Surgery in GEP-NETs

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Chairs:
J.Y. Blay, FR
P.G. Casali, IT
R. Stahel, CH

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Primary GEP-NENs and NELM

- Primary location: prognostic impact and peculiar surgical aspects
- Primary GEP-NENs without metastatic spread → surgical resection with lymph node basin
- Tailored treatment based on biological aggressiveness and surgical burden
- Low aggressive NETs (eg. type 1 gastric NETs, small rectal NETs) → endoscopic management/local excisions
- High surgical burden and borderline disease (eg. <2 cm pNETs of the pancreatic head) → consider watchful wait policy
- Distant metastases in nearly 50% of NETs, mostly liver-limited
- NELM → high prognostic impact

*Frilling et al, Lancet Oncology 2014*
Available strategies and endpoints for NELM

**CURATIVE APPROACHES**
- **Liver resection** of NELM before (liver first), after or concomitant to resection of primary tumor and extrahepatic disease
- **Liver transplantation** after resection of primary tumor ± bridge/neoadjuvant treatment

**PALLIATIVE APPROACHES**
- **Resection of primary tumor** + medical or locoregional approaches to LM
- Medical treatment (SSA, CT, targeted agents, PRRT)
- **Debulking surgery**
- **Palliative liver transplantation**

**Endpoints**
- Overall survival
- Survival benefit (life gain of each strategy with respect to alternative options)
- Recurrence free survival (for curative approaches)
- Progression free survival (for palliative approaches)
- Symptom control
- Primary tumor resection in NELM

- Indications to liver resection for NELM

- Is debulking surgery ever indicated?

- Liver transplant for NELM
- Primary tumor resection in NELM

- Indications to liver resection for NELM

- Is debulking surgery ever indicated?

- Liver transplant for NELM
NELM: role of primary tumor resection

Zheng, Cancer Medicine 2019

Primary tumor resection:
- reduces tumor burden and controls endocrine and local tumor-related symptoms/complications
- delays the progression of LM (removes the source of LM and reduces essential hormones and growth factors)
- Eases liver-directed treatments

Citterio, EJSO 2017

Liu, Journal of Cancer 2019
NELM: guidelines treatment algorithm

Morphological and functional imaging

Resection of primary

(a) Simple pattern of LMs G1/G2 (unilobar or limited)
   - Resection (minor or anatomical)
   - Ablation (RFA, LITT)
   - TACE, TAE, SIRT*

(b) Complex pattern of LMs G1/G2 (bilobar)
   - One-step surgery
     - Major liver resection ± RFA
   - Two-step surgery
     - (1) Minor resection ± RFA, RPVE, RPVL
     - (2) Sequential major liver resection
   - Or surgery contraindicated

(c) Diffuse LMs G1/G2
   - Small intestinal
     - SSA (IFN)
     - PRRT
     - Everolimus
   - Pancreatic
     - SSA (IFN)
     - Chemotherapy
     - Everolimus
     - Sunitinib
     - PRRT

Selected cases (<1%)

Liver transplantation

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

ENETS guidelines, Neuroendocrinology 2016
- Primary tumor resection in NELM

- Indications to liver resection for NELM

- Is debulking surgery ever indicated?

- Liver transplant for NELM
Liver resection with curative intent: indications

- G1/G2 with type I or selected type II metastases
  type I: unifocal/oligometastatic
  type II: one involved hemiliver +/- limited contralateral disease

- Primary tumor and extrahepatic disease resected or resectable

- Liver disease can be macroscopically resected/ablated with the preservation of enough functional disease-free liver remnant according to the body surface area of the patient

- Overall, liver resection can be offered to a relatively small proportion of patients (10-25%)

Frilling A, Endocr Metab Clin N Am 2018
Lesurtel M, HPB 2014
Resection of LM from G1-G2 GEP-NETs has about 85% survival compared with 30% with no resection (irrespective of other treatment). Several non-randomized series document the benefit of surgical resection, either complete or cytoreductive, compared with non-resection treatment.
Liver resection offers a chance of definitive cure in a relatively small and selected proportion of patients

