNM 8 (however apical node involvement still included)
- Tumour deposits now included moving "8%" from stage II to III
  - Record precise number up to five, or >5 (stage pN1c if no involved nodes in TNM 8)
- Modified tumour regression grading description and score

Summary of changes

- Independent reporting of lymphatic (L1), venous (V1/2) and perineural (Pn1) invasion
  - Also identification of deepest level of invasion of these modes of spread (i.e. intramural vs. extramural)
- Simplification of separate abnormalities
- Local excision changes are minor and reflect the changes made to the resections
  - Separate lymphatic, venous and perineural invasion
  - New tumour regression grading system
- NICE recommendation on Lynch screening / dMMR

Why is the UK now moving from TNM5 to TNM8?

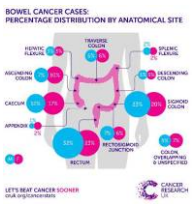
- The evidence base for tumour deposits is now robust
- Definition of tumour deposits has been improved (but still too loose!)
- Other changes are logical and mainly evidence based
- Need to create international consistency
- We have avoided two changes of TNM6 and TNM7 leading to more consistency of UK data and less stage migration
- Single changeover date for staging and screening – 01/01/2018
- If ongoing trials require TNM5, then both should be reported (but TNM8 should be going into COSD)

Site of tumour

TNM8 and RCPath

Site of tumour[1]:

Caecum / Right (ascending) colon / Hepatic flexure
Transverse colon / Splenic flexure / Left (descending) colon / Sigmoid colon / Rectum / Unknown



The staging system for appendiceal tumours described under TNM 8 should be used, as should the forthcoming Royal College of Pathologists dataset for reporting appendiceal tumours.[22]

Quality of specimen

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TNM8 (AJCC)

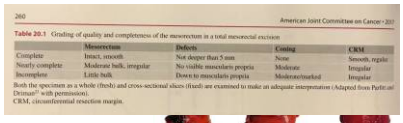
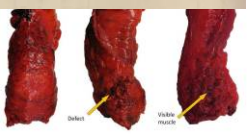


Table 20.1 Grading of quality and completeness of the mesorectum in a total mesorectal excision

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate/marked	Irregular

Both the specimen as a whole (fresh) and cross-sectional slices (fixed) are examined to make an adequate interpretation (Adapted from Parfitt et al. Dvirnas[33] with permission).
CRM, circumferential resection margin.



RCPath

Mesorectal
Intramesorectal
Muscularis propria

RCPath APE's

Extralevator
Sphincteric
Intrasphincteric

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Mesocolic
Intramesocolic
Muscularis propria

Differentiation grade

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TNM8

G	G definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

RCPath

G	G definition
GX	Grade cannot be assessed
G1/G2	Well/moderate
G3	Poorly differentiated

TNM 8 and the American Joint Committee on Cancer (AJCC) currently recommend the use of four grades; however, we believe that the use of two grades, poor and well/moderate, enhances agreement and quality control.[22,56]

The previous recommendation to test all colorectal cancers demonstrating features of mucinous carcinoma, or poorly differentiated adenocarcinoma, for MSI or MMR status, is now subsumed by the recommendation to test all colorectal cancers.[52]

pT staging and perforations

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TNM8

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ: invasion of lamina propria[a]
T1 Tumour invades submucosa
T2 Tumour invades muscularis propria
T3 Tumour invades subserosa or into non-peritonealized pericolic or perirectal tissues
T4 Tumour directly invades other organs or structures[b,c,d] and/or perforates visceral peritoneum
T4a Tumour perforates visceral peritoneum
T4b Tumour directly invades other organs or structures

Perforations:
Only occur through the peritoneal surface

RCPath

Do not use adenocarcinoma in situ!

Localised perforation through the tumour onto CRM (e.g. in the low rectum) is also recommended to be staged as pT4a (TNM 8 system).

Tumour cells have breached the serosa (pT4a)
Tumour has perforated below peritoneal reflection (pT4a) and/or tumour invades adjacent organs (pT4b)

Response to therapy

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TNM8 and RCPath

Description	Tumour regression score	
No viable cancer cells (complete response)	0	OK
Single cells or rare small groups of cancer cells (near-complete response)	1	OK
Residual cancer with evident tumour regression, but with more than single cells or rare small groups of cancer cells (partial response)	2	What does this mean?
Extensive residual cancer with no evidence tumour regression (poor or no response)	3	What does this mean?

