Next Generation Technologies for Intra-Operative Tumor Detection

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Background

- It is estimated that **40,000** new cases of primary brain tumors.
- More than **350,000** persons are living with a diagnosis of primary brain tumor in United Stated in 2000.
- Glioma is the second most common tumor, with very low survival rate.
- Glioblastoma one year survival rate is less than 5%.

**Figure. Distribution of All Primary Brain and CNS Tumors by Histology**

CBTRUS 1995-1999 (n=37,788)

- Glioblastoma: 23.0%
- Astrocytomas: 11.3%
- Ependymomas: 2.2%
- Oligodendrogliaomas: 4.0%
- Embryonal, including Medulloblastoma: 1.9%
- Other glial: 12.6%
- Nerve Sheath: 7.5%
- Craniopharyngioma: 0.8%
- Pituitary: 6.6%
- Meningioma: 27.4%
Treatment Options

• Chemotherapy
• Surgery with Craniotomy
• Radiation Therapy
• Stereotactic Radiation
• Linear Accelerator
• Gamma Knife
• Immunotherapy

Surgery remains the treatment of choice

The extent of tumor resection is the most important factor for survival in patients treated for malignant glioma.
Current Imaging

• Pre-operative:
  – CT, MRI and PET are all important pre-operative imaging techniques.
  – Multiple MRI images are also used for stereo-tactic surgery.

• All imaging techniques provide structural information.

• Only pathological diagnosis during surgery is “frozen Section”
• Intra-operative:
  – Intra-operative MRI is expensive and requires a special setup.
Neuro-Navigation

• Pre operative MRI is used for Neuro-Navigation

• But there is “Brain Shift”!
Operating Room 2.0

• Goal
  – To develop novel technology which can identify tumor against normal tissue intra-operatively in near real-time.
- TR-LIFS: (Smart tools)
  - Illuminate the tissue with ultra-fast laser
  - Record the fluorescent emissions from the tissue
  - Analyze the emissions and use the data to characterize the various tissues

- NIR imaging: (Augmented vision)
  - Tumor is tagged with a near-infra red dye with extremely high affinity
  - A full high definition fluorescence imaging system for visualization of tumor
  - Portable and safe
SMART TOOLS
Smart Sucker

• Basic Suction cannula is the most commonly used surgical device.

• What if the suction cannula can diagnose the tissue during surgical procedure?
Current Contenders

- A smart suction cannula can be include a novel tumor detection
  - Spectroscopy
    - Fluorescence Spectroscopy
    - Raman Spectroscopy
    - Reflectance Spectroscopy
    - Time resolved Laser Induced Fluorescence Spectroscopy (TRLIFS)

- TRLIFS measure decay characteristics of the intrinsic fluorescence (label free) of the tissue
Principle

- UV Light produces fluorescence
- Protein also emit light in different colors

\[ h(n) = \sum_{j=0}^{L-1} c_j b_j(n) \]
Intra-Operative Time Resolved Fluorescence Spectroscopy System

- Portable
- Safe: ~ 3µJ/pulse energy
- Near-real time
Near Real-Time
OR Data
Future Enhancements

• **Faster:** 30 times a second

• **Intelligent:** Machine learning classification algorithm

• **Integrate with the instruments:** Working with various companies to integrate the technology in the instruments
NIR IMAGING (AUGMENTED VISION)
Targeting Tumors
Chlorotoxin

- Chlorotoxin is a 36 amino acid knottin peptide with extremely high affinity to tumor cells and none towards normal mammalian cells.

- BLZ-100 (Blaze BioSciences) is a conjugate of chlorotoxin and the NIR dye indocyanine green (ICG)
Imaging System

• ICG is Near Infra Red Dye
  – Although NIR imaging system to image ICG are available in the market
  – They are used for vasculature
  – They do not have enough sensitivity to go down to cellular level concentrations

• Requirements for tumor visualization
  – High resolution (match current microscopes)
  – High sensitivity (detect a few cells)
  – Safe for intra-operative use (class 1 laser)
  – Combined visible and NIR view
  – Help surgeons achieve more complete surgical resections of cancerous growths

• Advantages of NIR imaging
  – No auto-fluorescence (great contrast)
  – Deeper penetration (tumor visible under normal tissue)
SIRIS Clinical prototype

- **Laser safety**
  - Class 1m (no safety regulations or goggles required)
- **Sensitivity**
  - SIRIS is 25 times more sensitive than Zeiss Pentero. It can detect concentrations as low as 1.6 nM
- **Field of View**
  - 150x80mm field at 45cm working distance
  - Working distance range of 30-70cm
- **Resolution**
  - Full HD at 30 frames / sec (VIS + NIR)
  - One pixel maps to 76µm at 45cm working distance
  - Combined with high sensitivity allows detection of up to 6 cells
  - Ability to record movies
- **Photo Bleaching**
  - No observed photo-bleaching
Animal Studies

• We have used our system to image
  – Glioblastoma implanted in nude mice
  – Lung cancer in Dogs
  – Brain Tumors in Dogs

• First human clinical trial in October at
  Department of Neurosurgery, Cedars-Sinai Medical Center
SIRIS in action
Acknowledgment

Fartash Vasefi, PhD
David Kittle, PhD
Adam Mamelak, MD

Blaze Bioscience, Inc

Dave Bruyette, DVM
OR 2.0: The Future

• Arther C. Clarke’s 2\textsuperscript{nd} Law:
  – The only way of discovering the limits of the possible is to venture a little way past them into the impossible.

• Terry Pratchett
  – It doesn't stop being magic just because you know how it works.