The reporting of colorectal cancer pathology: recent advances

Professor Neil A Shepherd
President, British Division of the IAP

IAP-AD, Beirut, Lebanon
1 December 2011

Colorectal cancer resection specimens

- their accurate reporting is one of the mainstays of the workload of both general & GI pathologists
- however, audits performed around the world have demonstrated that such reporting has been less than exemplary
- there have been important new developments

What we will talk about:

- everyday practical ways of improving the quality of CRC resection reporting
- pathology influencing surgical quality
- a bit on TNM 7 (if only to damn it) (and 6 for that matter)
- a bit on 'new' parameters & data – especially budding & the effects of neo-adjuvant therapy

What we will talk about:

- everyday practical ways of improving the quality of CRC resection reporting
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- a bit of new parameters & data – especially budding & the effects of neo-adjuvant therapy

Gloucestershire Cellular Pathology Laboratory

Pathological staging is the most important determinant of the decision to institute adjuvant therapy in colorectal cancer

Gloucestershire Cellular Pathology Laboratory

Dr Cuthbert E Dukes
Consultant Pathologist
St Mark's Hospital
London
(1924-1956)

616. 351—006. 46

THE CLASSIFICATION OF CANCER OF THE RECTUM.

Dukes, 1932; Dukes & Bussey, 1958

The adenoma-carcinoma sequence

Basil C Morson

H J R 'Dick' Bussey

Morson & Bussey, 1972

The Bill and Phil Show: the importance of exemplary surgery, pathological quality and margin assessment

Heald RJ et al, 1982 & 1986

Quirke P et al, 1986, etc

So with that background, pathological reporting of colorectal cancer in the UK should have been really good, eh?

NO

Quality of pathological reporting a decade (or so) ago

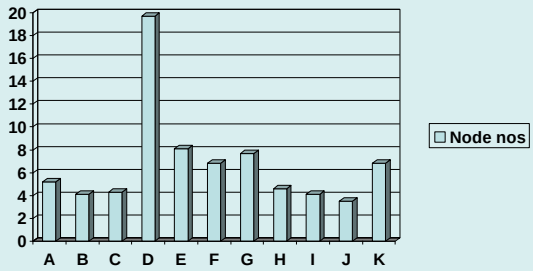
The Welsh audit

- only 51.5% of rectal cancer reports contained a statement on the completeness of excision at CRM
- only 30% of all reports stated the number of involved lymph nodes
- 6% of reports contained all 'minimum' data

- inadequate for quality patient management
- recommend template proforma reporting using nationally agreed standards
- improved education
- review of laboratory practices
- further motivation of pathologists through involvement in MDTMs

Bull AD, Biffin AH, Mella J, Radcliffe AG, Stamatakis J, Steele RJ, Williams GT. J Clin Pathol 1997; 50: 138-42.

South West Audit, 1995-6: mean lymph node harvests by hospital (A-K)



Pheby et al, 2004

Lymph node harvests in a regional audit, 1995-1996

	Hospital D	Others
Case number	628	917
Mean LN harvest	18.8	6.4
Mean number of positive LNs	2.5	1.2
% Dukes C	50.2%*	42.3%*

Most informative lymph node harvest range = 10-15 * p<0.001

Pheby et al, 2004

Colorectal cancer reporting proforma, 1997

RCPath Colorectal Cancer Minimum Dataset, 2nd revision (2007)
G T Williams, P Quirke, N A Shepherd

It is therefore recommended that pathologists audit their reports at regular intervals (perhaps yearly) to ensure that their overall results are not significantly different from what might expected. Three standards are recommended for this purpose, namely that in a series of at least 50 resection specimens:

a) *the median number of lymph nodes examined is 12*
b) *the frequency of serosal involvement is at least 20% for colonic cancers and 10% for rectal cancers*
c) *the frequency of extramural vascular invasion is at least 25%*

We believe there is a reasonable evidence base to suggest that the mean harvest of lymph nodes should be at least 12 but accept that there is less evidence base for the two other outcome measures. Nevertheless, we believe that this is a start at setting such standards and evidence will follow to allow us to adjust these levels in the future.

