Optimal follow-up strategy for resected neuroendocrine tumours: A systematic review


Background

• The incidence of neuroendocrine tumours (NETs) has doubled over the last 20 years with an increasing number of proven systemic treatment strategies.
• The optimal follow-up protocol for this patient population is undetermined.
• We performed a systematic review of studies describing follow-up strategy for patients with resected NETs from 1996-2016.

Methods

• A search was carried out of the MEDLINE and Cochrane Library databases as well as abstracts of major meetings (ASCO, ESMO, NANETS, and ENETS).
• Prospective studies or retrospective studies of more than 25 patients that described follow-up strategy for surgically resected non-metastatic NETs were eligible for inclusion.
• Merkel cell cancer and small cell/large cell carcinomas of the lung were excluded as they are biologically different.

Figure 1: Study flow diagram

Table 1: Included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Primary</th>
<th>Follow-up</th>
<th>Follow-up  Imaging</th>
<th>Follow-up Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jung 2015 (R)</td>
<td>145</td>
<td>pNET</td>
<td>Variable at 3, 6 and 12 months</td>
<td>CT or MRI</td>
<td>Not specified</td>
</tr>
<tr>
<td>Birnbaum 2015 (R)</td>
<td>134</td>
<td>pNET</td>
<td>6 monthly for first 5 years and yearly after</td>
<td>CT</td>
<td>CgA</td>
</tr>
<tr>
<td>Kishi 2014 (R)</td>
<td>90</td>
<td>Non-functional pNET</td>
<td>6 monthly</td>
<td>CT or US</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sato 2014 (R)</td>
<td>82</td>
<td>Type I gastric NET</td>
<td>Every 6-12 months</td>
<td>Upper GI endoscopy, CT/MRI when possible</td>
<td>Not specified</td>
</tr>
<tr>
<td>Zerbi 2013 (P)</td>
<td>140</td>
<td>pNET</td>
<td>6 monthly for 2 years</td>
<td>CT</td>
<td>Not specified</td>
</tr>
<tr>
<td>Gaujoux 2013 (P)</td>
<td>46</td>
<td>Non-functional pNET</td>
<td>6-12 monthly for 18 months</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
<tr>
<td>Thomas 2013 (R)</td>
<td>111</td>
<td>Type I gastric NET</td>
<td>6 monthly</td>
<td>Endoscopy, CT/MRI if biochemical recurrence</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lopez 2011 (R)</td>
<td>38</td>
<td>pNET in MEN-1 patients</td>
<td>Yearly</td>
<td>EUS/MRI</td>
<td>Pancreatic polypeptide, CgA, insulin, gastrin, vasoactive polypeptide</td>
</tr>
<tr>
<td>Le Roux 2011 (R)</td>
<td>100</td>
<td>Ileal NET</td>
<td>Rigorous: yearly</td>
<td>CT/MRI/SRS/US</td>
<td>Not specified</td>
</tr>
<tr>
<td>Park 2011 (R)</td>
<td>347</td>
<td>Rectal NET</td>
<td>Not specified</td>
<td>Colonoscopy, CT/US</td>
<td>Not specified</td>
</tr>
<tr>
<td>Shields 2010 (R)</td>
<td>202</td>
<td>Rectal NET</td>
<td>6 monthly or yearly depending on institutional protocol</td>
<td>Colonoscopy/CT</td>
<td>Not specified</td>
</tr>
<tr>
<td>K. H. in’t Hof (R)</td>
<td>975</td>
<td>Appendix NET</td>
<td>Not specified</td>
<td>CT/SRS</td>
<td>Not specified</td>
</tr>
</tbody>
</table>


Results

• 39 articles were subjected to full text review.
• Only one study presented a retrospective comparison between follow up strategies.
  - This study (Le Roux 2011) included 100 patients with resected ileal NET.
  - The median follow-up was 56.5 months; 42 patients relapsed.
  - “Rigorous follow-up” was defined as consultation and radiology at least yearly, and “non-rigorous” as otherwise.
  - The proportion of patients who received rigorous follow-up in the relapsed group was similar to that in the non-relapsed group.
  - Relapse was suspected based on clinical signs for 10 (23.8%). 32 other patients (76%) had relapse detected during follow-up monitoring (29 radiologically, 3 with elevated biomarkers).
  - 12 studies (2920 patients) described follow-up strategies post-resection of NETs, but only one compared follow-up regimens.
  - The studies reported different follow-up strategies and were marked by limitations including insufficient data, methodological bias and between-study heterogeneity.
• No formal data synthesis was possible.

Discussion

• There is a significant lack of prospective (or retrospective) data to direct follow-up in resected NETs.
• Most identified studies contain heterogeneous populations and vary in their follow-up frequency, choice of modalities and length of follow-up.
• The number of patients who received specific blood tests was poorly reported by the above studies.
• In a disease where some patients have excellent recurrence-free survival (eg T1N0 appendiceal NET), there is a pressing need for evidence to minimize the amount of follow-up to minimize patient anxiety and resultant costs to the health care system.
• There is a need for validated non-invasive biomarkers for surveillance.

Conclusions

• Only one study identified which fulfilled the inclusion criteria.
• There is little reported evidence to definitively guide the optimal follow up strategy in resected NETs in terms of optimal frequency and modality.
• This systematic review has identified a gap in evidence and a need for research into different aspects of follow-up to optimize the patient journey in resected NETs.