Strategies in the Management of Neuroendocrine Tumors

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Dr. Elena Tsvetkova
A ZORSE
Neuroendocrine Tumour Classification

Neuroendocrine Tumours

- Carcinoid Tumours
  - Functioning
  - Non-functioning
  - Symptomatic
  - Asymptomatic
- Pancreatic Neuroendocrine Tumours
  - Functioning
  - Non-functioning
NET Incidence Is Increasing

US SEER data show a 5-fold increase in the past 30 years.
Annual age-adjusted incidence 5.25/100,000 in 2004 versus
1.09/100,000 in 1973.
Increasing Incidence of NETs: Ontario


Age-adjusted rates standardized to 1991 in rate per 1 million population by year of diagnosis.

NETs Are the Second Most Prevalent Type of GI Malignancy

2x more prevalent than pancreatic cancer

Prevalence in SEER Database
Carcinoid Tumours: Origin

Carcinoid site

Bronchopulmonary system

Digestive system

- Colon, except appendix – 9
- Appendix – 5
- Rectum – 14

Small intestine

- Duodenum – 3
- Jejunum – 2
- Ileum – 15
- NOS – 8
- Other – 0.5

Stomach

- Other

Colon and rectum

- Other

Other

- Other – 0.5

28%

64%

8%
Functioning Tumours: Overview

- Secrete biologically active hormones
  - Serotonin, vasoactive intestinal peptide, gastrin
- May present with vague abdominal symptoms, e.g., cramps, pain, diarrhea... misdiagnosed as irritable bowel syndrome
- Flushing: a challenge at perimenopausal age
- Symptoms lead to diagnosis at an early stage when tumour small and resectable
- Result in Carcinoid Syndrome
- Elevated 5-HIAA levels lead to higher risk for carcinoid heart disease
Non-functioning tumours: overview

- Well-differentiated, slow-growing tumours that can go undetected
- 1/3 to 1/2 of all NETs
- Not associated with hormone hypersecretion
- Incidental finding during surgery
- Histologic examination needed
- Tumours can produce mass effect
- Symptoms of intermittent intestinal entrapment due to mesenteric fibrosis
- Can evolve into a functioning tumour
- Monitor mainly with cGA
Pathology of Carcinoids: Ki67

• Marker of cell proliferation
  • Present in the nucleus during active phases of cell cycle, absent from resting cells
• Prognostic factor for survival and a marker of biologic behavior
• No well-established, validated cut-off points

Testing should be done in all patients
Pathology of Carcinoids: Ki67
# WHO Classification Groups NETs by Diagnostic Factors

## Prognosis of Patients With NETs

<table>
<thead>
<tr>
<th></th>
<th>Well-differentiated neuroendocrine tumor</th>
<th>Well-differentiated neuroendocrine carcinoma</th>
<th>Poorly differentiated neuroendocrine carcinoma</th>
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</thead>
<tbody>
<tr>
<td><strong>WHO classification</strong></td>
<td><strong>Biological behavior</strong></td>
<td><strong>Metastases</strong></td>
<td><strong>Ki-67 index (%)</strong></td>
</tr>
<tr>
<td></td>
<td>Low malignancy</td>
<td>–</td>
<td>&lt;2</td>
</tr>
<tr>
<td></td>
<td>Low malignancy</td>
<td>+</td>
<td>&gt;2</td>
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<tr>
<td></td>
<td>High malignancy</td>
<td>+</td>
<td>&gt;10</td>
</tr>
<tr>
<td></td>
<td>Any size</td>
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</tr>
</tbody>
</table>
Survival Is Associated With Tumor Grade

The graph illustrates the survival probability over time (in months) for different tumor grades. The survival probability decreases over time for all grades, with well-differentiated tumors having the highest survival rate. The graph shows:

- **Yellow** line represents well-differentiated tumors.
- **Orange** line represents moderately differentiated tumors.
- **Red** line represents poorly differentiated tumors.
- **Green** line represents anaplastic tumors.

