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

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CHU de Caen,
Normandy University,
France

ESMO preceptorship, Barcelona, 20.10.17
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.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>PHYSICIAN</th>
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Simple but rigorous
### Reporting proforma for colorectal resection specimen

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<td>Total colectomy</td>
<td>□ / Subtotal colectomy □ /</td>
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<td>Right hemicolecotomy</td>
<td>□ / Transverse colectomy □ /</td>
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<td>Left hemicolecotomy</td>
<td>□ / Anterior resection [AR] □ /</td>
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<tr>
<td>Sigmoid colectomy</td>
<td>□ / Hartmann’s procedure □ /</td>
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<tr>
<td>Abdominoperineal excision [APE]</td>
<td>□ /</td>
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<tr>
<td>Other (state)</td>
<td>..................................................</td>
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</table>
Useful histopronostic factors

Early colorectal cancer (CRC)
Useful histopronostic factors

1. Micrometastatic disease
2. Adjuvant chemotherapy
Useful histopronostic factors

Content

- 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

- Lieberkühnian
- Mucinous
- Micropapillary
- Signet ring cells
- Serrated
- Medullary
- Adenocarcinoma
- Adenosquamous
- Small cells
- Carcinoma

90%
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 (poorly/indifferenciated)

→ modulation according to MSI status
Useful histopronostic factors

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

- **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

Gross examination +++

tumour

Positive lymph node

serosa
Serosal involvement

pT4a

8th TNM UICC 2016 classification

Frankel et al. Mod Pathol 2015
Serosal involvement

Deeper block levels
Serosa involvement + reactive phenomenons *

pT3
<1mm

pT4a

8th TNM UICC 2016 classification

* Mesothelial Hyperplasia, inflammation, erosion, ulceration

Frankel et al. Mod Pathol 2015
Serosal involvement

pT4a

8\textsuperscript{th} TNM UICC 2016 classification
Tumour budding

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

Tumour budding

Tumor budding Score (0.785 mm²)
(Hot Spot method, X 20)
HE staining

<table>
<thead>
<tr>
<th>1 (Budd 1)</th>
<th>&lt; 5</th>
<th>Faible</th>
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</thead>
<tbody>
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<td>2 (Budd 2)</td>
<td>5-10</td>
<td>Intermédiaire</td>
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<tr>
<td>3 (Budd 3)</td>
<td>≥ 10</td>
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</table>

Immune adaptative microenvironment

Optionnal
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 adaptative microenvironnement

Tumour regions (CT & IM) Immunostainings
CD3 CD8

Digital Pathology
Quantification (cells / mm²)

Immunoscore (CT+IM)

Hi Hi Hi Hi 14
Hi Hi Hi 13
Hi Hi 12
Hi 11
10

optionnal
Useful histopronostic factors

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

MUCOSA
Muscularis Muscosae -->
SUB-MUCOSA
MUSCULARIS
SUB-SEROSE -->
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

N+
Organe infiltration and / or visceral peritoneal perforation

Adjuvant chemotherapy

TNM UICC 2016 8th Classification
Distant extension: lymph nodes

Recommendations > 12

But... More = Better
Distant extension: tumour deposits

<table>
<thead>
<tr>
<th>Nx</th>
<th>Lymph node status not assessable</th>
</tr>
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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>• N1a</td>
<td>1 positive lymph node</td>
</tr>
<tr>
<td>• N1b</td>
<td>2-3 positive regional lymph node</td>
</tr>
<tr>
<td>• N1c</td>
<td>Tumour deposits, satellites, in the sub-serosa or peri-rectal or peri-colic non peritonised tissue, without regional metastatic lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>≥ 4 or more positive regional lymph nodes</td>
</tr>
<tr>
<td>• N2a</td>
<td>≥ 4-6 regional positive lymph nodes</td>
</tr>
<tr>
<td>• N2b</td>
<td>≥ 7 regional positive lymph nodes</td>
</tr>
</tbody>
</table>

TNM UICC 2016 8th Classification
Distant extension: tumour deposits

Pericolic or -rectal tissue location
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
Impact of « tumour deposits »

