Colon Cancer Follow-up

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R 5
Case

- 64 years old women bleeding P/R and bowel habit changes colonoscopy showed near obstructing sigmoid colon cancer
- LFT normal, CEA increased
- Surgery sigmoid resection
- Pathology showed invasion of submucosa and local lymphnode +ve (stage 3)
- Course of chemotherapy and now asymptomatic
- What next?
Follow-Up

- Visit – History and Physical
- Blood test
  - CBC
  - LST
  - CEA
- Imaging
  - Direct
    - Colonoscopy
    - Sigmoidoscopy
  - Radiology
    - Chest Xray
    - Ultrasound
    - Barium Enema
    - CT Scan
    - PET Scan
Aims of follow-up

- Detect recurrent disease and earlier detection of potentially curable recurrence
- Detect metachronous tumours, (Polyps and Cancer)
- Patient support & reassurance
- To measure the efficacy of original therapy and positive feedback
- To offer palliative therapy for symptomatic recurrence
- Provide information for audit and clinical trials
RECURRENTS

- USA - 147,000 colorectal cancer diagnosed per year
- 80% - local and locally advanced cancer – curative surgery
- 30-50% after primary surgery
- 80% within 2 years; rare after 5 years
  Rosen et al 1998
- By stage
  Dukes A: 15%
  Dukes B: 30%
  Dukes C: 70%
TYPES OF RECURRENCES

Loco-regional recurrences:
- 10% (50% are symptomatic), Barillari et al 1996
- 60 - 90% have distant spread
- In isolated recurrences curative resection in 28% - 50% develop further recurrence

Liver metastasis (40%):
- 12 – 25% have liver metastases and no extra hepatic disease
- 45 – 55% of these are potentially resectable for cure
- Less than 5% will have solitary lesions
- In those resected: 25 - 35% chance of 5 year survival
- With chemotherapy survival is between 12 - 16 months
- Without chemotherapy 6 months

Lung metastasis (10 - 20%):
- 1.3 – 4% are candidate for resection
METACHRONOUS LESIONS

Cancer
• Annual incidence: 0.35%
• Cumulative incidence @ 18 years: 6% - Cali et al, DCR 1993
• Highest incidence: 5 - 12 years - Safi et al 1993

Adenomas
• 50% overall incidence
Meta-analysis

- Rosen 1998
- Kievet 2000
- American Society of Clinical Oncology 1999
- Cochrane review 2002
- Renehan 2002
- Clinical review – Mayerhardt 2002
### Aims of study

To assess the value of surgical intervention for recurrent colorectal cancer based on rising carcinoembryonic antigen (CEA) levels.

### Study design

- **RCT, 5 year follow-up.**
- CEA monitored monthly (blind), years 1–3, 3 monthly years 4–5 after primary resection, in 1447 patients; randomised 1982–93 if CEA rose significantly.

<table>
<thead>
<tr>
<th>“Aggressive” (A) group (n=108)</th>
<th>“Conventional” (C) group (n=108): clinician not informed of CEA rise.</th>
</tr>
</thead>
</table>

### Patient characteristics

- All apparently disease-free at clinical examination before CEA rise observed; symptomatic patients excluded.

### Outcome Measures

- 5 year survival; number undergoing 2nd look surgery.

### Results

- **Survival:** Group A: 20.4% at 5 years; group C: 22%.
- Survival Hazard ratio for “conventional” to “aggressive” 0.84 (95% CI: 0.62, 1.13).
- 62% in aggressive, 23% in conventional group had 2nd look surgery.

### Comments

- More detailed questioning showed some apparently disease free patients did have symptoms.
- Trial closed following recommendation that survival advantage for second-look surgery highly unlikely.
Ohlsson 1995, Sweden

<table>
<thead>
<tr>
<th>Aims of study</th>
<th>Study design</th>
<th>Patient characteristics</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>To compare intensive follow-up with no follow-up after curative surgery for colorectal cancer.</td>
<td>RCT, 5-year follow-up. 107 patients randomised 1983–6, 3 months after primary surgery &amp; colonoscopy to remove polyps. <strong>Intensive follow-up (FU) group</strong> (n=53): frequent clinical examination for &gt;5 years, plus colonoscopy, CT (in patients who underwent APER), lung x-ray, liver function tests, CEA &amp; FOBT monitoring. <strong>Control group</strong> (n=54): no follow-up.</td>
<td>Mean age 66, 33% tumour in rectum, 66% colon. Exclusions: patients with distant metastases, also those in whom age or severe illness might preclude treatment of recurrent disease.</td>
<td>5-year and cancer-specific survival. Tumour recurrence. Test that first signalled recurrence.</td>
<td>5 year survival, 75% in FU group, 67% in controls (p&gt;0.05); corresponding cancer-specific survival rates 78% and 71%. Tumour recurred in 33%. FU group: recurrence first signalled by symptoms in 47%, CEA in 41%. Controls: symptoms first sign of recurrence in 83%.</td>
<td>Authors conclude that intensive follow-up did not improve survival. However the study was too small to be conclusive.</td>
</tr>
</tbody>
</table>
Makela 1995, Finland