Survival probability decreases as time increases, indicating a higher risk of death over time for each grade.
Advanced TNM Stage Confers Worse Prognosis

In localized NET, 5-year survival rates after resection range from 60 to 90%
With regional lymph node involvement 5-year survival rates after surgery 50-75%

Distant metastases decrease 5 year survival rate to 25-40%
Biochemical Markers: 5-HIAA

- 24 hour urine 5-HIAA (metabolite of serotonin)
  - Sensitivity 73%, specificity 100%
  - Serotonin rich food affect accuracy
  - 50% reduction from pre-treatment levels indicative of response
  - Chronic elevation of 5-HIAA has been linked to carcinoid heart disease

5-HIAA = 5-hydroxyindoleacetic acid
Biochemical Markers: Chromogranin A

- Elevated in 85–100% of patients, irrespective of functional status
- Specificity 98.4%, sensitivity >62.9%
- Can be helpful when 5-HIAA is negative
- Other conditions cause increased CgA levels with false-positive results
  - Inflammatory conditions, renal insufficiency, type A gastritis, treatment with PPI
  - Change over time may be more useful as CgA levels independent of symptoms
- Issues: availability and methods of determination
Chromogranin A (CgA)

Serum CgA as an indication of tumor extent

- CgA measurements have become one of the most important parameters for NET diagnosis and monitoring.
CgA Levels: Diagnostic and Prognostic Values

• Correlation between serum CgA level and
  ➢ Tumor burden
  ➢ Number of metastases
  ➢ Symptoms

• Can indicate tumor activity in cases where imaging shows tumor volume is unchanged

• Independent predictor of survival

• data show Q-RT-PCR of CgA mRNA can detect micrometastases currently undetectable with immunoassays
CgA: an Indicator of Disease Recurrence

CT neg
US neg
Octreoscan neg

CT neg
US neg
PET neg
US shows liver metastases.

CgA (nmol/L)

0 1 2 3 4 5 6 7 8 9 10

0 6 12 18 24 30 36 42

Months

Interferon
Indium In-111 Pentetreotide (Octreoscan™)

• Detects and localizes primaries and metastases

• Staging of NETs

• Patient follow-up to evaluate recurrence

• Selection of patients with metastatic disease for peptide receptor radionuclide therapy
  • Highly sensitive for carcinoid tumours
  • Similar specificity for functioning and non-functioning tumours
Constellation of Symptoms Can Make a Differential Diagnosis Difficult

Nonspecific Symptoms Are Common to Multiple Diagnoses

Symptoms
- Sweating
- Flushing
- Diarrhea
- Intermittent abdominal pain
- Bronchoconstriction
- GI bleeding
- Cardiac disease

Menopause
Food Allergy
Neurosis
NET
Asthma
Thyrotoxicosis
Anxiety
Functional Bowel Disease
Irritable Bowel Syndrome
Alcoholism
Peptic Ulcer
Nonspecific Symptoms Lead to a Delayed Diagnosis

Presents to primary care

Vague abdominal symptoms
- May be diagnosed as IBS
- May be referred to specialists for evaluation when symptoms do not resolve

Referred to multiple specialists

Symptoms become worse
- Patient consults for another reason
- Diagnosis remains unclear

Seen by gastroenterologist or other specialist who orders imaging

A referral leads to a scan or patient scanned for another reason
- Liver metastasis or primary lesion is visualized
- May be an incidental finding

Surgeon, pathologist perform biopsy or resection

Biopsy provides diagnosis of NET
- Patient is referred to surgical oncologist, medical oncologist, or endocrinologist
- Treatment depends on stage, histology, symptoms

Estimated time to diagnosis: 5 to 7 years
Symptoms that Should Raise Index of Suspicion

