Nanofluorophore Assisted Fluorescence Image-guided Cancer Surgery

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ABSTRACT

The major challenge of the current cancer surgery is the inability to remove all existing tumor. Surgeons rely on presurgical imaging, intraoperative visualization/palpation, and experience to optimize tumor removal. In cases of uncertainty, biopsies are taken and sent to the pathology lab, and the surgical team will wait for the result, which may take thirty minutes or longer to return. Here we introduce an intraoperative image-guiding system of identifying tissues in cancer surgery: a portable visible/near-infrared camera system was designed to help surgeons visualize cancerous tumors intraoperatively; a hand-held spectroscopic device, together with a nanofluorophore - indocyanine green as imaging contrast agent, was developed as a tool for intraoperative tissue diagnosis. With the spectral analysis of the nanofluorophore in the tissues of interest, our device can help to diagnose the tissue properties in the surgery: the cancerous tissues show at least two times stronger fluorescence than the normal tissues do. This method provides a quick (< 1 sec) diagnosis of cancer intraoperatively.

Keywords

Nanofluorophore, Image-guided surgery, Cancer, Spectroscopy.

Introduction

There is a major clinical need to develop sensitive intraoperative imaging to aid the complete surgical resection of cancer to improve the prognosis of cancer patients. According to US and UK statistics, cancer occurs to one in every two men and one in every three women in their lifetime [1]. Surgery provides dramatic survival advantages across the major types of human malignant tumors [2]. Surgical judgment combined with frozen section analysis is currently the best methods we have to limit leaving cancer behind at time of surgery [3-7]. Frozen section analysis is costly and inefficient [6-9]. Tissues can only be sampled in several points; the quality of microscopic slides produced by the frozen section procedure intraoperatively is inferior to that of formalin fixed paraffin embedded tissue procedure postoperatively, which takes even longer time (several hours to days) to get the diagnosis result [6-8,10], due to the non-optimal pathological preparation of

the samples, the histological interpretation of the examination of these samples are limited [5,6,9,10].

Figure 1: The imaging system (left: overview) is designed to be used in the OR (top-right) to inspect the properties of tissues (bottom-right) based on the spectral information of the fluorescence of nanofluorophore.

Methods

To address this challenge, we designed a near-infrared (NIR) spectroscopy system [11-13] (Figure 1), together with NIR nanometer-sized fluorophore, to help surgeons and pathologists identify cancers and tumor margins intraoperatively and expediently. In the NIR wavelength range between 650 nm and 950 nm, the light has lower absorption by blood, water and lipids [14-16]; as a result, the signal-to-noise ratio in the imaging is greatly enhanced, while the autofluorescence is minimized [14-16]. NIR signal is out of the visible (VIS) range of human eyes; thus, the surgical field will not be altered by the introduction of NIR imaging contrast agents [16,17], and tissue penetration of light may be up to 1-2 cm [4,14-16]. Indocyanine green (ICG), is a nanometer-sized NIR fluorophore approved by US Food and Drug Administration (FDA), for its safety [18,19] and efficacy in image guided surgery [14-16]. Once injected intravenously, ICG binds to the serum proteins and preferentially accumulate in the tumor interstitial space than in the normal tissues, mainly by the enhanced permeability and retention (EPR) effect. The hand-held spectroscopic device can thus detect the tumors, positive margins, negative margins, from their fluorescence contrast to the normal tissues (Figure 2). We also engineered a VIS/NIR camera system to help the surgeons directly visualize this fluorescence contrast effect on a computer monitor (Figure 1). These two systems can provide intraoperative tissue identification within seconds, which provides surgeons with prompt feedback on whether further resections are necessary.

Figure 2: Spectroscopic diagnosis showed that the fluorescence in the cancerous tissue is much stronger than that in the normal fatty tissue.

Results

Using the spectroscopic device and the imaging systems, we have performed clinical trials on pancreatic cancers. The ex vivo studies on human cancer tissues were conducted according to the approved protocol by the Institutional Review Board at Emory University. The protocol was lead by Dr. Kooby; the clinical study was conducted at Emory Saint Joseph's Hospital. Our diagnosis

was verified by postoperative histopathology analysis.