LYMPH NODE HARVESTS

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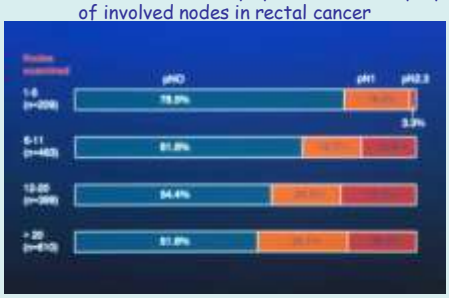
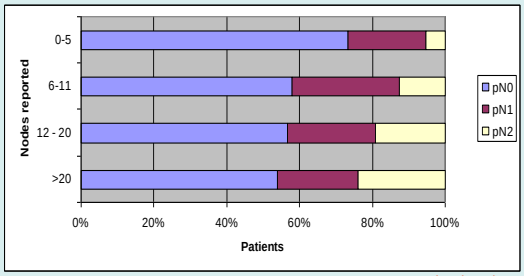
The influence of the number of lymph nodes on the proportion of involved nodes in rectal cancer



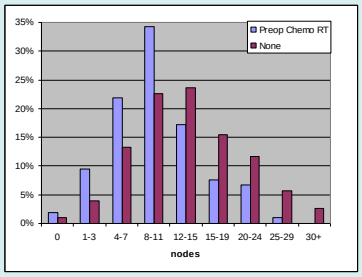
Hermanek et al, 1993

Influence of number of nodes on pN status: South & West Colorectal Cancer LN Audit



Weekes & Shepherd, 2007

Influence of adjuvant therapy on rectal LN harvest



Weekes & Shepherd, 2007

Lymph node harvests reflect the overall quality of pathology

lymph node harvest	CRM positive	extramural vascular spread	peritoneal involvement
0 - 6	14%	17%	6%
6 - 12	19%	21%	6%
> 12	23%	29%	10%

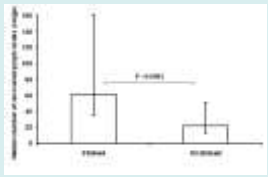
Yorkshire CRC audit data, 2008: thanks to Phil Quirke

What can we do to improve?

- time and motivation of pathologists and/or dissecting BMSs
- methods to improve identification of nodes:

  fat clearance
  tattooing
  intra-arterial injection

Postoperative intra-arterial methylene blue injection of colorectal cancer specimens increases the number of lymph nodes recovered



Tornroos et al, 2011

Gloucestershire BCSP QA visit, October 2010: Colorectal cancer quality standards

Parameter	median lymph node harvest	PI colon	PI rectum	EMVS
Quality standard	12 or more	> 20%	> 10%	> 25%
Pathologist A	24	36%	14%	51%
Pathologist B	19	49%	8.3%	42%
Pathologist C	19	33%	27%	48%

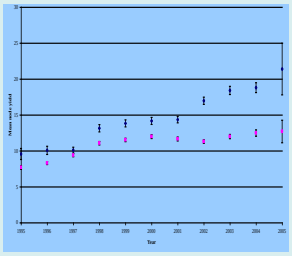
Subspecialisation in pathology

Lymph node harvests (200 cases) in Gloucestershire:

pre-subspecialisation	15.62
post-subspecialisation	21.58

$p < 0.001$

Subspecialisation in pathology



Lymph node yield over time
pink general pathologist v blue MDT pathologist

Yorkshire data:
Thanks to Phil Quirke

PERITONEAL INVOLVEMENT

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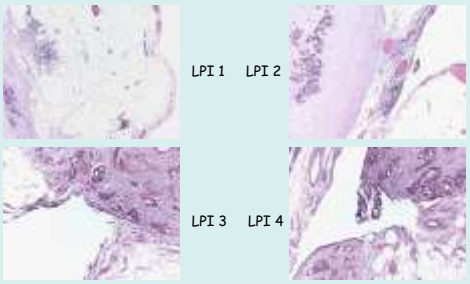
Classification of peritoneal involvement: the Shepherd classification