- Median OS after hepatic resection largely varies from 52 to 190 months
- 5-year OS between 41% and 100%
- Median RFS between 15 and 50 months (<40% at 5 years in most series)
Recurrence after R0 liver resection

Multi-institutional database, 322 patients
After curative intent liver surgery, 209 patients (64.9%) recurred
Recurrence was intrahepatic only ($n = 111$, 65.7%), extrahepatic only ($n = 19$, 11.2%) or intra- and extra-hepatic ($n = 39$, 23.1%)

Peak incidence at 12 months
Early recurrence ($\leq 1$ year)
Late recurrence ($>1$ year)

10-year OS among patients who underwent repeat surgery or IAT was 60.3% (95%CI, 34.1-78.8) and 52.0% (95%CI, 30.6-69.9)
Factors affecting prognosis after liver resection

Primary site

- Pancreatic NET
- Small Intestine NET
- Overall

Tumor grading

- Well differentiated (n=52)
- Poorly differentiated (n=11)
- Moderately differentiated (n=11)

Survival (mean, 95% CI)

Frilling, Lancet Oncology 2014
Saxena et al, Surgery 2011
### Factors affecting prognosis after liver resection

#### Extrahepatic disease

**Multi-institutional series, 339 pts (1985-2009)**

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Multivariate</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td></td>
<td>1.23</td>
<td>0.76–1.98</td>
<td>0.40</td>
</tr>
<tr>
<td>Patient symptomatic</td>
<td></td>
<td>1.17</td>
<td>0.65–2.11</td>
<td>0.60</td>
</tr>
<tr>
<td>Pancreatic primary NET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown location primary NET</td>
<td></td>
<td>1.29</td>
<td>0.61–2.71</td>
<td>0.51</td>
</tr>
<tr>
<td>Nonfunctioning NET</td>
<td></td>
<td>1.99</td>
<td>1.12–3.53</td>
<td>0.019</td>
</tr>
<tr>
<td>Synchronous disease</td>
<td></td>
<td>1.88</td>
<td>1.13–3.15</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt;50% Hepatic involvement</td>
<td></td>
<td>1.18</td>
<td>0.67–2.11</td>
<td>0.57</td>
</tr>
<tr>
<td>Type of first liver operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection plus ablation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2 resection</td>
<td></td>
<td>1.37</td>
<td>0.79–2.19</td>
<td>0.29</td>
</tr>
<tr>
<td>No adjuvant treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of extrahepatic disease</td>
<td></td>
<td>3.04</td>
<td>1.73–5.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Better prognosis is related to the absence of extrahepatic disease at the time of the first liver directed therapy.
Factors affecting prognosis after liver resection

Margin Status

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Total Patients, n</th>
<th>R0/R1 Resection, N</th>
<th>PFS</th>
<th>R2 Resection, N</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fairweather et al, 2017</td>
<td>649</td>
<td>58</td>
<td>5 y 90% 10 y 70%</td>
<td>NR</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Maxwell et al, 2016</td>
<td>228</td>
<td>—</td>
<td>—</td>
<td>108</td>
<td>Median 10.5 y 5 y 76.1%</td>
<td>Median 5.2 y 5 y 30.2%</td>
</tr>
<tr>
<td>Saxena et al, 2011</td>
<td>74</td>
<td>48</td>
<td>Median 98 mo</td>
<td>Median 48 mo</td>
<td>26</td>
<td>Median 27 mo</td>
</tr>
<tr>
<td>Sci gliano et al, 2009</td>
<td>41</td>
<td>37</td>
<td>R0 88% R1 92%</td>
<td>R0 31%</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Frilling et al, 2009</td>
<td>119</td>
<td>23</td>
<td>100%</td>
<td>96%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gomez et al, 2007</td>
<td>18</td>
<td>15</td>
<td>86%</td>
<td>90%</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>Elias et al, 2003</td>
<td>47</td>
<td>37</td>
<td>R0 74% R1 70%</td>
<td>R0 66%</td>
<td>10</td>
<td>47%</td>
</tr>
<tr>
<td>Sarmiento et al, 2003</td>
<td>170</td>
<td>75</td>
<td>76%</td>
<td>—</td>
<td>95</td>
<td>—</td>
</tr>
</tbody>
</table>