• Cutaneous flushing (in up to 94% of patients)
  – begins as erythema of face and neck, may spread and is accompanied by a sensation of warmth
  – May persist for minutes or hours

• Wheezing
  – Asthma-like symptoms

• Chronic diarrhea (in up to 80% of patients)
  – 2 to 30 watery stools/day, may be accompanied by abdominal pain, cramping

• Symptoms of right-sided heart failure
  – Tricuspid valve regurgitation and pulmonic stenosis
Surgery

- Surgery of the primary tumour
  - Mainstay of treatment, whatever the stage, when technically feasible
  - Oncologic resection
  - Even in the presence of non-resectable metastases, always resect primary
  - Likely improves outcome
- Prophylactic cholecystectomy
- Surgery the only potentially curative treatment
Liver Metastases

• Surgical intervention can be palliative
  • limited liver resection
  • Resection may be combined with other ablation techniques

• Multiple liver metastases
  • Debulking surgery, radio-frequency ablation, cryoablation, chemoembolization, medical therapy
Embolization of Liver Metastases

- Embolization/ or chemoembolization, can reduce symptoms and liver metastases
  - Chemical response: 70–90%
  - Tumour reduction: 30–50%
  - Symptomatic response lasting 15–30 months
  - Mortality rate 7%
- Contraindications: complete portal vein obstruction, hepatic insufficiency, >50% of liver volume involved, ascites, tumours >7 cm, non-permissive vascular supply
- Complications: gallbladder necrosis, acute renal failure, pancreatitis, liver abscess
Medical Treatment: Principles

- Goals of carcinoid tumour management
  - Symptom control
  - Biochemical control
  - Objective tumour control
  - Improving quality of life
- Strategies differ for functioning and non-functioning tumours
- Alternative management
  - Isotope therapy
  - Addition of interferon and/or chemotherapy
Octreotide: A Somatostatin Analogue

Octreotide

半胱氨酸 (cys) → 赖氨酸 (lys) → 亮氨酸 (trp) → 赖氨酸 (lys) → 精氨酸 (arg) → 色氨酸 (trp) → 精氨酸 (arg)

D-苯丙氨酸 (D-phe) → 半胱氨酸 (cys) → 色氨酸 (trp) → 赖氨酸 (lys) → 精氨酸 (arg)

氨基酸对于受体结合至关重要

半衰期：90分钟

Human somatostatin

谷氨酸 (ala) → 甘氨酸 (gly) → 半胱氨酸 (cys) → 赖氨酸 (lys) → 谷氨酰胺 (asn) → 苯丙氨酸 (phe) → 苯丙氨酸 (phe) → 亮氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) → 色氨酸 (trp) → 赖氨酸 (lys) → 色氨酸 (trp) → 赖氨酸 (lys) → 苏氨酸 (ser) 

半衰期：3分钟
Medical Treatment: Somatostatin Analogues

- Can relieve symptoms and decrease hormone levels
- Use to prevent/treat carcinoid crises before, during and after procedures such as surgery and embolization
- Treatment likely to be lifelong
Safety: Adverse Events

- Hair loss
- Vomiting
- Nausea
- Steatorrhea
- Abdominal Pain
- Flatulence
- Diarrhea
- Loose stools

Comparison between 7th Injection and 1st Injection.
Somatostatin Analogues in Asymptomatic Carcinoid Tumours: Heated debate!

- Somatostatin analogues may have a role in tumour stabilization or regression, regardless of the secretory status of the tumour.

