Management of pT1 polyps

Maria Pellise
0.75–5.6% of large-bowel polyps removed in general diagnostic colonoscopy practice

10% of detected cancers (British BCSP)

Screening programmes

Advances in diagnostic & therapeutic endoscopy

Early colorectal cancer

Malignant polyp

SM Invasive adenocarcinoma

pT1 polyps

Early Cancers Classification According to Depth of Invasion

- Epithelial Layer
- Lamina Propria
- Muscularis Mucosae
- Submucosa

ENDOSCOPIC TREATMENT

LYMPHATIC INVOLVEMENT

Tis

T1

T1sm

T2

m1, m2, m3, sm1, sm2, sm3

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M, 57yo, FIT +
10mm rectal sessile polyp; 8cm from anal verge
Invasive adenocarcinoma within a tubular adenoma

- Tumor size: 8mm
- Adenoma size: 9mm
- Depth of submucosal invasion: 2mm
- Low grade histology (moderately differentiated)
- Absence of lymphovascular invasion
- Absence of perineural invasion
- Negative margin
- pTNM Staging: pT1
Recurrence can be lethal

Recurrence rate: 1–5%

**BANKER**

**GAMBLER**

**SURGERY**

Morbidity
Anastomotic leak - mortality rate up to 3-6%
Costs

**FOLLOW-UP**

Under-staging
Local recurrence
Systemic recurrence

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Management of pT1 polyps

- No RCT
- Heterogeneity and deficiencies in reporting histology
- Heterogeneity and deficiencies in reporting endoscopic data
- Surgical series
- Different outcomes measures
- Clinical significant outcomes are rare events
Incidence of synchronous LNM in pT1= 6–12%
Risk factors for LNM in pT1 surgical series:

- poor differentiation
- lymphovascular invasion
- presence of positive (R1) or unable to determine (Rx) resection margins
- deep submucosal invasion (i.e., ≥1,000 μm/SM2–3 in non-pedunculated tumors, and Haggitt 4 in pedunculated tumors)
- presence of intense tumor budding
- Rectal location
- Sessile or flat morphology
- Clusters of undifferentiated cells
<table>
<thead>
<tr>
<th>Factor</th>
<th>Studies, n</th>
<th>References</th>
<th>Patients, n</th>
<th>Low risk group</th>
<th>LNM+/total</th>
<th>LNM, %</th>
<th>High risk group</th>
<th>LNM+/total</th>
<th>LNM, %</th>
<th>RR [95%CI]</th>
<th>P value¹</th>
<th>Heterogeneity²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location</td>
<td>10</td>
<td>[28,38,45–47,49–51,53, 55]</td>
<td>2722</td>
<td>Colon</td>
<td>169/1699</td>
<td>9.9</td>
<td>Rectum</td>
<td>141/1023</td>
<td>13.8</td>
<td>1.4 [1.1–1.7]</td>
<td>&lt;0.001</td>
<td>x² = 8.12</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>10</td>
<td>[28,44–48,50,53–55]</td>
<td>1931</td>
<td>Negative</td>
<td>71/1324</td>
<td>5.4</td>
<td>Positive</td>
<td>162/607</td>
<td>26.7</td>
<td>5.2 [4.0–6.8]</td>
<td>&lt;0.001</td>
<td>x² = 8.74</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>10</td>
<td>[28,44–48,50,53–55]</td>
<td>1931</td>
<td>Negative</td>
<td>154/1552</td>
<td>9.9</td>
<td>Positive</td>
<td>79/379</td>
<td>20.8</td>
<td>2.2 [1.4–3.2]</td>
<td>&lt;0.001</td>
<td>x² = 17.32</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>5</td>
<td>[38,42,49,51,52]</td>
<td>1332</td>
<td>Negative</td>
<td>75/1053</td>
<td>7.1</td>
<td>Positive</td>
<td>73/332</td>
<td>22.0</td>
<td>3.9 [2.7–5.6]</td>
<td>&lt;0.001</td>
<td>x² = 4.30</td>
</tr>
<tr>
<td>Submucosal invasion depth (cut-off 1 mm)</td>
<td>5</td>
<td>[38,42,47,48,51]</td>
<td>1835</td>
<td>&lt;1 mm</td>
<td>6/405</td>
<td>1.5</td>
<td>≥1 mm</td>
<td>176/1430</td>
<td>12.3</td>
<td>5.2 [1.8–15.4]</td>
<td>&lt;0.003</td>
<td>x² = 6.26</td>
</tr>
<tr>
<td>Submucosal invasion depth (cut-off 2 mm)</td>
<td>3</td>
<td>[42,47,51]</td>
<td>1463</td>
<td>&lt;2 mm</td>
<td>25/464</td>
<td>5.4</td>
<td>≥2 mm</td>
<td>133/999</td>
<td>13.3</td>
<td>2.4 [1.6–3.7]</td>
<td>&lt;0.001</td>
<td>x² = 1.55</td>
</tr>
<tr>
<td>Submucosal invasion width (cut-off 5 mm)</td>
<td>3</td>
<td>[42,51,53]</td>
<td>620</td>
<td>≤5 mm</td>
<td>12/213</td>
<td>5.6</td>
<td>≥5 mm</td>
<td>69/407</td>
<td>16.9</td>
<td>2.7 [1.4–5.4]</td>
<td>&lt;0.004</td>
<td>x² = 2.40</td>
</tr>
<tr>
<td>High vs. low grade histology</td>
<td>13</td>
<td>[8,38,40,42,44,45,47,48, 51–55]</td>
<td>2847</td>
<td>Low grade</td>
<td>229/2578</td>
<td>8.9</td>
<td>High grade</td>
<td>66/269</td>
<td>24.5</td>
<td>4.8 [3.3–6.9]</td>
<td>&lt;0.001</td>
<td>x² = 16.04</td>
</tr>
<tr>
<td>Budding</td>
<td>7</td>
<td>[42,44,46,47,51,54,55]</td>
<td>1991</td>
<td>Negative</td>
<td>59/1173</td>
<td>5.0</td>
<td>Positive</td>
<td>174/818</td>
<td>21.3</td>
<td>5.1 [3.6–7.3]</td>
<td>&lt;0.001</td>
<td>x² = 7.54</td>
</tr>
<tr>
<td>Poor differentiation at invasive front</td>
<td>4</td>
<td>[45–47,51]</td>
<td>1307</td>
<td>Negative</td>
<td>111/1083</td>
<td>10.2</td>
<td>Positive</td>
<td>48/250</td>
<td>19.2</td>
<td>2.5 [1.8–3.5]</td>
<td>&lt;0.001</td>
<td>x² = 0.04</td>
</tr>
</tbody>
</table>