- In R0-R1 resection both symptomatic relief (> 90%) and survival benefit are achieved
- Outcomes of R1 and R2 resection do not differ significantly
- Considered as a **debunking procedure** since tumor is frequently left behind
- No adjuvant strategies are designed yet for marginal resections
- Primary tumor resection in NELM
- Indications to liver resection for NELM
- Is debulking surgery ever indicated?
- Liver transplant for NELM
Debulking surgery

“In view of the high rates of disease recurrence regardless of margin status [...] and also data suggesting a lack of “penalty” on OS/PFS in terms of margins, one may posit that all resections for NELM are in actuality cytoreductive and differ only in the duration of disease control”
Debulking surgery
Symptoms relief and survival

**Indications:**
1. Uncontrolled hormonal syndrome
2. Tumor-related pain
3. Obstructive symptoms

Symptomatic relief is achieved in >90% of patients, with a mean duration of 16 to 26 months

**Wright, Surg Oncol Clin N Am 2007**
**Cramer, Clin Nucl Med 2016**

- Attaining 70% disease resection may be beneficial, possibly without inferior outcomes with respect to 90%
- No differences in OS based on % debulked, only max diam ≥5 cm correlated with death
Debulking surgery vs. locoregional treatments

339 LR vs. 414 IAT → no survival benefit
52 LR vs. 66 IAT after propensity score matching:

Patients with high-volume symptomatic disease obtained the greatest benefit from surgical management.

There is no evidence to support improved outcomes from cytoreductive hepatic surgery over intra-arterial therapies in NELM.

Osborne, Ann Surg Oncol 2006

Mayo, Ann Surg Oncol 2011

Cochrane 2009
- Primary tumor resection in NELM
- Indications to liver resection for NELM
- Is debulking surgery ever indicated?
- Liver transplant for NELM
Resection of primary

(a) Simple pattern of LMs G1/G2 (unilobar or limited)
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     - SIRT*

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     - SSA (IFN)
     - PRRT
     - Everolimus
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     - Chemotherapy
     - Everolimus
     - Sunitinib
     - PRRT

   - Liver transplantation

Selected cases (<1%)
Endpoints of surgical treatments

- Liver transplant → limited resource depending on graft availability
- Pure overall survival perspective is an unsuitable endpoint
- **Transplant benefit** = survival achieved with LT - survival obtained by non-transplant options
- Liver transplant has to be justifiable in terms of organ allocation

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**Liver Resection**

- Magnitude of adverse prognostic factors
- Magnitude of survival
- Avoidance of futility

**Liver Transplantation**

- Survival rates obtained through non-transplant alternative options
- Demonstration of transplant **benefit**

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Droz dit Busset, Mazzaferro
Updates in Transplantation and Hepatobiliary Surgery, Springer Nature, 2020
Clinical presentation of NELM defines treatment allocation based on curative or palliative perspectives.
Clinical presentation of NELM defines treatment allocation based on curative or palliative perspectives.

- Curative resection
- Curative transplantation
- Debulking/ Palliative transplantation
Late stage

5-yr survival <50% (rescue)

Early stage

5-yr survival >90% (curative)

Reduce tumor burden and subtract adverse prognostic factors (restrictive selection criteria)

Improve patients’ outcome
Milan NET criteria for patients with NELM

1. Confirmed histology of low-grade (G1-G2) neuroendocrine tumors

2. Primary tumor drained by the portal system removed with all extrahepatic deposits in a separated pre-transplant curative resection

3. Metastatic diffusion to liver parenchyma <50%

4. Response/stable disease for at least 6 months during the pre-LT period

5. Age <65 years

Reduce tumor burden and subtract adverse prognostic factors (restrictive selection criteria) ▶ Improve patients’ outcome

1. [Coppa, Transpl Proc 2001]
2. [Stutcliffe, Am J Surg 2003]
3. [Mazzaferro, J Hep 2007]
Milan NET criteria for LT: matched comparison