- Treatment with somatostatin analogues should be considered for asymptomatic patients with elevated 5-HIAA (>70 mg/24 h).
Advantages of Sandostatin® LAR®

- Convenient once-monthly dosing
- Increased patient compliance
- Stable serum octreotide concentrations
- Sustained suppression of GH and IGF-1
- Effective clinical improvement
Medical Treatment: Interferon-Alfa

- **Inhibits**
  - Protein and hormone synthesis
  - Angiogenesis

- **Stimulates immune system**

- **Primary medical treatment for low-proliferating gastroenteropancreatic tumours**

- **Used as second-line therapy**

- **Combination with SSAs has additive and possible synergistic effects**
Medical Treatment: Cytotoxic Treatment

- Tumours with high proliferative capacity (Ki67 >5–10%)
- Midgut tumours with low proliferation (Ki67 <2%) will not benefit

- Agents
  - Single agents: limited benefit

- Combinations
  - Streptozotocin + 5-FU + doxorubicin: response rate >50%
  - Etoposide + cisplatin: 67% response rate in poorly differentiated NETs

- Standard endpoints are not always valid evaluations of benefits
Peptide Receptor Radionuclide Therapy

- Radionuclide attached to octreotide (binds to SSR 2 and 5)
- Molecule internalized and delivers radiation energy
- Radionuclides
  - Indium 111
  - Yttrium 90 (less favorable)
  - Lutetium 177 (increasing importance)
- Results and tolerance differ with radionuclide
- Availability?
- Centres of expertise
Monitoring and Follow-up: Recommendations

• **Symptomatic patient**
  • Follow-up depends on aggressiveness of disease
  • In second and subsequent years, follow-up every 4–6 months are appropriate, with annual OctreoScan
  • OctreoScan or MIBG if surgery, radiation or a change in treatment modality is considered

• **Asymptomatic patient**
  • Watchful waiting
  • Following complete resection, follow-up every year, with an annual evaluation of 5-HIAA, CgA and MIBG
  • If any results positive, consider CT and OctreoScan
Carcinoid Heart Disease (40%)

- Associated with release of serotonin and other vasoactive substances
- Most common lesions
  - Tricuspid regurgitation / stenosis
  - Pulmonary regurgitation / stenosis
- Right ventricular failure major cause of morbidity and mortality
- Commonly associated with chronic elevations of 5 HIAA
Carcinoid heart disease: pathology

- Pathology:
  - Thickening of right heart valves due to formation of fibrotic plaques
  - Affects valve function
  - Leads to valve insufficiency, heart failure
  - Involvement of left side of heart uncommon
Carcinoid Heart Disease: Recommendations

- Echocardiogram at diagnosis; annually if predisposed to carcinoid heart disease
- Patients with 5-HIAA levels of >50 mg/24 hours should be considered for octreotide therapy
- Cytoreductive surgery to reduce number of serotonin receptors
- Follow-up with a cardiologist, particularly those with any cardiac changes or elevated 5-HIAA
- Cardiac valve replacement may be indicated
Somatostatin Analogues: Asymptomatic Carcinoid Tumours: Answer to the debate!

Somatostatin analogues may have a role in tumour stabilization or regression, regardless of the secretory status of the tumour.
PROMID study objective and design

- To evaluate the antitumor effect of octreotide LAR
- Randomized, double-blind, placebo-controlled, Phase III
- 85 patients treated from a planned 162
Significantly increases TTP when hepatic tumor load ≤10%

Patients with tumor load ≤10%
- Octreotide LAR: 32 patients / 18 events
  - Median TTP 27.14 months
- Placebo: 32 patients / 31 events
  - Median TTP 7.21 months

Stratified log-rank test
- \(P<0.0001; \text{HR}=0.26\ [95\%\ CI: 0.14–0.50]\)

Patients with tumor load >10%
- Octreotide LAR: 10 patients / 8 events
  - Median TTP 10.35 months
- Placebo: 11 patients / 10 events
  - Median TTP 5.45 months

Stratified log-rank test
- \(P=0.345; \text{HR}=0.64\ [95\%\ CI: 0.25–1.63]\)

Based on the ITT analysis
Prognostic factors for TTP

• Most favorable treatment outcome in:
  • Hepatic tumor load $<10\%$ ($P<0.0009$)
  • Resected primary ($P<0.0104$)