CI: confidence interval; LNM, lymph node metastasis; RR, relative risk.

* This result is mainly based on one large study [47], which contributed 69.6% of the weight in this analysis.
¹ P value of effect size.
² P value for heterogeneity.
## Accuracy for predicting LNM

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor location in rectum</td>
<td>45.5</td>
<td>63.4</td>
<td>13.8</td>
<td>90.1</td>
</tr>
<tr>
<td>Lymphatic invasion +</td>
<td>69.5</td>
<td>73.8</td>
<td>26.7</td>
<td>94.6</td>
</tr>
<tr>
<td>Vascular invasion +</td>
<td>33.9</td>
<td>82.3</td>
<td>20.8</td>
<td>90.1</td>
</tr>
<tr>
<td>Lymphovascular invasion +</td>
<td>49.3</td>
<td>79.1</td>
<td>22.0</td>
<td>92.8</td>
</tr>
<tr>
<td>Submucosal invasion depth ≥ 1 mm</td>
<td><strong>96.7</strong></td>
<td><strong>24.1</strong></td>
<td>12.3</td>
<td>98.5</td>
</tr>
<tr>
<td>Submucosal invasion depth ≥ 2 mm</td>
<td>84.2</td>
<td>33.6</td>
<td>13.3</td>
<td>94.6</td>
</tr>
<tr>
<td>Submucosal width of invasion ≥ 5 mm</td>
<td>85.2</td>
<td>37.3</td>
<td>17.0</td>
<td>94.4</td>
</tr>
<tr>
<td>High grade histology</td>
<td>22.4</td>
<td>92.0</td>
<td>24.5</td>
<td>91.1</td>
</tr>
<tr>
<td>Budding</td>
<td>74.7</td>
<td>63.4</td>
<td>21.3</td>
<td>95.0</td>
</tr>
<tr>
<td>Poor differentiation at invasive front</td>
<td><strong>30.2</strong></td>
<td><strong>82.8</strong></td>
<td>19.2</td>
<td>89.8</td>
</tr>
<tr>
<td>sm2/3 (vs. sm1)</td>
<td>92.7</td>
<td>30.4</td>
<td>16.8</td>
<td>96.6</td>
</tr>
<tr>
<td>sm3 (vs. sm1/2)</td>
<td>72.0</td>
<td>63.5</td>
<td>22.6</td>
<td>93.9</td>
</tr>
</tbody>
</table>

NPV, negative predictive value; PPV, positive predictive value.
## Indications for additional treatment

