The malignant colorectal polyp

Dr Ian Brown
Envoi Pathology

Envoi data reproduced from J Clin Path 2015 article
Definition

- Adenocarcinoma found in an endoscopically resected polypoidal tumour
- Submucosal invasive tumour in a pre-existing adenoma (conventional or serrated)
- Polypoidal carcinoma
- (‘intramucosal’ adenocarcinoma)
Importance

• Detection is increasing – NBCSP

• A quality marker for pathology practice standards

• Surgery versus conservative
  – Patient risk and economic benefit
What do we know?

1) **RISK**

   **Resection specimens**
   - **LN metastasis in 7-9%** (Envoi - 8.0%) * most important
   - Residual adenocarcinoma at polypectomy site ≤ 5%
   - Residual adenoma at polypectomy site ≤ 5-10%
   - **Overall rate of residual disease = 10-15%**

   **All specimens**
   - 50-60% of endoscopic MCP are followed by resection
   - Overall risk of **LN mets all MCP = 4%**
   - Overall risk of **residual disease all MCP = 7-10%** (Envoi =8.7%)
What do we know?

2) CLINICAL

– Males (55-60%)
– Mean age 60-65 years
– 3/4 are in rectum or sigmoid
– Sessile: pedunculated
  • 6:4 (Envoi) to 4:1 (Ueno) when assessed by pathologist
  • 1:2 when assessed by endoscopist
– MCP may be small
  • 25% ≤ 10mm
  • 1.7% ≤ 5mm
What do we know?

3) RISK FACTORS

– predict: LN mets, residual disease in wall, overall tumour specific survival

– 2 groups:

1) Qualitative

• Differentiation, vascular invasion, margin status etc

2) Quantitative

• Tumour size - Depth of invasion, tumour width, Haggitt, Kikuchi etc

• Tumour size is the most important risk factor
What are we trying to do?

Cost benefit analysis for surgery

– Costs

  • Risk of surgery – morbidity and mortality
  • Economic cost of unnecessary surgery
  • (‘sunk’ cost = tumour may already have metastasized beyond bowel wall or patient might die of another condition before the benefit of surgery accrues)

– Benefits

  • Remove residual disease that might latter directly cause morbidity or mortality
## What are the issues?

1) Risk of residual disease for MCP is overstated

<table>
<thead>
<tr>
<th>Risk criteria</th>
<th>Degree of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection margin &lt; 1mm</td>
<td>4</td>
</tr>
<tr>
<td>Resection margin 1-2mm</td>
<td>1</td>
</tr>
<tr>
<td>Pedunculated Haggitt level 4</td>
<td>4</td>
</tr>
<tr>
<td>Sessile: Kikuchi 2</td>
<td>2</td>
</tr>
<tr>
<td>Sessile: Kikuchi 3</td>
<td>4</td>
</tr>
<tr>
<td>Poor differentiation</td>
<td>3</td>
</tr>
<tr>
<td>Mucinous tumour</td>
<td>1</td>
</tr>
<tr>
<td>Tumour budding</td>
<td>1</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total score</th>
<th>% risk of residual cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>1</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>2</td>
<td>5-10%</td>
</tr>
<tr>
<td>3</td>
<td>8-15%</td>
</tr>
<tr>
<td>≥4</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

What are the issues?

1) Risk of residual disease for MCP is overstated

<table>
<thead>
<tr>
<th>Number of risk factors</th>
<th>Nodal involvement</th>
<th>Ueno</th>
<th>Envoi</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>0.7%</td>
<td>2%</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>20.7%</td>
<td>8.2%</td>
</tr>
<tr>
<td>≥2</td>
<td></td>
<td>36.4%</td>
<td>12.2%</td>
</tr>
</tbody>
</table>

Risk factors = poor differentiation, lymphovascular invasion and tumour budding

Ueno et al Gastroenterology 2004;127:385-94 * half the MCP in this study were treated by primary surgical resection
What are the issues?

