Medical Treatment of Small Bowel Cancer

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South African Statistics 2006

- 0.27 cases per 100 000/year in men
- 0.20 cases per 100 000/year in females
Estimated new cases and deaths from small intestine cancer in the United States 2014:

- New cases 9160
- Deaths 1210

1-2 % of all GI malignancies
Problems with Small Bowel Cancer

- Very rare condition
- Does not respond well to medical treatment
- Very little data on treatment
Cellular Classification of Small Intestine Cancer

- Adenocarcinoma
- Lymphoma (NHL)
- Sarcoma
  - Gastrointestinal Stromal Tumor (GIST)
- Carcinoid
TNM staging system for carcinoid tumors of the small bowel and ampulla of Vater

Primary tumor (T)

- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **T1**: Tumor invades lamina propria or submucosa and size ≤ 1 cm or less* (small intestinal tumors); tumor ≤ 1 cm or less (ampullary tumors)
- **T2**: Tumor invades muscularis propria or size > 1 cm (small intestinal tumors); tumor > 1 cm (ampullary tumors)
  - Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa (jejunal or ileal tumors) or invades pancreas or retroperitoneum (ampullary or duodenal tumors) or into non-peritonealized tissues
- **T4**: Tumor invades visceral peritoneum (serosa) or invades other organs

For any T, add (m) for multiple tumors

Regional lymph nodes (N)

- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Regional lymph node metastasis

Distant metastases (M)

- **M0**: No distant metastasis
- **M1**: Distant metastasis

Anatomic stage/prognostic groups

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II A</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II B</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III A</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III B</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

* Tumor limited to ampulla of Vater for ampullary gangliocytic paraganglioma.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition.
Adenocarcinoma

- Radical surgical resection - if possible
- If unresectable/metastatic:
  - Radiotherapy
  - Clinical trials with new chemotherapeutics / biologicals - if available

Recurrence:
No standard treatment
2007 Cochrane analysis concluded that there were no suitable trials to analyze.

Failure patterns of resected small bowel cancer primarily systemic.

There are now prospective trials testing adjuvant strategy in small bowel cancer.

Few retrospective studies failed to suggest any OS benefit.
Adenocarcinoma

- Largest retrospective trial, Mayo Clinic (1970-2005):
  - 491 pt with small bowel adenocarcinoma
  - 33 received 5-FU based chemotherapy
  - 40 received adjuvant chemo/rad
  - Neither showed better outcomes
Adenocarcinoma

- No benefit of Adjuvant chemotherapy after complete resection
- Neo-adjuvant treatment:
  - Very small studies (largest 32 patients)
  - Might be beneficial
  - BUT no criteria for selecting patients
In the absence of RCT’s, there is no standard first-line chemotherapy

Systemic chemotherapy based on treatment principles established for metastatic colorectal cancer

5 yr survival rates for small bowel cancer are worse than for similarly staged colon cancers (esp LN+)

Retropective trials suggest that patients receiving chemotherapy might live longer
Possible benefit for Cetuximab (TKI for K-RAS wildtype) suggested in a report of 4 patients
No proper data
Carcinoid

- Indolent cancer
- NCI/SEER data (10 yr DFS rates):
  - Stage I+ IIA: 95% (95% CI 93-97%)
  - Stage II B: 77% (95% CI 71-83%)
  - Stage III A: 68% (95% CI 58-77%)
  - Stage III B: 77% (95% CI 74-80%)
  - Stage IV: 42% (95% CI 38-46%)
Carcinoid

- Potential to metastasize at size <2cm
- No role for adjuvant chemotherapy
- Most commonly found in the ileum
- Non-metastatic tumors should be resected
- Multiple carcinoids are present in 26% of cases
- Prognosis depends on disease stage and margin status.
Carcinoid

- Role of systemic therapy for progressive metastatic carcinoid tumors is not well defined.
- Standard cytotoxic agents have minimal activity.
- Somatostatin analogs are effective in controlling symptoms resulting from carcinoid syndrome, but limited ability to reduce tumor burden.
- Traditionally, tumor size and depth of invasion (T stage) - main determinants of prognosis.
- Additional prognostic factors - mitotic index and lymphovascular invasion (LVI).
### Table 2. Gastro entero pancreatic neoplasms: WHO Classification (2010)