A representative surgical case is shown in Figure 2. This patient had distal pancreatic cancer and went through a distal pancreatectomy, as well as a partial splenectomy. Using the ICG fluorescence of the normal fat as a reference, we indeed found that the ICG fluorescence of the tumor is dramatically higher (more than 6 times), which indicated the ICG-protein complex preferential accumulation at the cancerous tissues than in the normal tissues, mainly considered to be caused by the EPR effect [4,19,20].

Conclusions

In summary, we developed an imaging system to guide the cancer surgery: a portable VIS/NIR camera system was designed to help the surgeons within 1 sec to visualize the cancer location; a hand-held spectroscopic device, together with ICG as imaging contrast agent, was developed to provide the complete quantitative information of ICG NIR spectrum.

References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA: a cancer journal for clinicians. 2011; 61: 69-90.
2. Aliperti LA, Predina JD, Vachani A, et al. Local and Systemic Recurrence is the Achilles Heel of Cancer Surgery. Annals of Surgical Oncology. 2011; 18: 603-607.
3. Heppner GH. Tumor heterogeneity. Cancer Research. 1984; 44: 2259-2265.
4. Mohs AM, Mancini MC, Singhal S, et al. Hand-held spectroscopic device for in vivo and intraoperative tumor detection: contrast enhancement, detection sensitivity, and tissue penetration. Analytical chemistry. 2010; 9058-9065.
5. Peters SR. The art of embedding tissue for frozen section. Part I: a system for precision face down cryoembedding of tissues using freezing temperature-embedding wells. Journal of histotechnology. 2003; 26: 11-19.
6. Jaafar H. Intra-operative frozen section consultation: concepts, applications and limitations. The Malaysian journal of medical sciences: MJMS. 2006; 13: 4.
7. Prieto VG, Argenyi ZB, Barnhill RL, et al. Are en face frozen sections accurate for diagnosing margin status in melanocytic lesions? American journal of clinical pathology. 2003; 120: 203-208.
8. Balog J, Sasi-Szabo L, Kinross J, et al. Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. Science translational medicine. 2013; 5: 194ra193.
9. Bui MM, Smith P, Agresta SV, et al. Practical issues of intraoperative frozen section diagnosis of bone and soft tissue lesions. Cancer control. 2008; 15: 7-12.
10. Khalid A, Aul H. Touch impression cytology versus frozen section as intraoperative consultation diagnosis. Int J Pathol. 2004; 2: 63-70.
11. Ren J, Venugopalan J, Xu J, et al. Multi-channel LED light source for fluorescent agent aided minimally invasive surgery; 2014; 2017: 6927-6930.
12. Wu Y, Fu H, Quan H, et al. Modulation of Photocurrent in

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- Zinc-Based Metal Oxides Through Adjustment of a Magnetic Field and Localized Heating. *Science of Advanced Materials*. 2017; 7: 299-304.
13. Xu J, Kooby D, Kairdolf B, et al. New horizons in intraoperative diagnostics of cancer in image and spectroscopy guided pancreatic cancer surgery. *New Horizons in Clinical Case Reports*. 2017; 1: 2.
 14. Smith AM, Mancini MC, Nie S. Bioimaging: second window for in vivo imaging. *Nature nanotechnology*. 2009; 4: 710-711.
 15. Weissleder R. A clearer vision for in vivo imaging. *Nature biotechnology*. 2001; 19: 316-316.
 16. Frangioni JV. In vivo near-infrared fluorescence imaging. *Current opinion in chemical biology*. 2003; 7: 626-634.
 17. Troyan SL, Frangioni JV. The FLARE™ intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping. *Annals of surgical oncology*. 2009; 16: 2943-2952.
 18. Laperche Y, Oudea M-C, Lostanlen D. Toxic effects of indocyanine green on rat liver mitochondria. *Toxicology and applied pharmacology*. 1977; 41: 377-387.
 19. Madajewski B, Judy BF, Mouchli A, et al. Intraoperative near-infrared imaging of surgical wounds after tumor resections can detect residual disease. *Clinical Cancer Research*. 2012; 18: 5741-5751.
 20. Li X, Beauvoit B, White R, et al. Tumor localization using fluorescence of indocyanine green (ICG) in rat models. *International Society for Optics and Photonics*. 1995; 789-797.