1) Risk of residual disease for MCP is overstated

<table>
<thead>
<tr>
<th>T stage</th>
<th>N+ stage proportion (%)</th>
<th>Rectal cancer</th>
<th>Colon cancer</th>
<th>All untreated CRC Envoi</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>10.2%</td>
<td>4.3%</td>
<td>6.3%</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>22.3%</td>
<td>19.0%</td>
<td>15.0%</td>
<td></td>
</tr>
<tr>
<td>T3-4</td>
<td>51.2%</td>
<td>38.5%</td>
<td>46.2%</td>
<td></td>
</tr>
</tbody>
</table>

World J Gastroenterol. 2010 Nov 14; 16(42): 5375–5379
What are the issues?

2) Risk of surgical resection is overstated

- Quoted figures (overall)
  - mortality 2-5 %
  - morbidity 30 %
  - Anastomotic leak 1-4%

- Local colorectal surgeons are much better than this
What are the issues?

3) Risk for primary colonoscopic resection

Munich polypectomy study (Endoscopy 2005;37:1116-1122) – Major complication rate = death, perforation, bleeding

BSG audit – perforation - 0.04%, bleeding - 0.26%, readmission – 0.14%
What are the issues?

4) The 5 year survival for stage III colorectal carcinoma is quite good and is getting better!

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-year Relative Survival Rate Colon vs Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>92% vs 87%</td>
</tr>
<tr>
<td>IIA</td>
<td>87% vs 80%</td>
</tr>
<tr>
<td>IIB</td>
<td>63% vs 49%</td>
</tr>
<tr>
<td>IIIA</td>
<td>89% vs 84%</td>
</tr>
<tr>
<td>IIIB</td>
<td>69% vs 78%</td>
</tr>
<tr>
<td>IIIIC</td>
<td>53% vs 51%</td>
</tr>
<tr>
<td>IV</td>
<td>11% vs 12%</td>
</tr>
</tbody>
</table>

SEER data 2004 - 2010
Further treatment decision

1) Patient factors

- Age
- Co-morbidities
- Genetic syndrome (eg Lynch, FAP)
- Cancer phobia
Further treatment decision

2) Pathological factors

1) Qualitative
   • Differentiation, vascular invasion, margin status etc

2) Quantitative
   • Size of invasive tumour
Further treatment decision

3) Gastroenterologist/surgeon*
   - Feeling on adequacy of endoscopic resection
   - Personality
   - Experience – EMR/ESD (gastroenterologist) vs laparoscopic resection (colorectal surgeon)
   - Knowledge!!!


A. Lesions in colon
   a) Pedunculated Haggitt level 4 with invasion into distal third of submucosa, or pedunculated lesions with lymphovascular invasion
   b) Sessile lesions removed with margin <2 mm
   c) Sessile lesions removed piecemeal
   d) Sessile lesions with depth of invasion into distal third of submucosa (Sm3)
   e) Sessile lesions with lymphovascular invasion

B. Lesions in middle third and upper third rectum
   Same as lesions in colon

C. Lesions in distal third rectum
   a) Pedunculated Haggitt level 4 with invasion into distal third of submucosa, or pedunculated lesions with lymphovascular invasion
   b) All sessile lesions
Bottom line

– Better pathological risk assessment
– Better endoscopic resection
– Better surgical outcomes
– Better oncological therapy if a LN met is missed
– ?? imaging techniques to detect LN met
– NBCSP = smaller malignant polyps

The risk benefit data is changing

All we can control is the pathology input
Pathological factors
Quantitative factors

(Tumour size/depth of invasion)
1) Haggitt levels

- Depth of invasion

Haggitt et al. Gastroenterology 1985;89:328-36
1) Haggitt levels

- **Haggitt paper** Gastroenterology 1985;89:328-36
  
  - 129 cases (50% were level 0)
  - 70 (54%) pedunculated; 42 sessile, indeterminate 17
  - 51% underwent resection; 35% of all cases were primary resections
  - Lymphatic invasion - 2 cases
  - Venous invasion – 0 cases
  - 8 (6.2%) adverse outcome = LN mets in 4 (but not known in 3 cases who died); death from disease in 5
1) Haggitt levels