<table>
<thead>
<tr>
<th></th>
<th>NCCN</th>
<th>ESMO</th>
<th>JSCCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor differentiation</td>
<td>+ (grade 3,4)</td>
<td>+ (grade 3)</td>
<td>+ (poorly differentiated; signet ring; mucinous)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Resection margin</td>
<td>+</td>
<td>+</td>
<td>+ (vertical)</td>
</tr>
<tr>
<td>Submucosal depth invasion</td>
<td>+ (Level 4)</td>
<td>+ (≥ 1mm)</td>
<td>+ (grade 2 or 3)</td>
</tr>
<tr>
<td>Tumor budding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Artificial intelligence predictive model

<table>
<thead>
<tr>
<th></th>
<th>Artificial intelligence, % (95%CI)</th>
<th>NCCN, % (95%CI)</th>
<th>ESMO, % (95%CI)</th>
<th>JSCCR, % (95%CI)</th>
<th>P value Artificial intelligence vs NCCN</th>
<th>P value Artificial intelligence vs ESMO</th>
<th>P value Artificial intelligence vs JSCCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100 (72 to 100)</td>
<td>100 (72 to 100)</td>
<td>100 (72 to 100)</td>
<td>100 (72 to 100)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Specificity</td>
<td>66 (56 to 76)</td>
<td>44 (34 to 55)</td>
<td>0 (0 to 3)</td>
<td>0 (0 to 3)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PPV</td>
<td>23 (11 to 38)</td>
<td>15 (7 to 27)</td>
<td>9 (4 to 16)</td>
<td>9 (4 to 16)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NPV</td>
<td>100 (95 to 100)</td>
<td>100 (93 to 100)</td>
<td>–</td>
<td>–</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Accuracy</td>
<td>69 (59 to 78)</td>
<td>49 (39 to 59)</td>
<td>9 (4 to 16)</td>
<td>9 (4 to 16)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unnecessary additional surgery</td>
<td>77 (62 to 89)</td>
<td>85 (73 to 93)</td>
<td>91 (84 to 96)</td>
<td>91 (84 to 96)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missed LNM</td>
<td>0 (0 to 3)</td>
<td>0 (0 to 3)</td>
<td>0 (0 to 3)</td>
<td>0 (0 to 3)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

---

**Rate of additional unnecessary surgeries**

- Artificial intelligence: 29%
- NCCN: 50%
- ESMO: 80%
- JSCCR: 86%

**Missing rate of LNM-positive**

- Artificial intelligence: 0%
- NCCN: 0%
- ESMO: 0%
- JSCCR: 0%
It is not clear that surgery of a pT1 completely resected with high risk for LNM decreases mortality
Dutch T1 CRC working group

- Retrospective cohort study. Patients with T1 CRC diagnosed between 2000 and 2014 in 13 academic and non-academic hospitals.
- Netherlands Cancer Registry.
- Median follow-up time of 36.5 months (interquartile range 16.0–68.3)

Patients with pT1 CRC 2000-2014
13 Hospitals
N=2253

Patients included
N=1691
708 pedunculated
905 sessile or flat morphology

Endoscopic resection of pT1CRC
N=925
Macroscopic complete resection N=877

Endoscopic resection only
Wait and see
N=519

Low risk N=121
High risk N=198
Unknown N=200

Primary surgical resection
N=758
Including TAMIS N=105

Secondary surgery
N=358
High risk
N=602
Including N=282 of secondary surgeries

Surgical resection and low risk or undefinable risk
N=440
Including secondary surgeries low risk
N=19; unknown N=57

Backes Y et al. Am J Gastro 2017; Overwater et al. Gut 2018; Bakes Y Gastroenterol 2018

High-risk T1 CRC if one or more:
- poor differentiation,
- deep submucosal invasion (i.e., ≥1,000 μm/SM2–3 in non-pedunculated tumors, and Haggitt 4 in pedunculated tumors),
- lymphovascular invasion,
- positive (R1) or unable to determine (Rx) resection margins.

R0 resection was defined as a cancer-free resection margin irrespective of distance in millimeters.
Endoscopic resection before surgical resection of a high-risk T1 CRC has no adverse effect.

Of all T1 CRCs treated with surgical resection, still 5% develops a local or distant recurrence.

CRC-related death among patients with recurrence: 41.7%

The decision to conduct a wait-and-see policy in high-risk T1 CRC should be cautiously made given the poor prognosis when cancer recurs.

Previous biopsies of the scar negative for cancerous tissue did not guarantee recurrence free survival.

There is an increasing need for identification of malignant polyps before endoscopic resection to guide resection technique and optimise specimen handling.
N= 485
Follow up =50 months (minimum 16 months).