<table>
<thead>
<tr>
<th>WHO 1</th>
<th>NET G1, Ki-67 ( \leq 2% )</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO 2</td>
<td>NET G2, Ki-67 3%–20%</td>
</tr>
<tr>
<td>WHO 3</td>
<td>NEC G3, Ki-67 &gt;20%</td>
</tr>
<tr>
<td></td>
<td>MANEC</td>
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<tr>
<td></td>
<td>Tumor-like lesions</td>
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NEN, neuroendocrine neoplasms; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; MANEC, mixed adenocarcinoma and neuroendocrine carcinoma.
Carcinoid-ESMO guidelines

[Diagram showing treatment algorithm for carcinoid tumors]
ESMO guidelines

- **G1/2:**
  - Interferon
  - Somatostatin analogue/ Octreotide
  - Everolimus and Octreotide
  - Radio Immunotherapy

- **G3:**
  - Cisplat/ Etoposide
RCT, Phase 3, Double blind, placebo controlled
>18 yr, Low/IM grade NET-unresectable, with progression in past 12m
Primary endpoint PFS
Randomized to
- Everolimus + Octreotide vs
- Placebo + Octreotide

Results
- 429 pt
- PFS: E+O 16.4m (95%CI 13.7-21.2)
  - P+O 11.3m (95%CI 8.4-14.6) (p=0.026)
Placebo-controlled, double-blind, phase IIIB study, well-differentiated metastatic midgut NETs. Treatment-naive pts. Placebo or Octreotide LAR 30 mg IM monthly until progression/death. Primary end point: time to tumor progression. Median time to tumor progression:

- 14.3 (O) and 6(P) months, ([HR] = 0.34; 95% CI, 0.20 to 0.59; P = 0.000072).

After 6 m of treatment, stable disease in 66.7% (O) and 37.2%.
Functionally active and inactive tumors responded similarly.
Because of low number of observed deaths, survival analysis was not confirmatory.
Sarcoma

- Malignant mesenchymal tumours of GI-tract
- 2 categories:
  - GIST - >85% of sarcomas arising within GIT
  - Non-GIST - leiomyosarcoma, fibrosarcoma, liposarcoma, Kaposi's sarcoma, and angiosarcoma
- GISTs and leiomyosarcomas can have a similar morphologic appearance
- Distinction is important - treatment differs markedly.
- Primary treatment: surgery
- The role of adjuvant or neo-adjuvant chemotherapy for small bowel sarcomas other than GIST tumors is undefined.
>80% GISTs- activating mutations in KIT proto-oncogene (c-KIT + on IHC)
- Mutational activation of KIT or PDGFRA stimulates the growth of cancer cells
- In 50% of pts, complete resection not possible (m-survival 10-23 months without Rx)
- Growth can be inhibited with orally active small molecule TKIs i.e Imatinib
Given the importance of complete resection to long-term outcomes, initial therapy with imatinib might downstage pts and allow resection in otherwise unresectable pts.

Prognosis of small intestine GISTs depends upon the tumor site, adequacy of resection, tumor size and mitotic activity.

No evidence-based guidelines on what constitutes appropriate follow-up after treatment of a GIST, and there is no consensus on this issue.
The CD117 molecule is part of the KIT (c-kit) receptor, a membrane tyrosine kinase, that is a product of the KIT proto-oncogene. In 80% of cases, KIT over-expression is the result of an activating mutation in the KIT proto-oncogene. Majority of GISTs are KIT+, some KIT-negative GISTs have activating mutations in PDGFRA. Imatinib is an oral TKI used in CML Targets bcr/abl and c-Kit Very little data available on its use in Small bowel GIST
In gastric GIST

- Exon 11 more likely to respond
- Exon 9 may require higher doses of Imatinib

Response monitored by:

- Size of tumour
- Density on scan
- CHOI criteria vs RECIST
- PET scan may be helpful in determining early response in neo-adjuvant treatment
Imatinib

- Stage IV disease: 80% objective response / stable disease, m-PFS 20-26 months, and m-OS 51-57 months
- Locally advanced disease:
- Trial by the American College of Surgeons Oncology Group, (completely resected GIST > 3 cm) randomly assigned to 1 year of adjuvant imatinib (400 mg daily) or placebo.
  - Accrual halted when planned interim analysis showed that treated patients had significantly fewer recurrences (3% vs 17%, hazard ratio 0.325). Differences in OS not been seen,
  - Adjuvant imatinib is considered a standard approach following complete resection of all small bowel GIST tumors >3 cm.
Second line in gastric GIST is Sunitinib
An oral TKI against VEGFR, PDGFR, c-kit
Limited data in Small bowel GIST