- 8/64 (12.5%) submucosal invasive carcinoma (levels 1-4) had an adverse outcome (LN mets/tumour related death). These were:
  - Levels 0-2 = 0 cases (0%)
  - Level 3 = 1 case (12.5%)
  - Level 4 = 7 cases (87.5%)** (2 were pedunculated, 6 were sessile)

- Level 4 is the significant factor
- 7/28 polyps were level 4 = PPV for adverse behaviour = 25%
- How many level 4 were pedunculated
1) Haggitt levels

• Problems:
  1) 59 non pedunculated polyps were by definition level 4
     – (6 had adverse outcome = 10%)
  2) 70 pedunculated polyps
      • ? how many level 4 invasion (2 adverse)
      • Data from paper suggests PPV of risk for pedunculated Level 4 > sessile level 4 (but data is incomplete)
1) Haggitt levels

3) Difficult to apply in practice
   • poor orientation
   • Piecemeal specimen
   • Pedunculated vs sessile
   • Levels 1 vs 2 and 2 vs 3

4) Over interpretation by surgeons

5) Small series, not contemporary
• Envoi data

  – Less pedunculated polyps than reported in clinical series (43% vs 66%)
  – Pedunculated Haggitt level 4 = nil
  – Haggitt level 3 = 14%
    • 2 (12.5%) had LN mets (one was pT3 at resection)
    • 1 other case had residual adenocarcinoma in lymphatics
  – Haggitt level 2 = 19%
    • 1 (5.9%) had LN mets; large mucinous LVI
  – Haggitt level 1 = 10%
    • no LN mets
2) Kikuchi/Kudo levels

Sessile polyps

- sm1: slight submucosal invasion from the muscularis mucosa.
- sm2: intermediate between sm1 and sm3.
- sm3: carcinoma invasion near the inner surface of the muscularis propria.


LN metastasis risk

- 3% (0% in contemporary studies)
- 8%
- 23%

Overall pT1 – 6-12%
2) Kikuchi/Kudo levels

- Problems:
  1. Fragmented specimen
     - Invasion <0.3mm = Kikuchi sm1
     - Mid submucosal venous plexus is good surrogate for sm2
  2. Muscularis mucosae destroyed by tumour and/or extensive tumour ulceration
  3. Full thickness of submucosa is not included in standard endoscopic resection specimens (need ESD)
  4. Not applicable to pedunculated polyps
3) Tumour size - measured

- Width and Depth (surrogate of tumour volume) of invasive carcinoma
- The most important prognostic feature – now confirmed in multiple studies

Ueno et al Gastroenterology 2004;127:385-94

292 pT1 adenocarcinoma (mostly in a pre-existing polyp)

LN metastasis risk

- Width <2mm = 0%
- Depth <0.5mm = 0%
- Width ≥ 4mm = 18.2%
- Depth ≥ 2mm = 17.1%
- Width ≥ 4mm and/or Depth ≥ 2mm predict LN metastasis

Y1 or Y2 depends on intactness of MM
3) Katajima depth modification for pedunculated polyps

- Useful when sessile polyp is ulcerated or muscularis mucosae is destroyed
- Correlates tumour size in pedunculated polyps to sessile polyps

A Pedunculated

B Sessile 1

C Sessile 2

No lymph metastases if:
1) Pedunculated < 3 mm
2) Sessile < 1 mm

4) Current Japanese criteria

Japanese society for cancer of the colon and rectum – Kawachi et al Mod Path 2015

- **T1 colorectal cancer**
  - **Pedunculated tumor**
    - Beyond Haggitt's line?
      - Yes → Measure distance from Haggitt's line ($d'$)
        - pT1, head invasion
      - No → pT1, stalk invasion, $d'$ μm
  - Non-pedunculated tumor
    - Is muscularis mucosa (MM) identifiable?
      - Yes → Measure distance from MM ($d$)
      - No → Measure tumor thickness ($d$)
        - pT1, $d'$ μm
Tumour size - measured