**Table 2. Logistic Regression Model for the Various Metastatic Locations**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Liver Metastases</th>
<th>Lung Metastases</th>
<th>Peritoneal Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0/TD−</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>N0/TD+</td>
<td>3.57 (2.38 to 5.35)</td>
<td>2.86 (1.71 to 4.78)</td>
<td>6.44 (3.04 to 13.65)</td>
</tr>
<tr>
<td>N+/TD−</td>
<td>2.60 (1.96 to 3.44)*</td>
<td>2.49 (1.81 to 3.44)†</td>
<td>3.21 (1.75 to 5.90)‡</td>
</tr>
<tr>
<td>N+/TD+</td>
<td>5.54 (4.23 to 7.25)*</td>
<td>4.29 (3.11 to 5.93)†</td>
<td>6.97 (3.96 to 12.25)‡</td>
</tr>
</tbody>
</table>

**EMVI**

<table>
<thead>
<tr>
<th></th>
<th>Liver Metastases</th>
<th>Lung Metastases</th>
<th>Peritoneal Metastases</th>
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<tbody>
<tr>
<td></td>
<td>1.38 (1.08 to 1.77)</td>
<td>2.01 (1.48 to 2.72)</td>
<td>1.25 (0.76 to 2.05)</td>
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</table>

**Hosmer and Lemeshow goodness of fit**

<table>
<thead>
<tr>
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<th>Liver Metastases</th>
<th>Lung Metastases</th>
<th>Peritoneal Metastases</th>
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<tbody>
<tr>
<td></td>
<td>(P = .476)</td>
<td>(P = .688)</td>
<td>(P = .498)</td>
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</tbody>
</table>

**NOTE.** Data are given as adjusted odds ratio (95% CI). Data are corrected for cohort and all other listed variables. Abbreviations: EMVI, extramural vascular invasion; TD−, tumor deposit negative; TD+, tumor deposit positive.

*\(P < .001\).
†\(P = .004\).
‡\(P = .018\).

N+/TD+: Next TNM classification (9th edition)?
Distant extension : N+ subdivision

<table>
<thead>
<tr>
<th>Nx</th>
<th>Lymph node status non assessable</th>
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</thead>
<tbody>
<tr>
<td>N0</td>
<td>No positive regional lymph node</td>
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<td>N1</td>
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<tr>
<td></td>
<td>• N1a 1 positive lymph node</td>
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<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 without regional metastatic lymph node</td>
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<td>N2</td>
<td>≥ 4 or more positive regional lymph nodes</td>
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<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 2017 8th Classification

→ 3 vs 6 months CT ?
→ Clinical trials stratification
Distant extension: VELIPI*

Lymphatic invasion  
Venous invasion  
Perineural invasion

Harris et al, Am J Surg Path 2008  
Mori et al. Histopathology 2009  
Liebig et al J Clin Oncol 2010

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
Useful histopronostic factors

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

Distal and proximal very rarely positive

Circumferential
(Rectum)
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

Pierre Laurent-Puig

lecture +++
Perspectives

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

- 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 $N^+$ (including N1c= tumour dep.) adjuvant CT

- Grade

- VELIPI

- MSI
Useful histopronostic factors for treatment

Early CRC in 2016

Stage II

- pTNM $N_0$ pT4 (serosa +), <12 N
- Grade high (poor differentiation)
- VELIPI +
- MSI -

Adjuvant CT (Multidisciplinary team discussion)
Pathology report key elements
Multidisciplinary board

Histologic type

Differenciación (Grade)

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

Margins
- Distal/proximal
- Circumferential (Rectum)

Vasculo-lymphatic and perineural invasions

OMS

Lymphatics

Veins

Nerves
# Minimum Data Set

## Proforma for Colorectal Cancer Resections

Note: This document is designed to be used as a template to allow capture of minimal data set information within the pathology report. It is not intended to replace the pathology report, in which inclusion of other items, or further description of existing items is often warranted.