Shepherd et al, 1995; Shepherd et al, 1997; Petersen et al, 2002; Mitchard et al, 2011

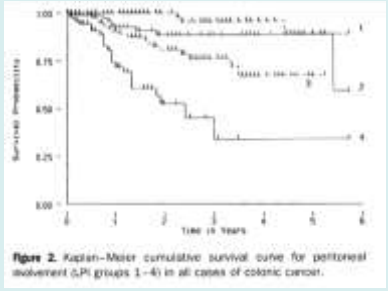
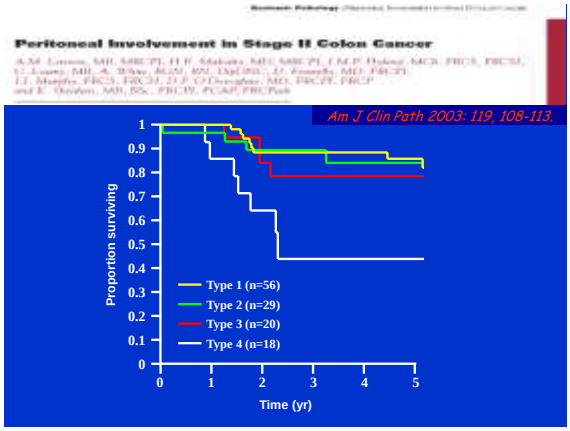


Figure 2. Kaplan–Meier cumulative survival curve for peritoneal involvement (LPI groups 1–4) in all cases of colonic cancer.

Shepherd et al, 1997



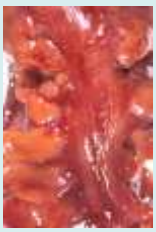
Macroscopic assessment of peritoneal involvement in colorectal cancer

- where does it occur?

  unusual on flat surfaces: much more likely in fat-lined crevices

- how to assess it?

  at least two blocks of most likely areas may need levels



To paint or not to paint?

There remains considerable contention about the practice of painting surgical specimens in the GI tract. Indeed we believe that there has been an unfortunate explosion in this practice such that barely a specimen can escape the dissection room without being covered in paints of various colours, often to the detriment of accurate macroscopic pathological assessment. No more so is this apparent, in our view, than in GI cancer specimens. We firmly believe that ***only surgical resection margins*** should be painted.

We advocate the intelligent, thoughtful (and restricted) use of paint on such surgical specimens.

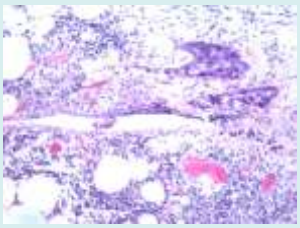
Ludeman & Shepherd, 2005

Peritoneal involvement in colorectal cancer

Microscopic:

where does it occur?

- in the crevices…



The relationship of the peritoneum to the rectum

Peritoneal involvement in rectal cancer

- second most powerful predictor of locoregional recurrence after MRM involvement
- independent prognostic parameter in Concord, Australia series
- perhaps relatively more important now in the days of TME, neo-adjuvant treatment, etc
- incidence varies (Glos 20-25%; Concord 10%)

Shepherd et al, 1995; Mitchard et al, 2011; Keshava et al, 2007

Peritoneal involvement in rectal cancer

Factor	Type of tumour recurrence			Total
	Local	Local + peri	Peritoneal	
Peritoneal involvement	4	3	6	13
Peritoneal involvement and/or extramural venous spread	6	0	0	6
Extramural venous spread	11	0	1	12
Deep margin involvement	5	2	0	7
Distal margin involvement	3	1	0	4
Deep margin and/or peritoneal involvement	2	1	0	3
Mucinous carcinoma (no other adverse factors identified)	1	0	1	2
Intraluminal seeding	1	0	0	1
Total	33	7	8	48

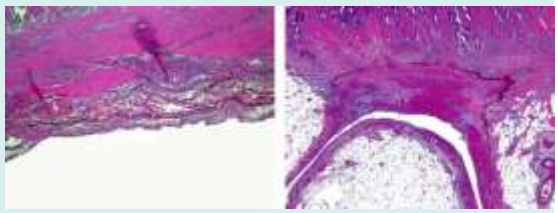
Mitchard et al, 2011

Serosal involvement in colonic cancer

- about 50% of all-comers demonstrate involvement
- strongest adverse prognostic factor in multivariate analysis
- predictor of locoregional recurrence
- controversies in classification
- could it select those patients for IP chemotherapy?