Problems:

1) Poor orientation (levels might help)

2) Fragmented specimen
   – Often one or two pieces contain the majority of the carcinoma
   – Can give a minimum size which often exceeds 2mm depth or 4mm width

3) Muscularis mucosae destroyed
   - Measure full thickness of adenocarcinoma

4) Sessile vs pedunculated
   - if no definite stalk – measure as per sessile polyp
### Tumour size - measured

- **Envoi data**

<table>
<thead>
<tr>
<th>Size</th>
<th>LN mets</th>
<th>No LN mets</th>
<th>Odds ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width of invasion &gt;4mm</td>
<td>91.7%</td>
<td>51.5%</td>
<td>10.34 (1.31-81.43)</td>
<td>0.007</td>
</tr>
<tr>
<td>Depth of invasion &gt;2mm</td>
<td>83.3%</td>
<td>48.0%</td>
<td>5.41 (1.16-25.26)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Size <1mm depth or <2mm width = 0% LN mets
Qualitative factors
1) Poor tumour differentiation

<table>
<thead>
<tr>
<th></th>
<th>Envoi (N=239)</th>
<th>Pooled analysis (Hassan et al N=1400)</th>
<th>Ueno et al (N = 292)</th>
<th>Butte (N=143)</th>
<th>Kawachi Mod path 2015 (N=805)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor differentiation</td>
<td>18.4% (all CRC = 20%)</td>
<td>7.2%</td>
<td>26.7%</td>
<td>11.9%</td>
<td>32.2%</td>
</tr>
</tbody>
</table>

- Wide variation in frequency
  - Poor interobserver agreement
    
    Kappa - 64-70% Cooper et al Gastroenterology. 1995;108:1657-65; 0.14 Terris et al Mod Path 2012;25(2)182A

- Studies are moving toward the concept of tumour grade rather than differentiation
- Requires MMR status
1) Poor tumour differentiation

<table>
<thead>
<tr>
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<th>Residual disease</th>
<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (average)</td>
<td>18%</td>
<td>23%</td>
<td>15%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>2</td>
<td>4</td>
<td>9**</td>
</tr>
<tr>
<td>%/Odds ratio - Ueno</td>
<td>29%/3 (multivariate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consistently associated with adverse outcome in all studies

Probably because we all agree on the significant high grade lesions

Hassan et al Dis Colon Rectum 2005;48:1588-96
Ueno et al Gastroenterology 2004;127:385-94
1) Poor tumour differentiation

- Poor differentiation in **any** part of tumour but particularly at invasive edge
- Some studies require 50% of adenocarcinoma to be poorly differentiated

**Patterns:**
- <50% gland lumina
- Mucinous (MLH-1 def)
- Signet ring
- Tumour ‘buds’ with >5 cells (poorly differentiated clusters)
- Cribriform comedo
- Undifferentiated carcinoma (?neuroendocrine)
- **NOT** true tumour budding (<5 cells)
Cribriform and mucinous

Large buds – focal ‘dedifferentiation’ ‘poorly differentiated clusters’
Beware!!! Neuroendocrine – very high risk of metastatic disease
2) Margin of resection

- positive variously defined
  - In diathermy artefact
  - ≤1mm
  - <2mm from margin

- Ueno et al. *Gastroenterology* 2004;127:385-94 → only involvement of diathermy artefact is significant

- ≥1 mm clearance  

- General agreement that ≥ 2mm is definitely clear
> 2mm - clear

POSITIVE
2) Margin of resection

- **Risk:**

<table>
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<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (average)</td>
<td>30%</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>15**</td>
<td>1</td>
<td>6</td>
</tr>
</tbody>
</table>

Hassan et al Dis Colon Rectum 2005;48:1588-96

- Interobserver agreement – good 86-93%
- positive margin = inadequate treatment **NOT** a risk for metastatic disease

Too high – Ueno = 12.5%; Envoi 12%, Butte 11.2% (INTACT polyps)
2) Margin of resection

