Features of telemedicine focusing on predictive cancer diagnosis

Klaus Kayser, Stephan Borkenfeld, Amina Djenouni, Bathuyag Sereejav, Gian Kayser

Tissue – based diagnosis
Definition & recent approaches
Present stage of telemedicine
Predictive Diagnosis
Definition & Algorithms
Applications in Cancer diagnosis
Perspectives
Definition of tissue based diagnosis

• Tissue based diagnosis is the interpretation of images obtained from the human body at light microscopy and higher magnification in combination with clinical data.

• It includes histology, cytology, molecular biology, cytogenetics, molecular genetics, electron microscopy, and biochemistry images.

Medical Diagnosis is mainly derived from Visual Information
Tissue – based diagnosis types

- **Classic diagnosis:** H&E, PAS, cytoskeleton, organ origin markers
- **Prognosis estimation:** quantitative immune/ligand histochemistry
- **Therapy advises (predictive):** gene analysis & receptors.
- **Risk estimation (array technique):** gene analysis
Definition / Background

Telepathology is tissue based diagnosis at a distance, part of telemedicine.

Telepathology can serve for

• Medical diagnosis assistance independent on distance, date, language: frame of laboratory data;
• Use in daily routine, science, education, training;
• Direct transfer of diagnosis to centers of treatment and patients’ care.
• Technology: According to social forums (php).
Workflow of a TMCC tuned for developing countries

- **Client**
  - Upload image
  - External Information
    - Language Translation
    - Access Library NIH
    - Measurements
    - ROI Low Magnification
  - Quality Control
  - Confirmed Report (pdf)
  - Teaching Tools, Tests

- **Experts on duty**
  - Diagnosis Assistants

- **Client Expert Communication**
  - Off line: email, SMS, Facebook, Twitter
  - On line: Skype, Chat, Videoconferencing

- **Relational Database**

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(Forum: MECES, www.diagnomx.eu)
Tumor cell sociology

- Definition (analogous to epigenetics)
- Epigenetics involves modifications of the activation of certain genes, but not the basic structure of DNA.
- Cancer cell neighbors involve the behaviour of the involved cancer cell but not its basic features.
- Properties of nearest neighbor:
  - Cell type (cancer cell – macrophage)
  - Membrane receptors
  - Proliferation stage (cell cycle)
  - Structural differences
- How to measure?

http://en.wikipedia.org/wiki/Epigenetics
Tumor cell sociology and syntactic structure analysis

Definition

Syntactic structure analysis is the measure of any structure by "decomposition" into its basic units.

- The aim is to figure out how the texture of any image is generated.
- Measure: <structural entropy>. 


<table>
<thead>
<tr>
<th>Entropy calculation</th>
<th>H &amp; E</th>
<th>Calretinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shannon‘s entropy:</td>
<td>2.84</td>
<td>4.36</td>
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<tr>
<td>Texture entropy:</td>
<td>6.58</td>
<td>6.79</td>
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<tr>
<td>Total entropy (cluster)</td>
<td>14.35</td>
<td>19.94</td>
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<tr>
<td>Entropy Primitives</td>
<td>0.51</td>
<td>0.79</td>
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<tr>
<td>Structure entropy</td>
<td>0.58</td>
<td>0.83</td>
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<tr>
<td>No of clusters:</td>
<td>23</td>
<td>51</td>
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</table>

![Image of entropy calculation](image1.png)

![Image of H & E staining](image2.png)

![Image of Calretinin staining](image3.png)
Example protein - carbohydrate recognition

It is probably a “high order” biological steering mechanism, and important for cell to cell and cell to matrix interactions, thus for

- growth regulation (apoptosis)
- cellular maturation
- organ development
- organ - environment behavior
Predictive Pathology in human Cancer

• **Aim:** to analyze extra- and intracellular pathways of cellular proliferation
• Provides information on membrane proteins in combination with intracellular pathways (gene expression)
• Specifies the potential therapy (by adding specific antibodies to cytostatic therapy)
• **Guides the oncologist**
• **Examples:** Her2_neu breast carcinoma, EGFR lung cancer
## Algorithms of predictive diagnosis

<table>
<thead>
<tr>
<th>Surgery, Radiology H&amp;E, IHC</th>
<th>Conventional diagnosis</th>
<th>Tumor extension</th>
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</thead>
<tbody>
<tr>
<td>IHC, FISH</td>
<td>Membrane receptors (*)</td>
<td>Cellular communication</td>
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<tr>
<td>IHC, PCR, FISH, TMA</td>
<td>Proteins, RNA, miRNA (**)</td>
<td>Intracellular pathways</td>
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<tr>
<td>PCR, RNA, DNA assays</td>
<td>Cancer-related target genes (***))</td>
<td>Gene anomalies</td>
</tr>
</tbody>
</table>

(*) EGFR, VGFR, etc.; (**) \(BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A\); (***\) raf, myc, EML4,...
Her2_neu breast carcinoma / entropy

Score 2+ Trastuzumab therapy?