<table>
<thead>
<tr>
<th>Aims of study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>To assess the value of intensified follow-up after curative surgery for colorectal cancer.</td>
<td>RCT, 5 year follow-up. 106 consecutive patients randomised after primary surgery, 1988–90. All seen in outpatient clinic 3 monthly for 2 years, then 6 monthly; FOBT &amp; CEA tests, chest x-ray, CBC count. <strong>Intensified follow up group</strong> (n=52): yearly colonoscopy, sigmoidoscopy 3 monthly for rectal or sigmoid cancer. Liver ultrasound 6 monthly, CT scan yearly. <strong>Conventional group</strong> (n=54): barium enema yearly, rigid sigmoidoscopy 3 monthly if rectal cancer.</td>
<td>Mean age 66, no information on exclusions. 26% stage A, 45% stage B, 28% stage C. 29% had rectal tumours, 71% colon (including sigmoid).</td>
<td>Time of detection of recurrence, resectability &amp; survival.</td>
<td>Cumulative 5 year survival 59% in intensive group, 54% in controls (p=0.5). Recurrence identified earlier in intensive group (mean 10 vs. 15 months) Endoscopy &amp; ultrasound useful, not CT. Reresections on 22% of intensive group, 14% of conventional group. Over half asymptomatic when recurrence diagnosed.</td>
<td>Authors conclude that more intensive follow-up does not improve survival. However the study was too small to be conclusive.</td>
</tr>
<tr>
<td>Study</td>
<td>No. of Patients</td>
<td>Randomization and Stage</td>
<td>Intensive Follow-Up Group</td>
<td>Control Group Follow-Up</td>
<td>Recurrence</td>
</tr>
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<tr>
<td>Pietra et al[^4]</td>
<td>207</td>
<td>Randomized after surgery</td>
<td>Physical exam, ultrasound, CEA every 3 mo × 2 yr then every 6 mo × 3 yr then every 1 yr</td>
<td>Physical, ultrasound, CEA every 6 mo × 2 yr then every 1 yr</td>
<td>Recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All patients had one full colonoscopy 3 months after surgery if not performed prior to surgery</td>
<td>Chest x-ray, colonoscopy and CT scan every yr</td>
<td>Chest x-ray, colonoscopy every 1 yr</td>
<td>Ext. 25%</td>
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<tr>
<td></td>
<td></td>
<td>Dukes B (59%), Dukes C (41%)</td>
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<tr>
<td>Shoemaker et al.</td>
<td>325</td>
<td>Randomization and Dukes Stages</td>
<td>Intensive Follow-Up Group</td>
<td>Control Group Follow-Up</td>
<td>Curative Attempts</td>
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</tr>
<tr>
<td></td>
<td>325</td>
<td>• Randomized after surgery</td>
<td>• History, physical exam, complete blood count, liver function tests, CEA, fecal occult blood every 3 mo × 2 yr then every 6 mo × 3 yr</td>
<td>• History, physical exam, complete blood count, liver function tests, CEA, fecal occult blood every 3 mo × 2 yr then every 6 × 3 yr</td>
<td>int. 34% v Cont.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dukes A (22%), Dukes B (47%), Dukes C (28%)</td>
<td>• Chest x-ray, CT liver, colonoscopy every 1 yr</td>
<td>48%</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

*Note:* The table details include randomized patients, Dukes stages, follow-up procedures, recurrence rates, curative attempts, and survival rates. The table compares intensive and control group follow-ups with different recurrence and survival outcomes.
<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Randomization and Dukes Stages</th>
<th>Intensive Follow-Up Group</th>
<th>Control Group Follow-Up</th>
<th>Recurrence</th>
<th>Curative Attempts*</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>597</td>
<td>- Randomized after radical surgery and clearance of remaining colon by colonoscopy or double contrast barium enema</td>
<td>- History, physical exam, digital rectal examination, gynecological examination, fecal occult blood test, colonoscopy, chest x-ray, hemoglobin, erythrocyte sedimentation rate, liver enzymes at 6, 12, 18, 24, 30, 36, 48, 60, 120, 150, 180 mo</td>
<td>- Same as intensive follow-up but at 60, 120, 180 mo only</td>
<td>int. 26% vs Cont. 26%</td>
<td>int. 22% vs Cont. 7%</td>
<td>int. 70% vs Cont. 68% at 5 yr ($P = .48$)</td>
</tr>
</tbody>
</table>
Visit – History and Physical

