ICG Fluorescence Imaging

Takeaki ISHIZAWA and Norihiro KOKUDO
Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Surgery, The University of Tokyo
Clinical applications of fluorescence imaging to cancer surgery have been limited to:

- Malignant gliomas (five-aminolevulinic acid)\(^1\)
- Sentinel lymph nodes in breast cancers (Indocyanine green [ICG])\(^2\)
- Liver cancers (ICG)\(^3,4\)

2. Kitai T. Breast Cancer 2005
3. Ishizawa T & Kokudo N. Cancer 2009
Background ICG-fluorescence imaging

LED (760nm)

Fluorescence (830nm)

Long-pass filter

CCD
Background  ICG-fluorescent cholangiography

Kawaguchi, Ishizawa, Kokudo. JACS 2011
Background ICG-fluorescent cholangiography
Background

ICG-fluorescent cholangiography

HCC shows fluorescence before ICG administration!!
Background  Fluorescence imaging of HCC

Ishizawa T & Kokudo N. Cancer 2009
Background

Preoperative ICG-retention test

- Ascites
  - None or controlled
    - Total bilirubin
      - Normal
        - ICG R15
          - Normal
            - Tri/bi-sectoriectomy
        - 1.1-1.5
          - Limited resection
        - 1.6-1.9
          - Enucleation
        - >= 2.0 mg/dL
          - Contraindication
            - >= 40%
    - Uncontrolled

Background

Aims

1) To demonstrate mechanistic background of ICG-fluorescent imaging of liver cancers

2) To introduce clinical applications of ICG-fluorescent imaging during liver resection
Methods of ICG-fluorescence imaging

Administration of ICG

- ICG (0.5 mg/kg) was intravenously injected within 2 weeks before surgery as part of a routine liver function test.
Methods of ICG-fluorescence imaging

Fluorescent imaging system
- 36 LEDs (760 nm) and a CCD camera, which can filter out light below 820 nm.

PDE (Hamamatsu Photonics, Hamamatsu, Japan)
Examination on the liver surfaces

- Fluorescent images of liver surfaces were obtained using fluorescein imaging system.

Methods of ICG-fluorescence imaging
Methods of ICG-fluorescence imaging

Examination on the resected specimens

- All of the cut surfaces were investigated following liver resection in the OR.
Fluorescent patterns of HCC

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Total</th>
<th>Partial</th>
<th>Rim</th>
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<tbody>
<tr>
<td>Well</td>
<td>58</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>72</td>
<td>100</td>
<td>14</td>
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<td>Poor</td>
<td>0</td>
<td>5</td>
<td>18</td>
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(Non-fluorescing HCCs, n = 3)
Cancer detectability of ICG-fluorescence imaging

- Sensitivity: 99%, PPV: 94%
Fluorescent patterns of HCC

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(Non-fluorescing HCCs, n = 3)
Fluorescent patterns

- **Total**
- **Partial**
- **Rim**

Cancerous fluorescence

( c )

( r )
Fluorescent microscopy

HCC showing cancerous fluorescence
Fluorescent microscopy

HCC showing rim-type fluorescence
Mechanistic background of ICG-fluorescence imaging of HCC

Non-cancerous liver
C/N ratio of gene expression (n = 19)

Uptake transporters

Excretion transporters
Immunohistochemical staining

NTCP

OATP8

Rim-type

Cancerous-type
Cancerous-type HCC
Rim-type HCC

ICG-fluorescence imaging of CRLM

Ishizawa T & Kokudo N. Cancer 2009
ICG-fluorescence imaging of CRLM

van der Vorst JR, Frangioni JV, Vahrmeijer AL. Cancer 2013
ICG-fluorescence imaging of CRLM

van der Vorst JR, Frangioni JV, Vahrmeijer AL. Cancer 2013
Clinical application of ICG-fluorescence imaging

Advantages:
• Safety and feasibility
• High sensitivity
• Real-time examination

Limitations:
• Tissue permeability (up to 5-10 mm)
• False positives
Expected role of ICG-fluorescent imaging is to detect:

- peripherally-located but invisible liver cancer
- new lesions to be resected (close to $\phi 1$cm)
- HCC tissues left on the raw surface
- small (early) HCCs in the resected specimen
- cholestatic areas caused by cancer invasion
Case 1 Identification of HCC before resection
Case 1: Identification of HCC before resection
Case 1  Identification of HCC before resection
Case 1
Identification of HCC before resection
Laparoscopic partial hepatectomy (S VI) using ICG-fluorescence imaging

University of Tokyo
Ishizawa T, Kokudo N
Clinical application of ICG-fluorescent imaging

Expected role of ICG-fluorescent imaging is to detect:

- peripherally-located but invisible liver cancer
- new lesions to be resected (close to \( \phi 1 \text{cm} \))
- HCC tissues left on the raw surface
- small (early) HCCs in the resected specimen
- cholestatic areas caused by cancer invasion
Case 3 Identification of HCC before resection
HCC (S2) with intrahepatic metastases
Case 3  Identification of HCC before resection
Clinical application of ICG-fluorescent imaging

Expected role of ICG-fluorescent imaging is to detect:

- peripherally-located but invisible liver cancer
- new lesions to be resected (close to $\phi 1\text{cm}$)
- HCC tissues left on the raw surface
- small (early) HCCs in the resected specimen
- cholestatic areas caused by cancer invasion
Case 4
Examination of the raw surface
Fluorescent lesions on the raw surface of the liver after resection
Case 4

Examination of the raw surface
Clinical application of ICG-fluorescent imaging

Expected role of ICG-fluorescent imaging is to detect:

- peripherally-located but invisible liver cancer
- new lesions to be resected (close to $\phi 1\text{cm}$)
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- cholestatic areas caused by cancer invasion
Case 5
Examination of the resected specimen

Partial resection of S2 and S3
Case 5 Examination of the resected specimen
Case 5  Examination of the resected specimen
Case 6 Examination of the resected specimen

Main tumor and a daughter nodule
Case 7

Examination of the resected specimen
Case 7
Examination of the resected specimen
Conclusion

NTCP and OATP8 play a major role in the portal uptake of ICG in differentiated HCC cells, enabling highly sensitive identification of cancerous tissues by intraoperative ICG fluorescence imaging.
• Ishizawa T & Kokudo N. Mechanistic Background and Clinical Applications of Indocyanine Green Fluorescence Imaging of Hepatocellular Carcinoma. Ann Surg Oncol 2013 (e-pub)
Fluorescent Imaging
Treatment of Hepatobiliary and Pancreatic Diseases

Editors
N. Kokudo
T. Ishizawa

KARGER