PRACTICAL SUGGESTION:
Use the Mandard /Dworak criteria to distinguish TRS2 & TRS 3
TRS2 = fibrosis>tumour
TRS3 = tumour>fibrosis

Don't report Mandard/Dworak

Complete pathological response

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RCPath

Five blocks from tumour site
If no tumour, embed the whole area
Still no tumour, cut three levels
No further work
No tumour = complete response

PRACTICAL SUGGESTION:
Do not use the terms "complete response" or "complete pathological response" except for ypT0 ypN0
ypT0 ypNx = TRS0
ypT0 ypN0 = TRS0 and pCR

Although tumour regression grade is based on evaluation of the primary tumour site, it is worthwhile adding a descriptive comment on any such features evident in regional lymph nodes, or at any other potential metastatic sites. Cases with complete regression are recorded as ypT0 ypN0 (e.g. cases with complete regression of the primary tumour but viable tumour epithelium in one lymph node are recorded as ypT0 ypN1a).

Seen in ~7% of pCR

pN staging

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TNM8 and RCPath

NX Regional lymph nodes cannot be assessed
No No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N1a Metastasis in 1 regional lymph node
N1b Metastasis in 2 to 3 regional lymph nodes
N1c Tumour deposit(s), i.e. satellites,* in the subserosa, or in non-peritonealized pericolic or perirectal soft tissue *without* regional lymph node metastasis
N2 Metastasis in 4 or more regional lymph nodes
N2a Metastasis in 4–6 regional lymph nodes
N2b Metastasis in 7 or more regional lymph nodes

Micrometastases and Isolated Tumour Cells

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TNM

- Contradictory reports in the literature due to variable definition (clusters of 10-20 cells or ≥ 0.2 mm diameter)
- Recent meta-analysis showed > 0.2 mm is a significant poor prognostic factor
- Should be considered involved (rather than pN1mi)

RCPath

- Deposits ≥ 0.2 mm are considered involved
- Deposits < 0.2 mm are negative
- May need multiple serial sections
- If not all node submitted, should revisit specimen

PRACTICAL SUGGESTION:
Cut three deeper levels on all ITCs (< 0.2 mm) and embed remaining nodal tissue if applicable – but only if this makes a difference to staging

What is a lymph node?

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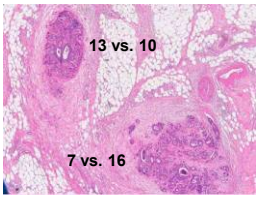
Major controversy and the major reason we did not change from TNM5

TNM version	Definition of a lymph node
TNM 4	None
TNM 5	3 mm deposit without nodal structure
TNM 6	Round deposit (irregular = venous invasion)
TNM 7	Pathologist discretion
TNM 8	Rule out venous, lymphatic, perineural first



Variability in assessing 'round' vs. 'irregular' 23 pathologists Williams, Cardiff, UK

Tumour deposits

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Tumor Deposits in Colorectal Cancer: Improving the Value of Modern Staging—A Systematic Review and Meta-Analysis

Iris D. Nagtegaal, Nikki Knijn, Nick Hugen, Helen C. Marshall, Kenichi Sugihara, Tibor Tot, Hideki Ueno, and Philip Quirke

J Clin Oncol. 2017; 35: 1119-1127

- Meta-analysis of 17 studies (10,106 patients)
- Present in 22% (8.7% pN0 = now pN1c)
- Increasing number of TD's worse prognosis
- DFS (n=1,200) HR 2.0 and OS (n=1,536) HR 2.2

Factor	Liver metastases Adjusted OR (95%CI)*	Lung metastases Adjusted OR (95%CI)*	Peritoneal metastases Adjusted OR (95%CI)*
N0/TD-	1.00	1.00	1.00
N0/TD+	3.57 (2.38-5.35)	2.86 (1.71-4.78)	6.44 (3.04-13.65)
N+/TD-	2.60 (1.96-3.44)	2.49 (1.81-3.44)	3.21 (1.75-5.90)
N+/TD+	5.54 (4.23-7.25)	4.29 (3.11-5.93)	6.97 (3.96-12.25)
EMVI	1.38 (1.08-1.77)	2.01 (1.48-2.72)	1.25 (0.76-2.05)

Tumour deposits have additional significance to involved lymph nodes

Definition of tumour deposits

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- Discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma
- Discontinuous from the primary
- Without histological evidence of residual lymph node or identifiable vascular or neural structures
  - Venous invasion (V1/V2)
  - Lymphatic invasion (L1)
  - Perineural invasion (Pn1)
- Does not change the pT category but changes the node status to pN1c if all regional lymph nodes are negative on pathological examination