• Benefit of octreotide LAR versus placebo seen irrespective of:
  • Functioning or non-functioning NETs
  • Elevated or non-elevated CgA
CLARINET

CLARINET (Placebo Controlled study of Lanreotide Antiproliferative Response in Neuro-Endocrine Tumors) - 1 end point – PFS; intestinal and pancreatic non-functional NET+ well controlled gastrinomas; Ki 3-10% in 22% pts

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Lanreotide Autogel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cohort (N=204)</td>
<td>18 months</td>
<td>NR (&gt; 27 months)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P = .0002$; $HR = 0.47$ (95% CI: 0.30-0.73)</td>
</tr>
<tr>
<td>HL ≤ 25% (n=137)</td>
<td>21 months</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P = .0002$; $HR = 0.34$ (95% CI: 0.18-0.62)</td>
</tr>
<tr>
<td>HL &gt; 25% (n=67)</td>
<td>9.4 months</td>
<td>24.1 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$P = .0170$; $HR = 0.45$ (95% CI: 0.23-0.88)</td>
</tr>
</tbody>
</table>

➢ No significant difference in OS: most patients in the placebo arm crossed over to lanreotide autogel upon progression
# PROMID vs. CLARINET

## PROMID and CLARINET: Key Differences

<table>
<thead>
<tr>
<th></th>
<th>PROMID[^a]</th>
<th>CLARINET[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSA</td>
<td>Octreotide LAR 30 mg</td>
<td>Lanreotide autogel 120 mg</td>
</tr>
<tr>
<td>Patients</td>
<td>85</td>
<td>204</td>
</tr>
<tr>
<td>Tumor site</td>
<td>Midgut</td>
<td>Enteropancreatic</td>
</tr>
<tr>
<td>Disease status at baseline</td>
<td>Unknown</td>
<td>96% stable disease</td>
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<tr>
<td>Functional status</td>
<td>Functional and nonfunctional</td>
<td>Nonfunctional only (+ well-controlled gastrinoma)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>&lt; 2%</td>
<td>&lt; 10%</td>
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<tr>
<td>Response assessment</td>
<td>WHO</td>
<td>RECIST</td>
</tr>
<tr>
<td>Resected primary</td>
<td>~70%</td>
<td>~40%</td>
</tr>
</tbody>
</table>

Clinical Implications of PROMID / CLARINET Results

• A Significant achievement in the context of an uncommon tumor

• The use of LAR should be indicated in the following clinical settings:

  1. Asymptomatic patients with progressive disease

  2. Asymptomatic patients with stable disease particularly if 5 HIAA rising

  3. As adjuvant therapy post resection?
Sunitinib Phase III Study: Randomized, Double-Blind Study Design (placebo-controlled)

Eligibility criteria
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months
- Not amenable to treatment with curative intent

Balanced by region
- Europe, Asia, Americas, Australia

Primary endpoint: PFS
Secondary endpoints: OS, ORR, time to tumor response, duration of response, safety, PROs

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>11.4 months</td>
<td>5.5 months</td>
</tr>
<tr>
<td>95% CI</td>
<td>7.4–19.8</td>
<td>3.6–7.4</td>
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</table>
RADIANT (progressive advanced PNET, Hx of carcinoid syndrome)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>Primary Endpoints</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>RADIANT-3[^1]</td>
<td>Progressive advanced pNET</td>
<td>Everolimus + BSC vs placebo + BSC</td>
<td>PFS Statistical boundary: $P \leq .025$</td>
<td>OS; ORR; biomarkers; safety; PK</td>
</tr>
<tr>
<td>(Phase 3)</td>
<td>N = 410</td>
<td></td>
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</tbody>
</table>

- PFS 16.4 months in the combination group and 11.3 months in patients receiving octreotide only
Ongoing Studies

