CURSO REGIONAL DE CAPACITACIÓN EN GANGLIO CENTINELA Y CIRUGÍA RADIOGUIADA

Tumores gastrointestinales

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« Aut tace aut loquere meliora silentio »
GOSTT in gastrointestinal surgery

No standard procedures

Radiopharmaceuticals:
- 99mTc-macroaggregates
  - for lymphoscintigraphy and sentinel lymph node biopsy
  - for intraoperative localization of occult lesions
- radiolabeled monoclonal antibodies (RadioimmunoGuided Surgery, or RIGS)
- receptor-based radiopharmaceuticals (OctreoScan®)
- metabolic agents ([¹⁸F]FDG)
Injection technique

Tracers:
• Both blue dye and radiocolloids

Interstitial injection:
• Submucosa, around the tumour (during endoscopy prior to surgery)
• Subserosa (during open or laparoscopic surgery)

Endoscopic Injection of $^{99m}$Tc-colloids (100 MBq MAA) in Colonic Lesions (T1-T2 N0)
Sentinel lymph node biopsy

Endoscopic detection

Laparoscopic Gamma-Probe

Courtesy
G.Mariani, Pisa
Lymph nodal status is the most powerful prognostic factor in esophageal cancer, and accurate staging is necessary to distinguish potentially curable patients from those with locally advanced disease.

The overall 5-year survival rate for patients with esophageal cancer is 20% to 25% (60% to 70% for patients with stage I disease, 5% to 10% for patients with stage III disease).

Sentinel lymph node biopsy is especially useful in early-stage tumours, to confirm the indication of esophagectomy.
Sentinel lymph node biopsy

Esophageal cancer

Sentinel lymph node biopsy

Gastric cancer

The standard treatment for early cases is gastrectomy with en-bloc lymph node dissection. Lymphatic mapping has disclosed unexpected and/or aberrant sites of drainage, thus guiding surgeons to perform a regional dissection approach tailored to the individual patient.

Radiocolloids generally injected endoscopically in up to four submucosal sites around the tumour between 2 to 24 hours before surgery.
Gastric cancer

Results in presumed cT1N0 or cT2N0 gastric cancer

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Patient (n)</th>
<th>SLN visualization</th>
<th>SLN positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n)</td>
<td>(%)</td>
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<tr>
<td>Kitagawa (2002)</td>
<td>145</td>
<td>138</td>
<td>95.2</td>
</tr>
<tr>
<td>Uenosono (2005)</td>
<td>104</td>
<td>99</td>
<td>95.2</td>
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</tbody>
</table>

- Possibility to individualize the surgical approach in early stage gastric cancer
- Additional studies are required to evaluate clinical impact
Sentinel lymph node biopsy

Gastric cancer
Colorectal cancer

Aberrant lymph drainage leading to modification of the surgical approach in 5% to 8% of colorectal cancer.

Lymphatic mapping and sentinel lymph node analysis
- does not modify surgical procedure (standardized approach)
- can identify a subgroup of patients who can benefit from adjuvant chemotherapy

Bilchik A, Ann Surg Oncol. 8 (2001)
- 492 consecutive patients (401 colon, 91 rectal cancers)
- overall SLN identification: 97.8% (most of the failures in rectal cancers due to local submucosal lymphatic fibrosis induced by neoadjuvant radiation therapy)
- overall accuracy: 95.4% (89.3% sensitivity)
- overall incidence of skip metastasis: 10.9%.
Sentinel lymph node biopsy

Colorectal cancer

PET/CT staging before radiation-chemotherapy
4 subdermal or submucosal injections are performed around the primary tumour, with a total administered activity ranging from 5 to 37 MBq

SLN visualization in 75% to 100%

very frequent finding of bilateral lymphatic drainage: importance of preoperative lymphoscintigraphy
Sentinel lymph node biopsy

Anal cancer

Local recurrence
Radioguided Occult Lesion Localisation (ROLL)

Radioguided surgery of occult colonic lesions

Difficulties in resecting:
- residual tumour (after endoscopic excisional biopsies)
- small lesions (most in the right or left colonic flexure)
- in the presence of perivisceritis
  → marking the site to be resected with tattooes or metallic clips (placed during endoscopy)
  → endoscopic intralesional $^{99m}$Tc-MAA injection few hours before surgical resection, guided by probe

Preliminary results:
- high rates of surgical success
- reduce the invasiveness and the overall duration of surgery
RadioImmunoGuided Surgery

Technique simple and well known

Limitations:
- Scarce availability of specific MABs (not in colorectal cancer)
- Choice of the radionuclide to label the MoAb

Perspectives:
- Growing knowledge of antigen-antibody relationships
- Development of better tumour-targeting agents

‘Magic bullets’

Paul Ehrlich (1854-1915)
Monoclonal antibodies (MoAb)

- Globular protein (150,000 Dalton)
- Long circulatory half-life
- Affinity for antigen ($10^8$-$10^{11}$ M$^{-1}$)