FISH amplification: Her2/neu gene

Microstages: tumor cells
IHC macrostages:
Tumor cells \{3+, 2+, 1+, 0\}
Connecting membranes \{n,M^+\}, \(n=1-4, M=0-3\)
\(\Sigma = 16\)

Microstages: tumor cells
FISH macrostages:
Nuclear signals \{n, F^+\}
n number of neighbors \(n=1-4, F=0-3\)
\(\Sigma = 16\)
## Results: IHC

Microstages: $\Sigma$ tumor cells: 320

$M(0+) = 22$, $M(1+) = 66$, $M(2+) = 214$, $M(3+) = 38$, $N = \text{No neighbors}$

Entropy: 1.03 Macrostages: 16

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<thead>
<tr>
<th></th>
<th>N</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>19</td>
<td>16</td>
<td>3</td>
<td>0</td>
<td>1.09</td>
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</table>
Results: FISH

Microstages: Σ tumor cells: 120
FISH(0+) = 8, FISH(1+) = 16, FISH(2+) = 46, FISH(3+) = 50
Entropy: 1.18  Macrostages: 16

<table>
<thead>
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<td>3</td>
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<tr>
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<td>6</td>
<td>4</td>
<td>6</td>
<td>0</td>
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<tr>
<td>FISH</td>
<td>2</td>
<td>6</td>
<td>9</td>
<td>17</td>
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<tr>
<td>FISH</td>
<td>3</td>
<td>9</td>
<td>23</td>
<td>13</td>
<td>5</td>
</tr>
</tbody>
</table>
Molecular markers – potential EGFR inhibition

**Extracellular:** Erbitux

**Intracellular:** Erlotinib Gefitinib

230 Patients with therapy relevant mutation in EGFR-Gene

**Standard-Chemotherapy:** Carboplatin + Paclitaxel

Maemondo et al. NEJM 2010

362:2380-2388
Molecular markers that add to EGFR therapy

- ERCC1 gene product functions in the nucleotide excision repair pathway involved in recombinational DNA repair and in the repair of inter-strand crosslinks, and is required for the repair of DNA

- RRM1 gene encodes one of two non-identical subunits which constitute ribonucleoside-diphosphate reductase that produces deoxyribonucleotides prior to DNA synthesis in dividing cells.
Molecular marker – ERCC1

83 Patients with N2-stage confirmed by mediastinoscopy
Molecular marker – ERCC1, entropy micro- and macrostages

Hwang Cancer 2008 113:1379-1386

| 320 | Σ No cells | 160 |
| {0, 30, 210, 80} | {0, 1+, 2+, 3+} | {148, 12, 0, 0} |
| 0.84 | Entropy | 0.28 |
| 1.67 ± 0.3 | MST Entropy | 1.43 ± 0.2 |
| 2.43 | Σ Entropy macrostages | 0.92 |
Workflow of a TMCC tuned for predictive diagnosis

FTP Forum (MECES, www.diagnomx.eu)

Upload images

Experts on duty

Email, SMS; phone

Video conference

Relational Database

Quality Control

Measurements

Teaching Tools

Tests

Confirmed Report

External Information
Pathologists agreed to found a virtual international pathology institute (VIPI) to:

- organize themselves under the umbrella of the European Society of Pathology (ESP)
- perform consultation & definite diagnosis
- work in an institute – like organization
- Advice for additional tissue examinations
- organize continent – based virtual slide centers in collaboration with industry.
Conclusions

IT on tissue – based diagnosis starts with conventional morphology & image standards -> **diagnosis** & MST entropy (flow) -> **survival**

Identification of molecular subtypes involved in cellular proliferation (EGFR), etc.. -> **therapy advices**

Quantitative analysis of cellular communication opens new perspectives for „targeted cancer therapy“. 

Open Forums (MECES) can steer diagnostic information at different levels between different pathologists and laboratories.
Predictive and Communicative Pathology acts as Pilot in Cancer Therapy

thank you very much for your attention