Definition of tumour deposits

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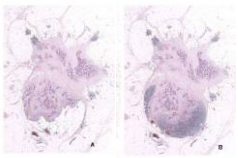
- Assessment is difficult in practice
- Need to be suspicious of the origin

PRACTICAL SUGESTION:
Consider doing deeper levels on TDs although this may not be helpful and has additional cost



Number of tumour deposits: 0☐1☐ 2☐ 3☐ 4☐ 5☐ >5☐

~~Not applicable (if node positive) ☐~~

Tumour deposits post treatment

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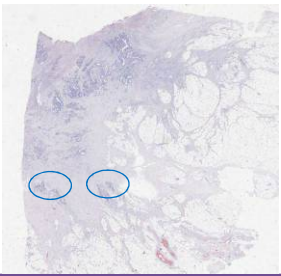
- Very difficult!
- Need to determine whether TDs (ypN) or discontinuous primary tumour (ypT)

PRACTICAL SUGGESTION:
Don't report TDs in the primary tumour area after treatment. Only report TDs which are clearly separate to the primary tumour (normal fat in between, not fibrosis)



Lymphatic, venous and perineural invasion

UICC

L – Lymphatic invasion
- LX Lymphatic invasion cannot be assessed
- L0 No lymphatic invasion
- L1 Lymphatic invasion

V – Venous invasion
- VX Venous invasion cannot be assessed
- V0 No venous invasion
- V1 Microscopic venous invasion
- V2 Macroscopic venous invasion

Pn – Perineural invasion
- PnX Perineural invasion cannot be assessed
- Pn0 No perineural invasion
- Pn1 Perineural invasion

AJCC

If the vessel wall or its remnant is identifiable on H&E, Elastin, or any other stain, the lesion should be classified as lymphovascular invasion (LVI) present.

Further documentation should subclassify LVI as small vessel invasion ("L" positive for either lymphatic or small venule involvement) or venous invasion ("V" positive for tumour within an endothelial lined space that contains red cells or is surrounded by smooth muscle [adapted from the RCPath Colorectal Cancer Dataset 2014].

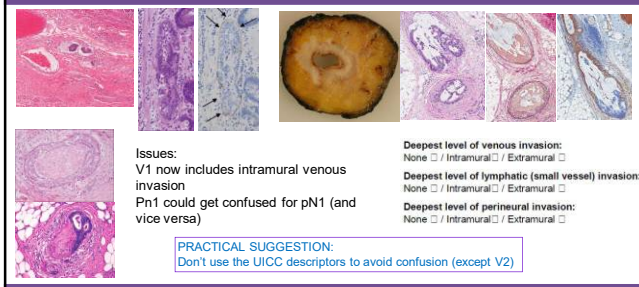
These definitions are similar to those for large vessel invasion on page 122 of the AJCC 6th edition.

If neural structures are identifiable, the lesion should be classified as perineural invasion.

RCPath

State whether lymphatic, venous or perineural invasion is present and if so whether deepest extent is intramural or extramural

Lymphatic, venous and perineural invasion



Issues:
V1 now includes intramural venous invasion
Pn1 could get confused for pN1 (and vice versa)

Deepest level of venous invasion:
None ☐ / Intramural ☐ / Extramural ☐

Deepest level of lymphatic (small vessel) invasion:
None ☐ / Intramural ☐ / Extramural ☐

Deepest level of perineural invasion:
None ☐ / Intramural ☐ / Extramural ☐

PRACTICAL SUGGESTION:
Don't use the UICC descriptors to avoid confusion (except V2)

M staging

TNM

M1a Metastasis confined to one organ (liver, lung, ovary, non.regional lymph node(s)) without peritoneal metastases

M1b Metastasis in more than one organ

M1c Metastasis to the peritoneum with or without other organ involvement

RCPath

Note, pathologists can only base assessment of distant metastatic disease on submitted specimens and therefore should not use the terms 'pM0' or 'pMX'.

Overall stage

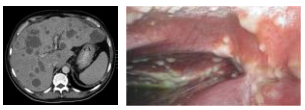
TNM

Stage 0	Tis	No	Mo
Stage I	T1, T2	No	Mo
Stage II	T3, T4	No	Mo
Stage IIA	T3	No	Mo
Stage IIB	T4a	No	Mo
Stage IIC	T4b	No	Mo
Stage III	Any T	N1, N2	Mo
Stage IIIA	T1, T2	N1	Mo
	T1	N2a	Mo
Stage IIIB	T1, T2	N2b	Mo
	T2, T3	N2a	Mo
	T3, T4a	N1	Mo
Stage IIIC	T3, T4a	N2b	Mo
	T4a	N2a	Mo
	T4b	N1, N2	Mo
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