### Macroscopic Description

- **Site of tumour**: 
- **Maximum tumour diameter**: 
- **Distance of tumour to nearer cut end**: 
- **Tumour perforation**: Yes (pT4) / No
- **Rectal tumours**: Relation of tumour to anterior peritoneal reflection: Above / Astride / Below

### Microscopic Description

- **Type**
  - Adenocarcinoma NOS
  - Mucinous carcinoma
  - Medullary carcinoma
  - Signet ring cell carcinoma
  - Small cell carcinoma
  - Undifferentiated carcinoma
  - Other (specify)

- **Differentiation by predominant area**
  - Well/moderate
  - Poor

- **Local invasion**
  - pT0: No evidence of primary tumour
  - pT1: Infiltrates or intramural
  - pT2: Invasion into muscularis propria
  - pT3: Beyond muscularis propria
  - pT4a: Tumour invades adjacent organs
  - pT4b: Tumour cells have breached serosa
  - pTX: Primary cannot be assessed

- **Tumour involvement of margins**
  - Margin (cut end): Involved / Not involved
  - Non-peritonealised circumferential margin: Involved / Not involved

- **Histological measurement from tumour to non-peritonealised margin**: 

### Lymphocytic Infiltrate

Intraepithelial lymphocyte counts are not considered necessary when MMRD status is assessed.

- < 5 per hpf (inconspicuous)
- ≥ 5 per hpf (conspicuous)
- Not assessed

### Lymph nodes

- No of lymph nodes present
- No of lymph nodes involved
- pN0: No regional LN metastases
- pN1: Metastases in 1-3 regional LNs
- pN2: Metastases in 4 or more regional LNs
- pNX: Regional LNs cannot be assessed

### Lymphovascular invasion

- Present / Absent

### Perineural invasion

- Present / Absent

### Histologically confirmed distant metastases

- pM0: No distant metastasis
- pM1: Distant metastasis

### Background abnormalities

- Adenoma(s) Type: Number
- Synchronous carcinomas: Complete a separate form for each cancer
- Ulcerative colitis
- Crohn's disease
- Other

### Residual tumour status

- R0: No residual tumour
- R1: Microscopic margin involvement
- R2: Macroscopic margin involvement
- RX: Cannot be assessed

### Summary – TNM (6th edition)

- pT
- pN
- pM
- (cM)
- R

### Mismatch Repair Deficiency (MMRD) status

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<tr>
<th>Staining (normal)</th>
<th>Loss of staining (abnormal)</th>
<th>Not assessed</th>
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<td>□</td>
<td>□</td>
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<tr>
<td>MSH2</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MSH6</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>PMS2</td>
<td>□</td>
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Reporting proforma for colorectal cancer

• www.sfpathol.org

• www.ecancer.fr
Translationnal research
Back up slides
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>
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<tr>
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<td>462</td>
<td>6.49%</td>
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<tr>
<td>6–10</td>
<td>596</td>
<td>8.89%</td>
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<tr>
<td>11–15</td>
<td>334</td>
<td>41.62%</td>
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<tr>
<td>16–20</td>
<td>138</td>
<td>31.16%</td>
</tr>
<tr>
<td>&gt;= 21</td>
<td>112</td>
<td>80.36%</td>
</tr>
</tbody>
</table>
Distant extension: lymph nodes

- Low disease stage
- Enlargement of regional lymph nodes
- Recovered node count
- Host immune response
- Tumor molecular characteristics
- Patient prognosis

Distant extension: lymph nodes

Gross examination +++

No magic number!
More = better
Distant extension: tumour deposits

TNM 5\textsuperscript{th} edition

- >3 mm
  - Lymph node

TNM 6\textsuperscript{th} edition

- Smooth shape
  - Lymph node

TNM 7, 8\textsuperscript{th} edition

- No residual lymph node
  - Tumour deposit

Frankel et al. Mod Pathol 2015
Impact of «tumour deposits» (N1c)

\[ P < 0.001 \]

Impact of « tumour deposits » (N1c)

P = 0.087

TNM Classification of Malignant Tumours - 8th edition

Changes between the 7th and 8th editions

December 2016

“We unite the cancer community to reduce the global cancer burden, to promote greater equity, and to integrate cancer control into the world health and development agenda.”
Colon and Rectum

Definition of tumour deposit clarified

Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to N1c if all regional lymph nodes are negative on pathological examination.
Colon and Rectum