Shepherd et al, 1997

Peritoneal elastic lamina invasion in colorectal cancer



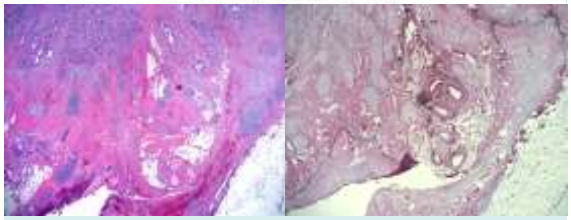
Normal – parallel to the mesothelial layer

Tumour-associated fibrosis alters the position of the lamina

Peritoneal Elastic Laminal Invasion of Colorectal Cancer

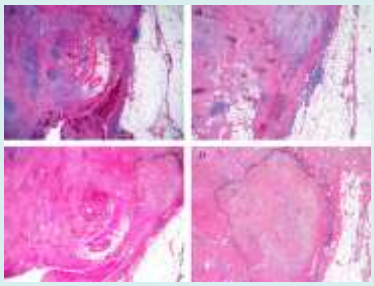
The Diagnostic Utility and Clinicopathologic Relationship

Masahiro Kojima, MD,* Kentaro Nakajima, MD,† Genichiro Ishii, MD,*
Norio Saito, MD,† and Atsushi Ochiai, MD*



Am J Surg Pathol 2010; 34: 1351-60.

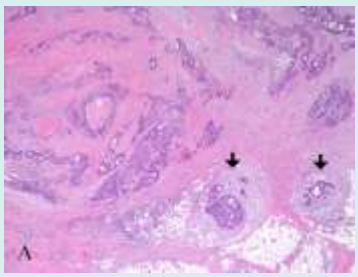
Peritoneal elastic lamina invasion in colorectal cancer



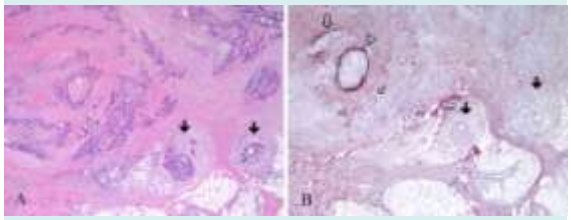
No LPI on H & E (A & B) but tumour beyond elastic lamina on Shikata stain (C & D)

EXTRAMURAL VENOUS SPREAD

Extramural vascular invasion



Extramural vascular invasion



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Extramural venous invasion

- In the UK, marked variations in demonstration rates
- good evidence from the literature of rates enhanced by elastic stains

Kingston et al, 2007; Howlett et al, 2009

- Ontario: 'DGH pathologists': less than 10% in majority specialist pathologists better

Messenger et al, 2011

- Glasgow

Extramural venous invasion: definitions

• tumour in an endothelium-lined space surrounded by a rim of muscle	89.4%
• well circumscribed tumour nodule adjacent to an artery where smooth muscle or elastin could be demonstrated within the nodule on routine or special stains	74.7%
• tumour within an endothelium-lined space containing red blood cells	51.5%

Messenger et al, 2011

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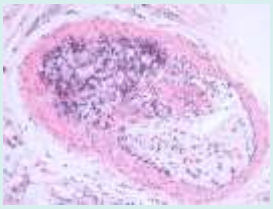
Elastica Staining for Venous Invasion Results in Superior Prediction of Cancer-Specific Survival in Colorectal Cancer

Campbell S. D. Roxburgh, MBChB,* Donald C. McMillan, PhD,* John H. Anderson, MD,* Ruth F. McKee, MD,* Paul G. Morgan, PhD,* and Alan K. Foulis, MD†

- elastica stains used since 2002
- 419 patients undergoing curative elective resection between 1997 and 2006.
- patients grouped prior to 1997–2001 (cohort 1) and following introduction of elastica staining (2003–2006: cohort 2).
- clinicopathologic characteristics & 3-year survival rates similar in both groups.
- rate of detected venous invasion increased from 18% to 58% by elastica staining.
- increased detection of venous invasion with elastica staining, compared with H&E staining, provided superior prediction of cancer survival in colorectal cancer.
- elastica staining should be incorporated into the routine pathological assessment of venous invasion in colorectal cancer.