RCPath

Not included in the dataset

Need to be careful if issuing as pathologists may not know the cM stage

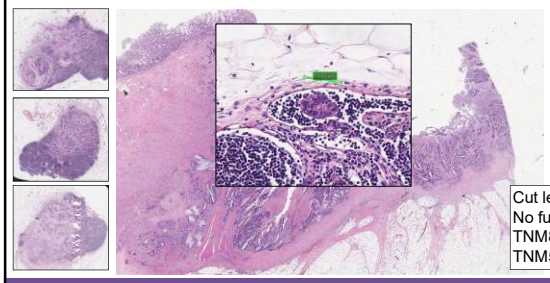


PRACTICAL SUGGESTION:
Issue the individual pT and pN (and pM if applicable) stages but not a combined TNM stage
Combined TNM staging should be performed by the MDT

Additional investigations

RCPath

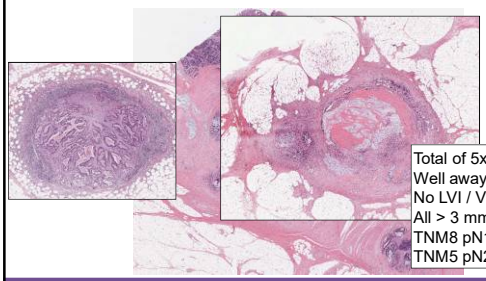
Case 1: ascending colon cancer



pT3
pN1 (3/29)

Cut levels x3
No further tumour
TNM8 pN1 (3/29)
TNM5 pN2 (4/29)

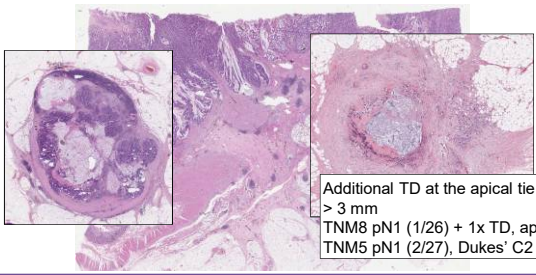
Case 2: Mid rectal cancer (post CRT)



ypT2
ypN1 (1/16)

Total of 5x TDs
Well away from primary tumour
No LVI / VI / PNI
All > 3 mm
TNM8 pN1 (1/16) + 5x TD's
TNM5 pN2 (6/21)

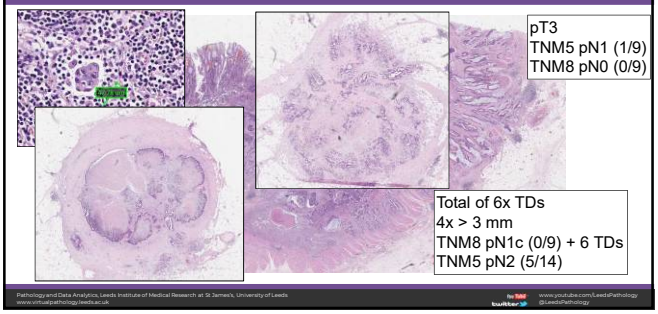
Case 3: Transverse colon cancer



pT3
pN1 (1/26)
EMVI

Additional TD at the apical tie
> 3 mm
TNM8 pN1 (1/26) + 1x TD, apical node -ve
TNM5 pN1 (2/27), Dukes' C2

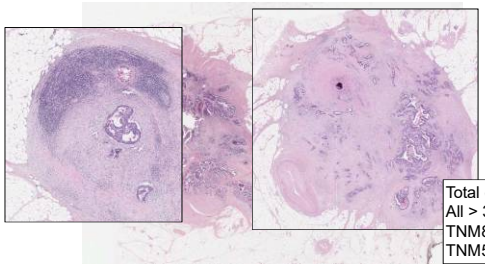
Case 4: Mid rectal tumour



pT3
TNM5 pN1 (1/9)
TNM8 pN0 (0/9)

Total of 6x TDs
4x > 3 mm
TNM8 pN1c (0/9) + 6 TDs
TNM5 pN2 (5/14)

Case 5: Upper rectal cancer (post CRT)



ypT3
ypN1 (1/21)

Total of 3x TDs
All > 3 mm
TNM8 pN1 (1/21) + 3 TDs
TNM5 pN2 (4/24)

Summary

- TNM8 started 01/01/2018
- New RCPath dataset approved Dec 2017 (updated Sep 2018)
- Compatible with NHS BCSP new guidance
- UICC based but compatible with AJCC
- RCPath guidance diverges on some things as previously
- Lymph node yields likely to go down!

Acknowledgements

Phil Quirke

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