Other TKI’s approved in Gastric GIST
- Dasatanib
- Nilotinib
- Regorafenib
- Sorafenib
GIST

- Data for the treatment of GIST of the small bowel, is mainly adapted from studies done on gastric GIST
- Small bowel GIST seems to be more difficult to treat- not sufficient data
Primary GI Lymphomas

- Heterogeneous group of B and T cell lymphoid malignancies.
- Clinical features, management, and prognosis differ from lymphomas of LN origin.
- Rare
- Optimal treatments have not been defined.
- Current recommendations based on data from case series
- HIV serology and Hepatitis B and Hepatitis C testing is important
- Use PET is controversial except in cases of DLBCL
- Evaluation of nutritional status
- Performance status often poor
Primary GI Lymphomas

- Main bulk of disease is confined to GIT
- Subtypes
  - DLBCL
  - Enteropathy-associated T-cell intestinal lymphoma
  - Extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
  - Mantle cell lymphoma
  - Burkitt and Burkitt-like lymphoma
  - Hodgkin lymphoma is extremely rare
- The treatment approach to a small bowel lymphoma generally parallels the standard treatment approach for that histological subtype of lymphoma arising in nodal regions.
Staging

- Ann Arbor staging system (used for most lymphomas) is inadequate for the staging of GI lymphoma-
  - it does not incorporate information on the depth of tumor invasion known to affect prognosis.
- Lack of a uniform staging system hinders comparison of clinical trials.
- The Lugano staging system (most widely accepted)
  - Early (stage I/II)- a single primary lesion or multiple, non-contiguous lesions confined to the GI tract, may have nodal involvement.
  - There is no stage III
  - Advanced (stage IV) disseminated extra-nodal involvement or concomitant supra-diaphragmatic nodal involvement.
GI-DLBCL

- Anywhere along the GI tract
- Most common histology for primary gastric lymphoma (50%).
- More systemic symptoms, more advanced stage at diagnosis, and a worse prognosis.
Treatment
Chemo-immunotherapy regimens used for non-GI DLBCL (i.e. combo chemotherapy+rituximab- R-CHOP)
Perforation - original concern that patients with lymphomatous involvement of the stomach given chemotherapy may develop gastric perforation and/or bleeding has not been confirmed in a number of comparative studies.
Non-gastric MALT

- Divided into
  - immunoproliferative small intestinal disease (IPSID) lymphoma, which secretes alpha heavy chains
  - "Western type" MALT, which does not.
- >1/3 of pts with non-gastric MALT lymphoma will have advanced disease at the time of diagnosis.
- Limited stage MALT- treated with local therapy
- Advanced disease- immunotherapy or chemo-immunotherapy in a similar fashion to follicular lymphoma.
- Patients with MALT lymphoma of any stage with co-existent large cell lymphoma are treated as diffuse large B cell lymphoma.
- IPSID- rare, with little data to guide treatment.
- Intestinal involvement - generally diffuse.
- Most pts relapse and present with an aggressive high-grade histology.
- For such patients, radiation therapy and/or combination chemotherapy.
Often a sequela of celiac disease
- Mostly high-grade histology
- Poor prognosis.
- Pts often malnourished
- Treatment-
  - chemotherapy used for other aggressive T cell lymphomas.
  - Autologous hematopoietic cell transplantation may be beneficial - more data required.
- The 5-year OS with anthracycline-based chemo is 10 - 20%.
Primary Intestinal Follicular Lymphoma

- Lymphomatous disease pathologically consistent with follicular lymphoma confined to the intestine without lymph node involvement
- Rare entity
- Four general treatment strategies available
  - Watch and wait
  - Radiation therapy
  - Rituximab monotherapy
  - Chemotherapy with or without radiation
Mantle Cell Lymphoma

- Older patients
- Multiple sites (lymphomatous polyposis).
- Systemic chemotherapy is the treatment of choice for advanced disease.
- Localized- chemotherapy followed by radiation
- No proper trials available
Not uncommon in context of widespread peritoneal carcinomatosis. However, hematogenous spread to small intestine is rare. Most common cancers to involve small bowel: melanoma, lung, breast, cervix, sarcoma, and colon. Treatment is palliative.
Summary

- Very rare disease
- Little data available
- No proven treatment that works
References

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- J Clin Oncol. 2009; 27(28):4656-63 (ISSN: 1527-7755)
THANK YOU