Murine (-mo-)
Chimeric (-xi-)
(50-70% human)
Humanized (-zu-)
(~90% human)
Human

Decreasing immunogenicity
RIGS in colorectal cancer

anti-TAG-72 MoAb labeled with $^{125}\text{I}$

Surgery performed 20-24 days post-administration (75 MBq)
- first generation $^{125}\text{I}$-labeled murine B72.3 MoAbs
- second-generation $^{125}\text{I}$-labeled murine CC49 MoAbs
- third-generation $^{125}\text{I}$-labeled humanized CC49 MoAbs

anti-CEA MoAb $^{99m}\text{Tc}$-Arcitumomomab

Surgery performed within 24 hours post-administration
## RadiolImmunoGuided Surgery

<table>
<thead>
<tr>
<th>Authors (year)</th>
<th>Recurrent tumour (n)</th>
<th>Primary tumour (n)</th>
<th>MoAb (n)</th>
<th>Clinical impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin (1991)</td>
<td>86</td>
<td>---</td>
<td>86</td>
<td>13/53 (24.5%)</td>
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<tr>
<td></td>
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<td></td>
<td>P&lt;0.0001/0.0008 for survival</td>
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<tr>
<td>Cohen (1991)</td>
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<td>32</td>
<td>104</td>
<td>3/30 (10%)</td>
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<td></td>
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</tr>
<tr>
<td>Arnold (1995)</td>
<td>---</td>
<td>31</td>
<td>---</td>
<td>10/37 (27%)</td>
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<td></td>
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<td></td>
<td>31</td>
<td>P&lt;0.0001 for survival</td>
</tr>
<tr>
<td>Bertsch (1995)</td>
<td>131</td>
<td>---</td>
<td>86</td>
<td>5/16 (31.3%)</td>
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<tr>
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<td>45</td>
<td>P&lt;0.0001 for survival</td>
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<tr>
<td>Bertoglio (1998)</td>
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<td>---</td>
<td>16</td>
<td>7/30 (23.3%)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>3/34 (8.8%)</td>
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<tr>
<td>Percivale (1998)</td>
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<td>---</td>
<td>30</td>
<td>P&lt;0.0002 for survival</td>
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### colorectal cancer

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### pancreatic adenocarcinoma

LaValle (10 patients): $^{125}$I-CC49 MoAb
**18FDG (2-deoxy-2[18F]fluoro-D-glucose)**

Otto Warburg, Nobel 1931

Non specific uptake

**Glucose**

- **Transporter**
- **Hexokinase**
- **ATP**
- **ADP**
- **Glucose-6-P**
- **Krebs**

**FDG**

- **Transporter**
- **Hexokinase**
- **ATP**
- **ADP**
- **FDG-6-P**
Specific probes

High energy emitting radionuclides

Positron emitting radionuclides

Specific probes for high-energy photons

Beta probes (detect emitted positrons prior to annihilation)

Problems: Efficiency? Short penetration range of $\beta+$
$^{18}\text{F}}$FDG in colorectal cancer

$^{18}\text{F}}$FDG i.v. 150 – 500 MBq, 60 to 110 minutes before surgery
Intraoperative evaluation with detection probe more sensitive in detecting abdominal and pelvic recurrence
Preoperative PET imaging more sensitive in detecting liver metastases and other distant metastases
False positive results (inflammation): more specific PET tracers
Cost effectiveness?
Octreotide

Specific somatostatin receptors:
- Normal neuro-endocrine cells
- Other tissues (thyroid, breast, lung, prostate kidney)
- Lymphocytes
- Derived tumors (neuro-endocrine and carcinomas)
Neuroendocrine tumours

Heterogeneous group of rare tumours secreting bioactive substances (amines and hormones)
Characterized by the presence of peptide receptors on their cell membrane
Generally good prognosis, but important disparities in their evolution/progression potential (in the aggressive forms, the therapeutic strategies are limited)
Surgery is the only curative therapeutic option for NETs. The effectiveness of surgical treatment is dependent on the complete excision of all tumour tissue; therefore, localization of primary as well as metastatic tumours is crucial.
Optimal strategy in NETs
to assess the uptake characteristics of the lesion, with a preoperative scintigraphy
to inject 100-150 MBq of $^{111}$In-labelled octreotide on the day before the surgery
to administer laxatives on the day before the surgery
to use appropriate probe for $^{111}$In detection
Fluorescent tracers

Bimodal tracers

Simultaneous radioguided and fluorescent detection

I. Miyashiro, J Gastric Cancer (2012)

Gastric cancer

Brouwer OR, Ann Surg Oncol (2012)
Conclusion

Potential advantages of lymphatic mapping in colorectal cancers less obvious than in breast cancer or melanoma → procedure performed in strictly controlled clinical trials. In the next future,
- development of more specific ligands
- modifications of the scintillation detector will concern both gamma and beta detection
→ Promising technique
Thanks for your attention

Congress 2013