- Cancer related death = 1.3%-2.8% ONLY!
- Systemic recurrence > local recurrence
- ¾ undergo surgery have no evidence of residual tumor
- independent predictors of residual tumour, disease recurrence and cancer-related death:
  - evidence of lymphovascular invasion
  - Incomplete excision

Therapeutic technique
pT1 good prognosis. Margin < 1mm

Impossible to identify the postpolypectomy scar

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KEEP CALM
AND
KNOW YOUR ENEMY
Paris classification

Polypoid
- Pedunculated: 0-Ip
- Sessile: 0-Is
- Mixed: 0-Isp

Non polypoid
- Slightly elevated
- Totally flat
- Slightly depressed

% sm invasion
- 11-15mm: 8%
- 16-20mm: 17%
- >20mm: more
- 6-10mm: 44%
- 11-15mm: 67%
- 16-20mm: 90%

Lambert R, Lightdale C. Gastrointest Endosc 2003;58 suppl6
Risk of Occult Submucosal Invasive Cancer (SMIC) According to Gross Morphology and Location

<table>
<thead>
<tr>
<th>Type</th>
<th>Proximal (%)</th>
<th>Distal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-Ila G</td>
<td>0.7%</td>
<td>1.2%</td>
</tr>
<tr>
<td>0-Ila NG</td>
<td>3.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>0-Ila+Is G</td>
<td>4.2%</td>
<td>10.1%</td>
</tr>
<tr>
<td>0-Ila+Is NG</td>
<td>12.7%</td>
<td>15.9%</td>
</tr>
<tr>
<td>0-Is G</td>
<td>2.3%</td>
<td>5.7%</td>
</tr>
<tr>
<td>0-Is NG</td>
<td>12.3%</td>
<td>21.4%</td>
</tr>
</tbody>
</table>

A typical proximally located 0-Ila Granular Lesion. Overall risk of SMIC 0.7%.

A proximal 0-Ila Non-Granular Lesion. Overall risk of SMIC 3.5%.

A rectal (distal) 0-Ila+Is Granular Lesion. Overall risk of SMIC 10.1%.

A transverse colon (proximal) 0-Ila+Is Non-Granular Lesion. Overall risk of SMIC 12.7%.

A sigmoid colon (distal) 0-Is Granular Lesion. Overall risk of SMIC 5.7%.

A ascending colon (proximal) 0-Is Non-Granular Lesion. Overall risk of SMIC 12.3%.

Burgess et al. Gastroenterol 2018
Superficial focal interrogation:
Pit & Microvascular pattern
## NBI International Colorectal Endoscopic classification (NICE)

<table>
<thead>
<tr>
<th>Western countries</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td><img src="Hyperplastic.jpg" alt="Image" /></td>
<td><img src="Adenoma.jpg" alt="Image" /></td>
<td>![Image](Deep submucosal invasion.jpg)</td>
</tr>
<tr>
<td>Vessels</td>
<td><img src="Hyperplastic.jpg" alt="Image" /></td>
<td><img src="Adenoma.jpg" alt="Image" /></td>
<td>![Image](Deep submucosal invasion.jpg)</td>
</tr>
<tr>
<td>Surface</td>
<td><img src="Hyperplastic.jpg" alt="Image" /></td>
<td><img src="Adenoma.jpg" alt="Image" /></td>
<td>![Image](Deep submucosal invasion.jpg)</td>
</tr>
<tr>
<td>Most likely histology</td>
<td>Hyperplastic</td>
<td>Adenoma</td>
<td>Deep submucosal invasion</td>
</tr>
</tbody>
</table>
58 endoscopists
17 centers
Polyps > 10mm
Prediction of deep SM invasion

Eeligible participants
n=1650

Participants included
n=1634

Lesions included
n=2136

No NICE 3
n=2004

NICE 3
n=132

No histology
n=4

Non-deep invasion
n=1961 98.1%

Deep invasion
n=37 1.9%

No histology
n=7

Non-deep invasion
n=73 58.4%

Deep invasion
n=52 41.6%

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Puig et al. under revision
NICE classification

1. Depressed area
   - NO
   - LST-G nodular mixed type p<0.001
     - NO
       - 1% (n=1812)
     - YES
       - 8.6% (n=93)
   - YES
     - 9.7% (n=93)
   - Pedunculated p=0.007
     - NO
     - 13% (n=31)
   - Ulceration p=0.026
     - NO
     - 44% (n=80)
     - YES
     - 93% (n=14)

Puig et al. Under revision

✓ Similar results for LNM risks
Puig et al. under revision

- NICE type 2 with depressed areas,
- NICE type 2 nodular mixed type
- NICE type 3 non-pedunculated polyps without ulceration
Final Remarks

(Too) Many open questions!

Imperative need for:
✓ standardisation of histological criteria, endoscopic description
✓ Multidisciplinary consensus protocols
✓ Large prospective cohort studies
✓ Prospective randomised controlled trials?

Improve identification of malignant polyps before endoscopic resection:
• In large polyps
• In small polyps

Talk to your pathologist!
Talk to your surgeon!
Thank you!!