Early colorectal cancer
Quality and rules for a good pathology report
Histoprognostic factors

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ESMO preceptorship, Valencia, 12.05.17
Quality and rules of a good pathology report

Formatting Pathology Reports
Applying Four Design Principles to Improve Communication and Patient Safety

Figure 4. The white square outlines 6 essential gauges that are identically positioned in the cockpit of almost all aircraft.

Simple but rigorous
Useful histopronostic factors

Early colorectal cancer (CRC)
Useful histopronostic factors

1. Micrometastatic disease
2. Adjuvant chemotherapy
Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
Colorectal cancer (CRC): heterogeneous disease

Different histologic types
CRC histologic types

Adenocarcinoma
- Lieberkühnian
- Mucinous
- Signet ring cells
- Medullary
- Micropapillary

Carcinoma
- Serrated
- Adenosquamous
- Small cells
MSI histologic features

Tumour
- Mucinous
- Signet ring cells
- Medullary

Microenvironment
- Crohn-like reaction
- Lymphocytic infiltrate
- CD3+
CRC grading

Low grade (well, moderately differentiated)

High grade (low, indifferenciated)

→ modulation according to MSI status
Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
MUCOSA
Muscularis Muscosae -->
SUB-MUCOSA
MUSCULARIS
SUB-SEROUSA -->
SEROSA -->

Tis T1 T2 T3 T4

pT
N0: no positive lymph node (LN)
N1: ≤ 3 positive LN
N2: ≥ 4 positive LN

pN
N0: no positive lymph node (LN)
N1: ≤ 3 positive LN
N2: ≥ 4 positive LN

pM
M0: No distant metastasis
M1: Distant metastasis

Organe infiltration
and / or visceral
peritoneal perforation

TNM UICC 2016 8th Classification
TNM classification

- **MUCOSA**
  - Muscularis Muscosae -->
- **SUB-MUCOSA**
- **MUSCULARIS**
- **SUB-SEROSA -->**
  - SEROSA -->

**pT**
- Tis
- T1
- T2
- T3
- T4

**pN**
- N0 : no positive lymph node (LN)
- N1 : ≤ 3 positive LN
- N2 : ≥ 4 positive LN

**pM**
- M0 : No distant metastasis
- M1 : Distant metastasis

Organe infiltration and/or visceral peritoneal perforation

TNM UICC 2016 8th Classification
Serosal involvement

Serosal surfaces, mucin pools, and deposits,
Oh my: challenges in staging colorectal carcinoma

Wendy L Frankel and Ming Jin

Department of Pathology, The Ohio State University Wexner Medical Center, Columbus, OH, USA

Gross examination +++
Serosal involvement

pT4a

8th TNM UICC 2016 classification

Frankel et al. Mod Pathol 2015
Serosal involvement

Deeper block levels

pT4a

8th TNM UICC 2016 classification

Frankel et al. Mod Pathol 2015
Serosal involvement

pT4a

8th TNM UICC 2016 classification

Frankel et al. Mod Pathol 2015
Tumour budding

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

Tumour budding

Which method?

Lugli et al. Br J cancer 2012
Immune adaptative microenvironment
Prognostic impact of immune response

TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

Elizabeth K. Broussard and Mary L. Disis, Tumor Vaccine Group, Center for Translational Medicine in Women’s Health, University of Washington, Seattle, WA
Immune infiltrate evaluation

Which method? Which markers?

Intra and peri-tumoral?

Linear quantification?

Pagès et al., New Engl J Med 2005

Allard et al. Diagnostic Pathology 2014
Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
TNM UICC 2016 8th Classification

**pT**
- Tis
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**pN**
- N0: no positive lymph node (LN)
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**pM**
- M0: No distant metastasis
- M1: Distant metastasis

Additional annotations:
- N+: Organe infiltration and / or visceral peritoneal perforation
- Adjuvant chemotherapy
Distant extension: lymph nodes

Recommendations > 12
But...