VASCULAR INVASION

- 'seek & you will find
  but seek especially in stage II'
- sensitivity increases with elastic stains
- should we recommend routine elastic stains?



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- RCPath dataset and guidelines

Controversially perhaps, pathology as the arbiter of quality of surgery

Pathologists assessing the quality of surgery

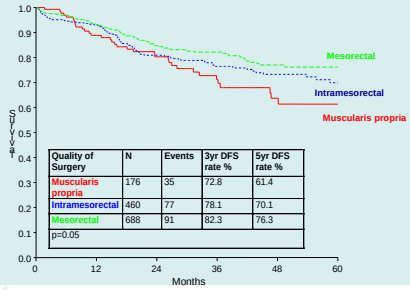
muscular plane (1 or poor)	intermesorectal plane (2 or moderate)	mesorectal (3 or good)
Poor bulk to mesorectum with defects down to muscularis propria and/or very irregular CRM	Moderate bulk to mesorectum but irregularity of mesorectal surface. Moderate coning of the specimen toward distal margin. At not site is MP visible except at the levator insertion. Moderate irregularity of CRM	Intact mesorectum with only minor irregularities of the smooth mesorectal surface. No defect deeper than 5mm. No coning at distal margin. Smooth CRM on sectioning.

MRC CRO7: *Sebag-Montefiore et al, 2008*

plane by pathology	pre-operative DXR	selected post-operative DXR based on CRM positivity	total
muscular plane (1 or poor)	9.0%	18.7%	14.0%
intermesorectal (2 or moderate)	4.5%	11.0%	7.8%
mesorectal (3 or good)	1.3%	6.1%	3.7%

3 year local recurrence rates

Three year disease free survival by quality of surgery all patients: MRC CR07 data



Quality of Surgery	N	Events	3yr DFS rate %	5yr DFS rate %
Muscularis propria	176	35	72.8	61.4
Intramesorectal	460	77	78.1	70.1
Mesorectal	688	91	82.3	76.3
p=0.05				

AP resection

- AP v AR
  - higher local recurrence
  - poorer survival
- cause
  - CRM +ve three times AR
  - 'perforation' x 4 AR
  - type and quality of surgery

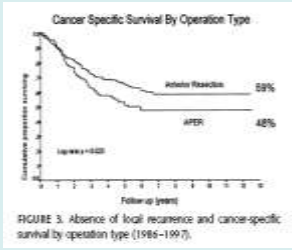


FIGURE 3. Absence of local recurrence and cancer-specific survival by operation type (1986–1997).

APER surgery

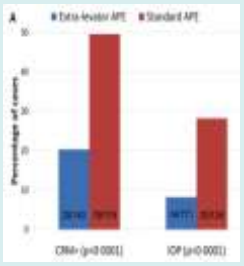
→

Original article

Multicentre experience with extralevator abdominoperineal excision for low rectal cancer

N. P. West[1], C. Anderin[1], K. J. E. Smith[2], T. Holm[3] and P. Quirke[1] on behalf of the European Extralevator Abdominoperineal Excision Study Group

British Journal of Surgery 2010; **97**: 588–599

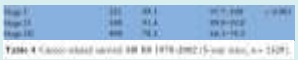


AP surgery

Standardized surgery for colonic cancer: complete mesocolic excision and central ligation – technical notes and outcome