- No data which addresses this issue and value is uncertain
- Regular visit facilitate better coordination
- 78% felt "rather reassured" or "very reassured" by follow up Stiggelboult et al, 1997
- Patients have greater confidence in check-ups Kjelsden et al 1999
- Routine physical examination is the first indication of recurrence in only 0-6%
- Symptoms / Signs: first sign of relapse in 21-48%
- Only 45-55% have asymptomatic recurrences despite follow-up (Tornquist et al 1982)
- Recommendation by ASCO – every 3 –6 months for 3 years and then annually
CEA

- 9% Increase in 5 yr survival rate in intense follow-up using CEA (Brunivels et al 1994)
- CEA should not be omitted in patients with normal pre-op levels (Tobaruela et al, 1997)
- 1st indication of tumour recurrence in 60%
- Sensitivity around 80% (17% - 89%)
- 30% do not express antigen
- False positive in 5 - 16%
- Better for distant recurrences, SHPIC 1999
- Median lead time: 6 months (range 1-30 months), McCall et al 1994
- Recommendation by ASCO at each visit
LFTs
• Recommendation by ASCO against LFTs
• 1971 Baden 327 patients - increased LFTs in 77% but 34% false +ve and few recurrence normal LFTs.

CBC
• ASCO panel against CBC

FOB
• ASCO panel against FOB
• Ohlesson – 3 recurrence found on FOB

Plain chest X-ray
• ASCO panel against chest X-ray
• Should be done if CEA is elevated
Ultrasound
• Sensitivity 53-83% limited role and operator dependent
• ASCO panel against ultrasound but ESCMO suggest annual ultrasound time x 3

CT Scan
• Sensitivity 61%
• Preferred method of detection of local recurrence and sensitivity is 95%, can show anastomosis, tumor bed and lymph node
• Makela – 2/22 recurrences before CEA increased
• Shoemaker – 10/14 recurrences while asymptomatic and 3 curative resections
• ASCO advises against routine CT

PET Scan
• Sensitivity 90 – 100%
• Useful in detection of distant metastasis
• Useful when increased CEA but normal CT Scan
Colonoscopy

The main reasons for performing a colonoscopy is to

1. identify patients with metachronous polyps,
2. to detect metachronous cancers and
3. to check the anastomotic site for recurrences.

- Colonoscopy was performed on an annual basis but there is now clear evidence that there is no role for annual colonoscopy. This is based on the better understanding of the polyp-carcinoma sequence.
- The current evidence suggests that colonoscopy should be carried out at 3-5 yearly intervals after making sure that the residual colon is free of synchronous polyps / tumours either around the time of the operation or 6 months later.
- Patients who did not undergo complete colonoscopy or barium enema before surgery should be offered a colonoscopy within six months of the primary operation.
**Meta-analysis by Renehan et al, BMJ 2002**

In intensive follow-up group
- Reduction in all cause mortality
- Earlier detection of all recurrences
- Increased detection rate for isolated local recurrences
- Absolute reduction in mortality of 9-13%

**Meta-analysis Bruinvels et al 1994**

- Increase in 5 yr survival for patients undergoing close monitoring.
- 9% Increase in survival rates of patients undergoing CEA monitoring
Meta-analysis by Rosen et al
DCR 1998

In intensive follow-up group:
• Higher cumulative 5-year survival
• More curative re-resections for recurrent cancer
• Higher survival rates for patients with recurrent cancer

The meta-analysis published by Rosen et al in 1998, which included 2005 patients (from two randomized and three comparative-cohort studies), found that in the intensive follow-up group:
• Cumulative 5-year survival was 1.16 times higher (P=0.003)
• Two and a half times more curative re-resections were performed for recurrent cancer (P=0.0001)
• Survival rates for patients with recurrent cancer was 3.62 times higher than the control (P=0.0004)
CONCLUSIONS FROM MAJOR STUDIES

Colorectal cancer follow-up (Review article), Kievit 2000

• Early recognition of cancer recurrences and metastases may have a marginally positive effect on outcome
• Post-op follow-up of CRC may improve survival by 1-2%
• Larger studies able to demonstrate better follow-up effectiveness
COSTS