<table>
<thead>
<tr>
<th>Recovered lymph nodes</th>
<th>Total number of specimens</th>
<th>Percent of specimens with a lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–5</td>
<td>462</td>
<td>6.49%</td>
</tr>
<tr>
<td>6–10</td>
<td>596</td>
<td>8.89%</td>
</tr>
<tr>
<td>11–15</td>
<td>334</td>
<td>41.62%</td>
</tr>
<tr>
<td>16–20</td>
<td>138</td>
<td>31.16%</td>
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<tr>
<td>&gt;= 21</td>
<td>112</td>
<td>80.36%</td>
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</table>
Distant extension: lymph nodes

### Distant extension: tumour deposits

<table>
<thead>
<tr>
<th>Nx</th>
<th>Statut ganglionnaire non évaluable</th>
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<tbody>
<tr>
<td>N0</td>
<td>No positive regional lymph node</td>
</tr>
<tr>
<td>N1</td>
<td>Metastase(s) in 1-3 regional lymph node(s)</td>
</tr>
<tr>
<td></td>
<td>• N1a 1 positive lymph node</td>
</tr>
<tr>
<td></td>
<td>• N1b 2-3 positive regional lymph node</td>
</tr>
<tr>
<td></td>
<td>• N1c Tumour deposits, satellites, in the sub-serosa or peri-rectal or peri-colic non peritonised tissue, <strong>without</strong> regional metastatic lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>≥ 4 or more positive regional lymph nodes</td>
</tr>
<tr>
<td></td>
<td>• N2a ≥ 4-6 regional positive lymph nodes</td>
</tr>
<tr>
<td></td>
<td>• N2b ≥ 7 regional positive lymph nodes</td>
</tr>
</tbody>
</table>

TNM UICC 2016 8th Classification
Distant extension: tumour deposits

TNM 5th edition

>3 mm
Lymph node

TNM 6th edition

Smooth shape
Lymph node

TNM 7, 8th edition

No residual lymph node
Tumour deposit

Frankel et al. Mod Pathol 2015
Distant extension: tumour deposits

Pericolic or -rectal tissue location

Puppa et al. Modern Pathol 2007
Impact of «tumour deposits» (N1c)

Distant extension: tumour deposits

Recommendations for interprétation (F.A.Q*)

- N1c only if negative lymph node
- No N1c if positive lymph node
- Do not add tumour deposits to positive lymph node
- Do not modify T stage

*Frequently Asked Question
## Distant extension : N+ subdivision

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<td>• N2a</td>
</tr>
<tr>
<td></td>
<td>• N2b</td>
</tr>
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TNM UICC 2017 8th Classification

→ Clinical trials stratification
Distant extension: VELIPI*

Lymphatic invasion

Venous invasion

Perineural invasion

L category  V category  Pn1 category

8th TNM UICC 2016 classification

*Venous emboli and lymphatic and perineural invasion
Extra-mural venous invasion

30%: frequent underestimation?

Nagtegaal et al. histopathology 2015
Perineural invasion

Perineural Invasion Is a Strong Prognostic Factor in Colorectal Cancer
A Systematic Review

Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
Margins

Distal ans proximal

→ very rarely positive
Useful histopronostic factors

- Tumour
- Depth of invasion
- Distant extension
- Margins
Molecular profile
Microsatellite instability (15%)

Immunohistochemistry

Molecular biology

Normal DNA

MSI tumour

Less or supplementary nucleotides

→ Favorable prognosis in CCR stage II
Molecular profile

• Impact of KRAS et BRAF mutations
  • Poor prognosis in stage III CRC (MSS)*
  • Not used as prognostic factors in 2017...
  • Stratification for clinical trials ?

• MSI, RAS, BRAF status for all CRC, tomorrow ?

*Taieb et al JAMA Oncol 2016
Perspectives: liquid biopsy

Minimal residual disease *Tie J, sci Transl Med 2016*

Adapted from *Diaz et al J Clin Oncol 2014; 32:579-86*
Perspectives

TNM Staging in Colorectal Cancer: T Is for T Cell and M Is for Memory

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- Treatment for particular stage II ?
- No treatment for certain stage III ?
Take home messages
Useful histopronostic factors for treatment

Early CRC in 2017

- pTNM
- Grade
- VELIPI
- MSI
Useful histopronostic factors for treatment

Early CRC in 2016

Stage III

- pTNM \textbf{N+} (including N1c= tumour dep.) \textit{adjuvant CT}

- Grade

- VELIPI

- MSI
Useful histopronostic factors for treatment

Early CRC in 2016

Stage II

- pTNM **N0** pT4 (serosa +), <12 N
- Grade **high** (poor differenciation)
- VELIPI +
- MSI -

Adjuvant CT
(Multidisciplinary team discussion)
Pathology report key elements

Histologic type

Differenciation (Grade)

Extension
- Tumour (pT)
- Lymph node (pN)

Margins
- Distal/proximal
- Circumferential (Rectum)

Vasculo-lymphatic and perineural invasions
Translationnal research