• Positive margin 33% (using all definitions)

• Envoi
  – Diathermy involvement 27.2%
  – no residual disease if clearance >0.1mm above diathermy artefact

• Positive margin = 12% risk of residual disease (adenoma or adenocarcinoma) at site of polypectomy
3) Vascular invasion

- Lymphatic or venous invasion
  - 0-57% (average 18%)
    - Envoi LI = 23% VI = 9%, Butte = 18.2%, Ueno = 30%, Kawachi = 32%
  - PPV for LN mets is low (5-30%)
    - Only 7.3% of Envoi cases with LI had LN mets; 30% in Ueno, 19.2% in Butte
  - NPV for LN mets may also be poor
    - 50% in Butte; 67% at Envoi, 9% in Kawachi (resections) had LN mets despite no lymphatic invasion seen

- Has lead to inaccuracy/uncertainty in the significance of this prognostic factor
Sometimes easy!!
Often subtle – need to look carefully
Orcein stain – excellent for venous invasion detection
3) Vascular invasion

<table>
<thead>
<tr>
<th></th>
<th>Residual disease</th>
<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (average)</td>
<td>18%</td>
<td>35% (LN)/5% (H)</td>
<td>3%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>1</td>
<td>7/2**</td>
<td>1.5</td>
</tr>
<tr>
<td>%/Odds ratio - Ueno</td>
<td>31%/3 (multivariate)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- usually associated with another adverse prognostic factor
- Vascular invasion does not add to risk when other adverse factors are already present
- Interobserver agreement is poor/moderate – 37-77%

Hassan et al Dis Colon Rectum 2005;48:1588-96
Ueno et al Gastroenterology 2004;127:385-94
4) Tumour budding

- Identified as a significant prognostic factor in several papers
  - Ueno et al Gastroenterology 2004;127:385-94
  - Tateishi et al Mod Path 2010;1:1-5
  - Katajima et al J Gastroenterol 2004;39:534-43
  - Kawachi et al Mod Path 2015***

- Uniform definition lacking – range from any budding to strict definitions
Tumour budding

• Japanese criteria
  – Budding/sprouting was counted in a field measuring 0.95mm$^2$ using a 20 × objective lens and 10 × ocular lens and classified as grade 1 (0–4 foci in the field), grade 2 (5–9 foci), or grade 3 (≥10 foci)
  – Only grade 2/3 is significant “high grade”
  – Kawachi et al = no cases with high grade budding metastasized if invasive ca was <1mm deep

• US criteria
  – ≥ 10 buds = “high grade”
Tumour budding

1) Reproducibility
   - Apparently high (AJSP 2015)
   - But lots more buds if you use keratin

2) Field area of $0.95\text{mm}^2 = \text{diameter 1.1mm}$ so polyps $<1\text{mm}$ are not reliably assessed and in the polyps reliably assessed it is probably not helpful to prognostication
4) Tumour budding

- Present in ~ 20-30% - however, bias to resection specimens in all studies (Envoi 29% - any)
- Risk
  - Kawachi – Odds ratio 3.14
- Prognostic relevance in malignant polyps treated only by endoscopy is still not established
- Perhaps tumour budding and poorly differentiated clusters should be merged into “high grade”
5) Polyp morphology

• Pedunculated vs sessile

• Sessile polyps have overall mortality 8 x that of pedunculated polyps

• Reason why sessile is worse = increased adverse factors are usually present:
  • poor differentiation
  • vascular invasion
  • positive resection margin**
5) Polyp morphology

- Overall increased risk for sessile polyps

- Risk for sessile polyp Vs pedunculated polyp – pooled analysis*

<table>
<thead>
<tr>
<th></th>
<th>Residual/recurrent disease</th>
<th>Metastasis</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (average) - S</td>
<td>11%/6%</td>
<td>10%(LN)/4% (H)</td>
<td>5%</td>
</tr>
<tr>
<td>% (average) - P</td>
<td>3%/0.5%</td>
<td>10%(LN)/1% (H)</td>
<td>0.5%</td>
</tr>
<tr>
<td>Odds ratio - Hassan</td>
<td>4</td>
<td>1/4</td>
<td>10</td>
</tr>
</tbody>
</table>