NGICG, 1997 (CEA, US Liver (8), CxR (6), Colonoscopy (2))
- Basic cost of F/U programme: £ 1232 per patient
- Extended Ix for suspected relapse: £ 1943
- Cost per life year saved: £ 9525 - £ 16192

Makela cost of F/U $910 - $ 27000

Audsio
- cost of F/U was $1914000 141 recurrence – 18 were cured second operation (106,383 dollars per patient cured)
- Medicare cost per recurrence 1995
  - CEA $ 5696
  - Chest X - ray $ 10078
  - Colonoscopy $ 45810
Among these CEA was only cost effective
CONCLUSIONS FROM MAJOR REPORTS

Scottish Health Purchasing Information Centre (1999)
• Intensive follow-up is not worthwhile after curative surgery for colorectal cancer.

NHS Centre for Reviews and Dissemination (1997)
• There is insufficient evidence to justify routine follow-up.
• Reduction in intensity of follow-up may result in considerable savings with no reduction in quality of life.

Scottish Inter-Collegiate Guidelines Network (SIGN)
• No Intensive follow-up for patients who are not fit for further intervention
• Colonoscopy every 3-5 years after ensuring that the colon is free of synchronous benign & malignant tumours
• Hepatic imaging should be considered and, if carried out, should be undertaken at regular intervals in the first 2 - 3 years after surgery
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Percent recurrence</th>
<th>Recurrence time in months</th>
<th>Surgery percent</th>
<th>5-year survival percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish[4]</td>
<td>106</td>
<td>42 vs 39</td>
<td>10 vs 15</td>
<td>22 vs 19</td>
<td>59 vs 54</td>
</tr>
<tr>
<td>Swedish[5]</td>
<td>107</td>
<td>32 vs 33</td>
<td>20 vs 24</td>
<td>9.4 vs 5.5</td>
<td>75 vs 67 (Cancer specific = 78 vs 71)</td>
</tr>
<tr>
<td>Danish[18]</td>
<td>597</td>
<td>26 vs 26</td>
<td>18 vs 27</td>
<td>22 vs 7</td>
<td>70 vs 68</td>
</tr>
<tr>
<td>Australian[19]</td>
<td>325</td>
<td>33 vs 40</td>
<td>N/A</td>
<td>5 vs 6</td>
<td>76 vs 70</td>
</tr>
<tr>
<td>Italian[20]</td>
<td>207</td>
<td>colon 16 vs 13 rectum 45 vs 29</td>
<td>10.3 vs 20.2</td>
<td>65 vs 10</td>
<td>72 vs 58</td>
</tr>
<tr>
<td>Meta-analysis[6] (Bruinvels)</td>
<td>2824</td>
<td>32 vs 33</td>
<td>N/A</td>
<td>N/A</td>
<td>73 vs 74</td>
</tr>
<tr>
<td>Meta-analysis[21] (Rosen)</td>
<td>2005</td>
<td>31 vs 27</td>
<td>N/A</td>
<td>N/A</td>
<td>62 vs 48</td>
</tr>
<tr>
<td>Year</td>
<td>American Society of Clinical Oncology&lt;sup&gt;20,87&lt;/sup&gt;</td>
<td>National Comprehensive Cancer Network&lt;sup&gt;88&lt;/sup&gt;</td>
<td>European Society for Medical Oncology&lt;sup&gt;89&lt;/sup&gt;</td>
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<tr>
<td>History and physical</td>
<td>Every 3-6 mo × 3 yr then yearly thereafter</td>
<td>Every 3 mo × 2 yr then every 6 mo for total of 5 yr</td>
<td>Every 6 mo for distal cancer × 2 yr; else every year × 3 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>Against routine testing</td>
<td>Not recommended</td>
<td>Against routine testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver function test</td>
<td>Against routine testing</td>
<td>Not recommended</td>
<td>Against routine testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CEA</td>
<td>Every 2-3 mo for stage II and III patients for at least 2 yr&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Every 3 mo × 2 yr then every 6 mo for total of 5 yr (for T2 or greater lesions)&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Not recommended</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Annually × 3 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal CT scan</td>
<td>Against routine testing</td>
<td>If indicated for certain clinical situations</td>
<td>Against routine testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Against routine testing</td>
<td>If indicated for certain clinical situations</td>
<td>Against routine testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Pre- or perioperative documentation of a cancer- and polyp-free colon then every 3-5 yr</td>
<td>1 yr postop (or for obstructing lesion and unprepped bowel, after 3-6 mo), repeat in 1 yr if abnormal or every 3-5 yr if negative for polyps</td>
<td>Every 5 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexible proctosigmoidoscopy</td>
<td>For patients that do not receive radiation therapy, recommended at periodic intervals</td>
<td>Not recommended</td>
<td>Every 6 mo for distal cancers × 2 yr</td>
<td></td>
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</tr>
</tbody>
</table>
Ongoing Trials