- **T and N categories Unchanged**

<table>
<thead>
<tr>
<th>M1</th>
<th>Distant metastasis</th>
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<tbody>
<tr>
<td>M1a</td>
<td>Metastasis confined to one organ (liver, lung, ovary, non regional lymph node(s)) without peritoneal metastases</td>
</tr>
<tr>
<td>M1b</td>
<td>Metastasis in more than one organ</td>
</tr>
<tr>
<td>M1c</td>
<td>Metastasis to the peritoneum with or without other organ involvement</td>
</tr>
</tbody>
</table>

- **Stage Unchanged except for Stage IVA, IVB, IVC as below**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tr>
<td>Stage IV</td>
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<td>Any N</td>
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<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1b</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1c</td>
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</table>
**Conclusion**

**Prognostic Factors Grid – Colon and Rectum**

Prognostic factors for survival in differentiated colorectal cancer

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Tumour related</th>
<th>Host related</th>
<th>Environment related</th>
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<tbody>
<tr>
<td>Essential</td>
<td>T category</td>
<td>Age</td>
<td>Screening programme</td>
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<tr>
<td></td>
<td>N category</td>
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<td></td>
<td>M category</td>
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<td>Circumferential margin (rectal cancer)</td>
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<td>Additional</td>
<td>Vascular/lymphatic invasion</td>
<td>Race</td>
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<td>Grade</td>
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<td>New and promising</td>
<td>Molecular profile</td>
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<td>Change</td>
<td>Details of Change</td>
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<td>----------------------------------------------------------------------------------</td>
<td>------------------</td>
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<td>Definition of Distant Metastasis (M)</td>
<td>Introduced M1c, which details peritoneal carcinomatosis as a poor prognostic factor</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Definition of Regional Lymph Node (N)</td>
<td>Clarified the definition of tumor deposits</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>Additional Factors Recommended for Clinical Care</td>
<td>Lymphovascular invasion: reintroduced the L and V elements to better identify lymphatic and vessel invasion</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Additional Factors Recommended for Clinical Care</td>
<td>Microsatellite instability (MSI): clarified the importance of MSI as a prognostic and predictive factor</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Additional Factors Recommended for Clinical Care</td>
<td>Identified KRAS, NRAS, and BRAF mutations as critical prognostic factors that are also predictive</td>
<td>I and II</td>
<td></td>
</tr>
</tbody>
</table>
Ratio tumeur/stroma

Pronostic défavorable

Classification moléculaire CCR

Instabilité chromosomique
Voie CIN
80-85 %

Instabilité épigénétique
Voie CIMP
≈20 %

Instabilité microsatellitaire
Voie MSI
15-20 %

Carcinome classique

Tumeurs festonnées

Cancer du sujet âgé

Syndrome de Lynch

Lieberkühnien

Festonné

Médullaire/ lymphocytes

KRAS

TP 53

BRAF
Profil moléculaire CCR

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
<tr>
<td>MSI, CIMP high, hypermutation</td>
<td>SCNA high</td>
<td>Mixed MSI status, SCNA low, CIMP low</td>
<td>SCNA high</td>
</tr>
<tr>
<td>BRAF mutations</td>
<td>WNT and MYC activation</td>
<td>Metabolic deregulation</td>
<td>Stromal infiltration, TGF-β activation, angiogenesis</td>
</tr>
<tr>
<td>Immune infiltration and activation</td>
<td>Worse survival after relapse</td>
<td></td>
<td>Worse relapse-free and overall survival</td>
</tr>
</tbody>
</table>

- Corrélation morphologique?
- Intégration clinique ?
Profil moléculaire CCR

Amplifications: 2,5%
Mutations: 1,9%

- HER-2
- Mutation KRAS exon 2
- RAS muté: 50%
- RAS et BRAF WT: 40%
- MSI: 15%
- BRAF: 10%
- Mut KRAS ex 3, 4
- Mut NRAS

Penault-Llorca et al. ESMO 2016
Taieb et al. Jama Oncology 2016

Courtoisie Astrid Lièvre
Individualisation pronostique par IHC ?

BRAF + muté

MSI

BRAF + muté

MSS