Hassan et al Dis Colon Rectum 2005;48:1588-96
*approximation (multivariate)

? not an independent risk for LN metastasis

However, most (85%) of sessile polyps had surgery
5) Polyp morphology

- Kawachi paper
  - slight increased risk for sessile polyps
  - but 80% of their polyps were sessile

- Envoi – no difference

- Problem
  - what is sessile and what is pedunculated?
    - Japanese series – 80% sessile
    - Western meta-analysis – 35% sessile
      - Pedunculated = presence of definite stalk
6) Rectal location

- Rectal location, in particular, the distal 1/3 of rectum is an adverse factor for:
  1. LN metastases (up to 1/3)
  2. Recurrent/Residual disease (5-28%)

  Haggitt et al  Gastroenterology 1985;89:328-36

- Reason is not clear from the literature
- Problem = surgery is ULAR or APR
6) Others

- **Cribriform pattern** – adverse in Ueno paper

- **Lymphatic density** – Kaneko et al Dis Colon Rectum 2006;50:1-9

- **Various IHC markers** – Matrix metalloproteinase expression, p53, p27 Misaki et al Hirano et al

- **Carcinomatous destruction of muscularis mucosae vs retained muscularis mucosae** Tateishi et al Mod Path 2010;1:1-5
  - LN met rate
    - destroyed – 16%
    - preserved - 2%

- **Polypoid carcinoma**
Pathological risk assessment
Risk factors are additive

Ueno et al Gastroenterology 2004;127:385-94

Adverse Qualitative

1. Poor differentiation
2. Vascular invasion (L or V)
3. Tumour budding
   (NOT margin involvement)

<table>
<thead>
<tr>
<th>Nº Factors</th>
<th>LN met risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.7%*</td>
</tr>
<tr>
<td>1</td>
<td>20.7%</td>
</tr>
<tr>
<td>≥2</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

* 7% micrometastasis rate

Adverse Quantitive

1. Width ≥ 4mm
2. Depth ≥ 2mm
3. Haggitt level 3/4

Adverse Quantitive + Adverse Qualitative
= did not change the LN metastasis risk
### Risk factors are additive

<table>
<thead>
<tr>
<th>Numbers of risk factors</th>
<th>Ueno’s 3 risk factors</th>
<th>p value</th>
<th>Poor differentiation, cribriform pattern and invasive depth &gt;2mm</th>
<th>p value</th>
<th>Poor differentiation, cribriform pattern and invasive width &gt;4mm</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3/149 (2.0%)</td>
<td>0.016</td>
<td>0/97 (0%)</td>
<td>&lt;0.0001</td>
<td>1/91 (1.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>4/49 (8.2%)</td>
<td></td>
<td>5/112 (4.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 or 3</td>
<td>5/41 (12.2%)</td>
<td>7/30 (23.3%)</td>
<td></td>
<td></td>
<td>3/116 (2.6%)</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>8/32 (25.0%)</td>
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</tr>
</tbody>
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Envoi data
Risk factors are not equal

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<thead>
<tr>
<th>Histologic parameters</th>
<th>Odds ratio</th>
<th>(95% confidence interval)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of submucosal invasion ≥ 1000 μm</td>
<td>5.56</td>
<td>(2.14–19.10)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High-grade budding/sprouting (grade 2 or 3)</td>
<td>3.14</td>
<td>(1.91–5.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>High histologic grade</td>
<td>1.88</td>
<td>(0.63–5.09)</td>
<td>0.25</td>
</tr>
<tr>
<td>Positive lymphatic invasion</td>
<td>1.53</td>
<td>(0.94–2.50)</td>
<td>0.09</td>
</tr>
<tr>
<td>Nonpedunculated type</td>
<td>1.49</td>
<td>(0.64–4.11)</td>
<td>0.37</td>
</tr>
<tr>
<td>Positive venous invasion</td>
<td>1.08</td>
<td>(0.67–1.74)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Kawachi et al Mod Path 2015
How should we approach the MCP?
Size – as per Japanese