**SWOG 0518: Bevacizumab vs Interferon in Combination With Octreotide**

*Phase 3 Open-Label Study*

- Advanced carcinoid with poor prognosis (N = ~400)
  - Progressive disease
  - Refractory carcinoid syndrome
  - G2 with 6+ lesion
  - Rectal or gastric primary

Randomize

Bevacizumab 15 mg/kg every 21 d
Octreotide LAR 20 mg every 21 d

1:1

Interferon 5 μg 3 d/wk
Octreotide LAR 20 mg every 21 d

Multiphasic CT or MRI performed every 9 wks

Primary endpoint: PFS (RECIST)
Secondary endpoints: tumor response, OS, biomarkers, safety

ClinicalTrials.gov. NCT00569127.

**COOPERATE-2: Everolimus + Pasireotide vs Everolimus in Advanced Progressive pNET**

*Phase 2 Open Label Study (N = ~150)*

Randomize

Everolimus 10 mg/d

1:1

Everolimus 10 mg/d + Pasireotide LAR 60 mg every 28 d

Primary endpoint:
- PFS

Secondary endpoints:
- Safety and tolerability
- ORR and disease control rate
- Duration of response
- OS
What Does a Multi-Disciplinary Team Look Like?
This is How a Multi-Disciplinary Team Should Look Like?

• Multiple HCPs involved in the Patient Journey through NET diagnosis and treatment

• Advance training on NET diagnosis and treatment for each HCP

• Patient management optimized through tumor board and/or NET treatment protocols

- NET Regional Referral Center
- NET Treatment Guidelines
- NET Tumor Board
- Dedicated training (rounds)
- Capacity for clinical research
- Patient Outreach Initiatives & Support
- Utilization of latest Biomarker & Imaging techniques
- Disease Registry/Tumor Bank

We Forgot the Nurses!!
Multidisciplinary Treatment: Impact on Outcome

- Multidisciplinary treatment approach associated with improvement in patient outcomes
- Most individual physicians do not have specialized knowledge of NET due to low patient loads
- Optimal patient management is achieved through a multidisciplinary approach that takes advantage of multiple sources of expertise
- Diagnostic procedures should be critically reviewed to help establish consensus on the best evidence-based management

Noticeable improvements in survival in the MRC setting

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<tr>
<th>Year</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td>1973-1987 SEER database (all NET patients)</td>
<td>15</td>
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<tr>
<td>1988-2004 SEER database (all NET patients)</td>
<td>103</td>
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<tr>
<td>1973-2004 SEER database (all NET patients)</td>
<td>103</td>
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<tr>
<td>Midgut metastatic carcinoid only (Uppsala Center)</td>
<td>103</td>
</tr>
<tr>
<td>Midgut metastatic carcinoid only (Moffitt Cancer Center)</td>
<td>103</td>
</tr>
</tbody>
</table>

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

THANK YOU
Treatment Algorithm Part I

NET

Locoregional
Resectable
Follow up
NED
Metastatic
Unresectable

Metastatic
Follow up
Recurrence
Resectable

Unresectable or metastatic

Resectable
Low proliferative index Ki67 \leq 10%
Watchful observation

Unresectable or metastatic
High proliferative index Ki67 > 10%
Consider systemic chemotherapy
Treatment Algorithm Part II

Liver only or Liver dominant

Extrahepatic disease

Early consideration of primary debulking in abdomen

Stable disease

Watchful observation

Liver only or Liver dominant

Debulking measures (alone or in combination):
- Surgery
- RFA
- Hepatic arterial infusion

Consider transplant

Debulking measures (alone or in combination):
- Surgery
- RFA
- Hepatic arterial infusion

Observation

Debulking measures (alone or in combination):
- Surgery
- RFA
- Hepatic arterial infusion

Progression

Clinical trials
Chemotherapy/targeted therapy
Refer to a centre of expertise

Medical management:
- Symptomatic treatment
- Somatostatin analogues
- Interferon
- Radiopeptide therapy

RFA: Radiofrequency ablation