W. Hohenberger*, S. Weber*, K. Matzel*, T. Papadopoulos† and S. Merkel*

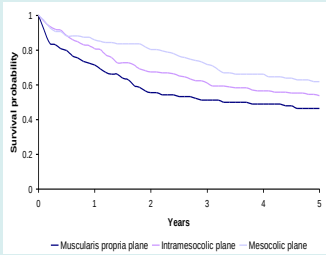
Colorectal Disease, **11**, 354–365



Pathology grading of colon cancer surgical resection and its association with survival: a retrospective observational study

Lancet Oncol 2008; 9: 857–65

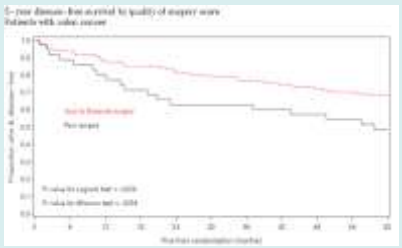
Pathological assessment of quality of colonic surgery & survival



West et al, 2010

Gloucestershire Cellular Pathology Laboratory

CLASICC trial: the planes of surgery



Gloucestershire Cellular Pathology Laboratory

Quality of colonic surgery

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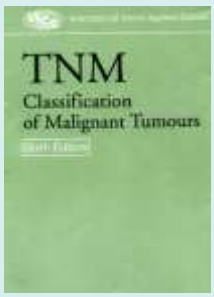
Some TNM changes in colorectal cancer

TNM 4	pN3 abolished
TNM 5	the 3mm rule for extramural deposits being defined as involved lymph nodes
TNM 6	round is node; irregular is venous
TNM 7	tumour deposits definition and pN1c/stage III reversal of pT4a & pT4b

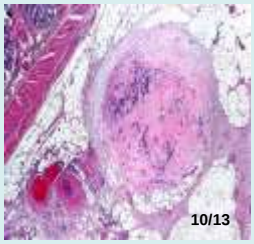
The TNM 6 debacle: 2003

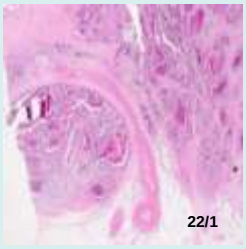
- a tumour nodule in the pericolic/perirectal adipose tissue without histologic evidence of residual lymph node is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node.
- if the nodule has an irregular contour, it should be classified in the pT category, and also coded as V1 (microscopic venous invasion) or V2, if it was grossly evident, because there is a strong likelihood that it represents venous invasion



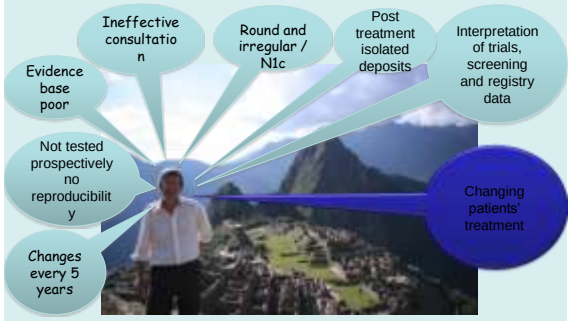
The Cardiff study of reproducibility of TNM 6 assessment of lymph node v venous spread

"smooth and round contour"
overall kappa 0.36 in 23 observers





UK and Western Europe issues with TNM



Quirke et al, J Pathol, 2010

TNM 7

tumour deposits definition pN1c/stage III	• major influence on management • stage II to stage III • without evidence base • especially problematic after neo-adjuvant therapy
reversal of pT4a and pT4b	• logical but mighty confusing

TNM for colorectal cancer

- in the UK and Western Europe, we are recommending that TNM 7 is not adopted
- we didn't recognise TNM 6 either
- we're sticking with TNM 5 until they come up with something better (and evidence-based)

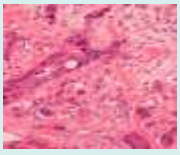
Quirke et al, 2010

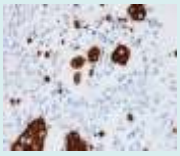
What we will talk about:

- everyday practical ways of improving the quality of CRC resection reporting
- pathology influencing surgical quality
- a bit on TNM 7 (if only to damn it) (and 6 for that matter)
- a bit of new parameters & data – especially budding & the effects of neo-adjuvant therapy

What is tumour budding?