- **<1mm deep and <2mm wide**
  - Lymph node risk = 0% (no matter what other factors are present)

- **1-2mm deep or 2-4mm wide**
  - Lymph node risk = 0-5%
  - (other adverse factors may additive to 10%)

- **>2mm deep or >4mm wide**
  - Lymph node risk = 5-10%
  - (other adverse factors additive to 10-20%)

Adverse factor risk: Poor differentiation > tumour budding > LVI > rectal site
Margin involvement = 10-15% risk of residual adenoma or adenocarcinoma at polypectomy site
The haematogenous metastasis rate is <1-2% (with adverse risk factors)
Piecemeal specimen

• Measure size of largest piece of invasive adenocarcinoma
  – If >2mm deep and >4mm wide then adverse
  – Other factors add to the risk
  – If <1mm deep and <2mm wide and only in one piece → no risk

• Margin status requires endoscopic determination
<table>
<thead>
<tr>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong> <em>(as per Japanese)</em></td>
</tr>
<tr>
<td>Depth of invasion (mm)</td>
</tr>
<tr>
<td>Width of invasion (mm)</td>
</tr>
<tr>
<td>Haggitt ± Kikuchi/Kudo level <em>(optional)</em></td>
</tr>
<tr>
<td><strong>Differentiation/grade</strong> <em>(based on least differentiated area)</em></td>
</tr>
<tr>
<td><strong>Tumour budding</strong> <em>(high level)</em></td>
</tr>
<tr>
<td><strong>Lymphatic invasion</strong></td>
</tr>
<tr>
<td><strong>Venous invasion</strong></td>
</tr>
<tr>
<td><strong>Margin status</strong></td>
</tr>
<tr>
<td>Clearance <em>(carcinoma to margin - deep/circumferential)</em></td>
</tr>
<tr>
<td><strong>Mismatch repair IHC:</strong></td>
</tr>
<tr>
<td><strong>Adjacent adenoma type</strong> <em>(if present)</em></td>
</tr>
</tbody>
</table>
| **Comment .....**
‘Intramucosal’ adenocarcinoma

• Tis in TNM
• Vienna classification (Japan/Europe)
• Just high grade dysplasia (HGD) in USA

• Increasingly encountering invasive adenocarcinoma with extension into a thickened reduplicated muscularis mucosae but not through this layer
• HGD does not seem appropriate but any metastatic risk
Pseudoinvasion

- 2-10% pedunculated polyps
- Left colon (sigmoid)
- Prolapse of dysplastic mucosa into submucosa following polyp torsion
- Note: can be associated with true invasive carcinoma
- Distinction from invasive carcinoma
  1. Architecture
  2. Stromal change
  3. Cytology
Pseudoinvasion - architecture

- Narrow gap in muscularis mucosae
  Tanazawa et al. Pathology International. 2003;53: 584–590
- Rounded appearance to focus
- Rounded appearance of glands within focus
Pseudoinvasion - stroma

- Lamina propria surrounds glands
- Dense fibrosis (not desmoplasia)
- Smooth muscle hypertrophy (and ‘fibromuscular’)
- Haemosiderin
- Chronic inflammation
- Extravasated mucin
  - No epithelium or epithelium at edge – not epithelium floating in mucin pools
Pseudoinvasion

Invasive carcinoma
Vs

Pseudoinvasion vs Invasive carcinoma
Pseudoinvasion - cytology

- Same as in overlying mucosa
- Pseudoinvasion of non-dysplastic normal epithelium

- If it looks like invasive carcinoma – it probably is!
Pseudoinvasion - other

- p53 negative
- MMP-1 and Stromelysin-3 - negative

Usually does not matter if we get it wrong since pseudoinvasive focus is clear of margin, vascular invasion negative and not poorly differentiated
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