• GILDA trial

• NHS trial
Conclusion

Follow up after colon cancer surgery is controversial with regards to its benefits. The main reasons for this are:

1. conflicting evidence from different studies,
2. inability to compare results from various studies due to the variation in follow up practices,
3. lack of sufficient randomized trials and
4. inadequate number of patients in the study group

Recent evidence emerging especially from meta-analyses, there seems to be some substantial benefit for the patients in terms of improved survival rates with intensive follow-up protocols and asymptomatic recurrence has better (6 months) survival rates with chemotherapy.
Conclusion

To determine the best follow-up strategy for colon cancer,
• Large trials would be required
• It should be multi centered and international cooperation will be required
• These should be randomized control studies
• It should address all aspects including survival benefit and cost effectiveness
• GILDA trial and NHS trial might answer some of the questions
Thanks!
<table>
<thead>
<tr>
<th>Test</th>
<th>Standard* (n = 158)</th>
<th>Intensive† (n = 167)</th>
<th>Extra Tests</th>
<th>No. of Patients With Recurrences Alive or Disease Free at 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Asymptomatic Recurrences† / Total Recurrences</td>
<td>No. of Tests</td>
<td>No. of Tests</td>
<td>505</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>1/5</td>
<td>162</td>
<td>0/3</td>
<td>609</td>
</tr>
<tr>
<td>Liver CT</td>
<td>0/23</td>
<td>153</td>
<td>12/20</td>
<td>674</td>
</tr>
<tr>
<td>CXR</td>
<td>2/10</td>
<td>114</td>
<td>4/8</td>
<td>417</td>
</tr>
<tr>
<td>Cumulative 5-year survival§</td>
<td>70%</td>
<td>76%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standard care comprised regular history, physical examination, and screening tests (CBC, LFTs, CEA testing, and fOBTs).
†Intensive care comprised standard care plus yearly CXR, liver CT, and colonoscopy.
‡“Asymptomatic Recurrences” includes asymptomatic recurrences when no other screening tests positive.
§P = .20.
<table>
<thead>
<tr>
<th>Absolute Survival Benefit of Colorectal Cancer Surveillance Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td><strong>No.</strong></td>
</tr>
<tr>
<td><strong>Recurrences</strong></td>
</tr>
<tr>
<td><strong>Salvage surgery attempted</strong></td>
</tr>
<tr>
<td><strong>Salvage surgery performed</strong></td>
</tr>
<tr>
<td><strong>Patients with 5-year disease-free survival after recurrence</strong></td>
</tr>
<tr>
<td><strong>Second cancers found by surveillance tests</strong></td>
</tr>
<tr>
<td><strong>Motivation for curative intent salvage procedures</strong></td>
</tr>
<tr>
<td><strong>CEA testing</strong></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
</tr>
<tr>
<td><strong>Standard follow-up tests (endoscopy, CXR)</strong></td>
</tr>
<tr>
<td><strong>Other (unrelated surgery, other tests)</strong></td>
</tr>
</tbody>
</table>

**NOTE.** Adapted from Goldberg et al.\(^22\)

*Patients alive and disease-free after curative intent salvage procedures based on motivating factors: CEA testing, 11 of 41; symptoms, five of 27; tests, 10 of 36; other, two of five.
<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high-power).</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least one well-designed experimental study. Randomized trials with high false-positive and/or false-negative errors (low power).</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, quasiexperimental studies such as nonrandomized, controlled, single-group, pre-post, cohort, time, or matched case-control series.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from well-designed, nonexperimental studies such as comparative and correlational descriptive and case studies.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence from case reports and clinical examples.</td>
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</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade of Recommendation</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>There is evidence of type I or consistent findings from multiple studies of type II, III, or IV.</td>
</tr>
<tr>
<td>B</td>
<td>There is evidence of type II, III, or IV and findings are generally consistent.</td>
</tr>
<tr>
<td>C</td>
<td>There is evidence of type II, III, or IV but findings are inconsistent.</td>
</tr>
<tr>
<td>D</td>
<td>There is little or no systematic empirical evidence.</td>
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</table>