- detachment of single tumour cells or in small aggregates (< 5 cells) = dedifferentiation
- now known to be adverse prognostic marker
- abnormalities in EMT (epithelial-mesenchymal transition)





Where are we with tumour budding?

independent prognostic significance in polyp cancers *Ueno et al, 2004*

independent significance in Dukes B/stage II colon cancers *Wang et al, 2009*

Budding in colorectal cancer

Tumor Budding is a Strong and Reproducible Prognostic Marker in T3N0 Colorectal Cancer

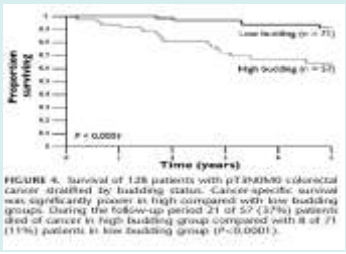
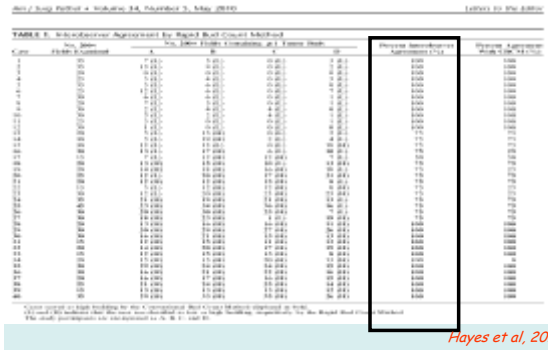


FIGURE 4. Survival of 128 patients with pT3N0M0 colorectal cancer stratified by budding status. Cancer-specific survival was significantly poorer in high compared with low budding groups. During the follow-up period 21 of 57 (37%) patients died of cancer in high budding group compared with 8 of 71 (11%) patients in low budding group ($P < 0.0001$).



Hayes et al, 2010

Where are we with tumour budding?

independent prognostic significance in polyp cancers
Ueno et al, 2004

independent significance in Dukes B/stage II colon cancers
Wang et al, 2009

much less powerful in Dukes C/stage III

issues:

varying methods of assessment

heterogeneity

reproducibility

more data required

Where are we with post neo-adjuvant pathology assessment?

- little evidence for TRG grading as a useful prognostic paramefer
- lots of systems (Mandard, Dworak, Wheeler, Rodel, AJCC, etc) using different methodology
- CRM positivity much more important than TRG in prediction
- ypCR do well but problems with assessment of ypCR
- more data required
- for now, let's keep it simple..

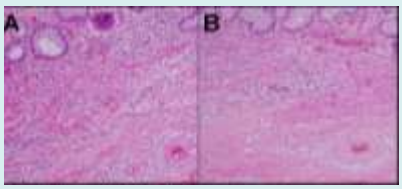
UK RCPath system:

no residual tumour cells and/or mucus lakes only

minimal residual tumour, i.e. only occasional microscopic tumour foci are identified with difficulty

no marked regression

Is step sectioning necessary for determination of pathological complete response in rectal cancer patients treated with preoperative chemoradiotherapy?



Stratifying of patient outcome by final regression grade after step sectioning did not yield different outcomes in patients with initial ypCR. If residual tumour cells were not identified on initial meticulous examination, further processing of step sections may not be necessary.

Chang et al, 2011

Take home messages

- the quality of pathology is all important in colorectal cancer management
- in the UK, we have come a long way from a sorry state in the mid 1990s and there is good evidence base for a major improvement in CRC reporting
- specialised techniques are with us but routine pathological methods will remain the main arbiter of management, prognosis & surgical quality assessment for many years to come
- extramural venous spread still full of controversies: definitions, how often?, routine special stains?, elastic to replace H&E?
- peritoneal involvement not much better: definitions, how often?, routine special stains? elastic to replace H&E?
- will we recommend routine elastic stains for EMVS/LPI? Yes, especially if rates are low and help is needed….
- what about budding? – watch this space
- In the UK and Western Europe, we will continue to reject TNM versions if they insist on lack of evidence base and illogicality