**OS**

- Group 1: LT
  - Survival probability: 88.8%
- Group 2: no LT
  - Survival probability: 22.4%

**TTP**

- Group 1: LT
  - Survival probability: 89%
- Group 2: no LT
  - Survival probability: 13.1%

### Patients at risk

<table>
<thead>
<tr>
<th>Months after diagnosis</th>
<th>Patients at risk Group 1: LT</th>
<th>Patients at risk Group 2: no LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>30</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>40</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>50</td>
<td>42</td>
<td>42</td>
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<tr>
<td>60</td>
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<tr>
<td>70</td>
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<td>42</td>
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<td>80</td>
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<td>90</td>
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<td>42</td>
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<td>100</td>
<td>42</td>
<td>42</td>
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<tr>
<td>110</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>120</td>
<td>42</td>
<td>42</td>
</tr>
</tbody>
</table>

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>GROUP 1: LT</th>
<th>GROUP 2: no LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-yr OS</td>
<td>97.2%</td>
<td>50.9%</td>
</tr>
<tr>
<td>10-yr OS</td>
<td>88.8%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Median OS</td>
<td>NR</td>
<td>62 months</td>
</tr>
<tr>
<td>Median TTP</td>
<td>NR</td>
<td>20 months</td>
</tr>
</tbody>
</table>
**SURVIVAL BENEFIT ESTIMATION**

**Univariable model**

<table>
<thead>
<tr>
<th></th>
<th>D-MST (CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 5 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 vs Group 2</td>
<td>12.79 (7.95,17.63)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 10 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 vs Group 2</td>
<td>48.62 (35.49,61.75)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Multivariable model (adjusted for propensity score)**

<table>
<thead>
<tr>
<th></th>
<th>D-MST (CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 5 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 vs Group 2</td>
<td>6.82 (1.10,12.54)</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 10 years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 vs Group 2</td>
<td>38.43 (21.41,55.45)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Impressive survival benefit has potential for radical changes in treatment algorithm**

*Mazzaferro, Am J Transpl 2016*
### Table 22.2 Literature review of liver transplantation for metastases from NETs (series reporting at least 10 patients)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Number of pts</th>
<th>Inclusion criteria</th>
<th>Median OS/DFS (months)</th>
<th>5-year/10-year OS</th>
<th>5-year/10-year RFS</th>
<th>Adverse prognostic factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mozzaferro et al. [7]</td>
<td>Prospective, single center</td>
<td>42</td>
<td>NELM from primary drained by portal system, previous resection of extrhepatic disease, ≤50% liver parenchyma involved, G1/G2, age &lt;60 years, PR/SD for 6 months (histology confirmed)</td>
<td>–</td>
<td>97.2%/88.8%</td>
<td>86.9%/86.9%</td>
<td>Age (&lt;42 and &gt;54)<em>, site of primary</em>, WHO grading, MIB-1</td>
</tr>
<tr>
<td>Sher et al. [12]</td>
<td>Retrospective, multicenter</td>
<td>85</td>
<td>NELM from GEP-NETs or other/unknown primary ± multivisceral transplant or visceral resection</td>
<td>–</td>
<td>32%/-</td>
<td>–</td>
<td>Macrovascular invasion*, grading, extent of resection added to LT*, Ki-67&gt;2%, G2, PRBC transfusions,</td>
</tr>
<tr>
<td>Grät et al. [13]</td>
<td>Retrospective, single center</td>
<td>12</td>
<td>NELM from GEP-NETs, G1/G2</td>
<td>–</td>
<td>78.6%/78.6%</td>
<td>51.6%/15.5%</td>
<td>Major resection added to LT*, G3*, hepatomegaly*, Wait time to LT &lt;2 months</td>
</tr>
<tr>
<td>Le Tréut et al. [14]</td>
<td>Retrospective, registry-based</td>
<td>213</td>
<td>NELM from bronchial or GEP-NETs ± visceral resection</td>
<td>67/24</td>
<td>52%/-</td>
<td>30%/-</td>
<td>Higher bilirubin*, higher donor creatinine*, lower albumin</td>
</tr>
<tr>
<td>Gedaly et al. [15]</td>
<td>Retrospective, registry-based</td>
<td>150</td>
<td>NELM from GEP-NETs or other/unknown primary ± multivisceral transplant</td>
<td>–</td>
<td>48%/-</td>
<td>32%/-</td>
<td>Age ≥55, simultaneous LT-pancreatic resection</td>
</tr>
<tr>
<td>Nguyen et al. [16]</td>
<td>Retrospective, registry-based</td>
<td>110</td>
<td>NELM</td>
<td>–</td>
<td>58.6%/-</td>
<td>57.8%/-</td>
<td>–</td>
</tr>
<tr>
<td>Maillé et al. [17]</td>
<td>Systematic review</td>
<td>85</td>
<td>NELM</td>
<td>–</td>
<td>54.45%/-</td>
<td>44%/-</td>
<td>–</td>
</tr>
<tr>
<td>Le Tréut et al. [18]</td>
<td>Retrospective, multicenter</td>
<td>85</td>
<td>NELM from bronchial or GEP-NETs ± visceral resection</td>
<td>56/-</td>
<td>47%/-</td>
<td>20%/-</td>
<td>Upper abdominal exenterations*, duodenopancreatic primary*, hepatomegaly* Ki-67&gt;2%</td>
</tr>
<tr>
<td>Olausson et al. [19]</td>
<td>Retrospective, single center</td>
<td>15</td>
<td>NELM from GEP-NETs ± multivisceral transplant</td>
<td>–/22.8</td>
<td>90%/-</td>
<td>20%/-</td>
<td>–</td>
</tr>
<tr>
<td>Frilling 2006 et al. [20]</td>
<td>Retrospective, single center</td>
<td>16</td>
<td>NELM, absent or resectable extrhepatic spread, progressive hepatic tumor load, refractory symptoms, Ki-67 &lt;10%</td>
<td>–</td>
<td>67%/-</td>
<td>48%/-</td>
<td>–</td>
</tr>
<tr>
<td>Van Vilsteren et al. [21]</td>
<td>Prospective, single center</td>
<td>19</td>
<td>NELM, complete resection of primary, absent extrhepatic spread with exception of perihepatic lymph nodes</td>
<td>–</td>
<td>88% (1 year OS)/-</td>
<td>80% (1yRFS)/-</td>
<td>–</td>
</tr>
<tr>
<td>Florman et al. [22]</td>
<td>Retrospective, single center</td>
<td>11</td>
<td>NELM from GEP-NETs (histology confirmed), unresectable, progressive or with uncontrolled symptoms</td>
<td>–</td>
<td>36%/-</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cahin et al. [23]</td>
<td>Retrospective, single center</td>
<td>10</td>
<td>NELM from bronchial or GEP-NETs ± multivisceral transplant</td>
<td>–</td>
<td>80%(2 years OS)/-</td>
<td>–</td>
<td>Ki-67 &gt;5%, aberrant staining for E-cadherin, positive regional lymph nodes at LT</td>
</tr>
<tr>
<td>Rosenau et al. [24]</td>
<td>Retrospective, single center</td>
<td>19</td>
<td>NELM from bronchial or GEP-NETs ± visceral resection, symptomatic</td>
<td>–/10.5</td>
<td>80%/50%</td>
<td>21%/21%</td>
<td>–</td>
</tr>
</tbody>
</table>
Take home messages

- In non-metastatic disease, resection of the primary and the lymph node basin is the mainstay of treatment.
- In selected cases of metastatic NETs, resection of the primary tumor is indicated both to prevent complications and improve survival.
- In selected patients with resectable NELM, surgical resection should be the first option, although a chance of definitive cure is possible only in a relatively small group of patients.
- Debulking surgery can improve both control of hormonal and cancer-related symptoms and survival.
- Under restrictive criteria, liver transplantation provides the best long-term outcome among any other available treatment; the survival-benefit increases over time.
Thank you!

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