Review of: "Tumor cell identification and classification in esophageal adenocarcinoma specimens by hyperspectral imaging"

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A commentary to *Tumor cell identification and classification in esophageal adenocarcinoma specimens by hyperspectral imaging*

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The most commonly used medical imaging techniques are represented by X-ray, computed tomography (CT), magnetic resonance imaging (MRI), optical imaging, ultrasonography and radionuclide imaging. CT and MRI can provide the imaging of whole body, but their imaging resolution is limited to about 1mm. Ultrasonic imaging achieves a greater resolution (10-100 μm) but possesses an imaging depth limited to few centimetres.

Optical imaging had the property of a high spatial resolution, but reaches a very limited imaging depth due the limited propagation of light when is propagated through biological tissues. Hyperspectral imaging is a novel technology of optical imaging with potential applications in cancer detection and diagnosis[1].

Hyperspectral imaging is a technology that combines optical imaging with light spectrum (from the visual to the near-infrared light) analysis, to obtain both spatial and spectrum information; the spatial information obtained in hyperspectral imaging provides analysis of the shape and size of target tissues, while the spectral analysis provides peculiar data on tissue composition, with specific spectral fingerprints for different tissue components[2]. The spectral features of a tissue derive from events of light propagation in biological tissues represented by light absorption due to the extraction of energy from light or refraction and reflection due to the speed and direction of light occurring when the light travels through biological tissues; the computational analysis of the spectral profile allows to define tissue identity[2][3].

Three types of applications of tumor imaging in tumor detection have been developed: (i)*in vitro* imaging for histological samples, aiming to differentiate the normal cell component from the tumoral cell component d to categorize the different cell types present in a tumor; (ii) *in vivo* imaging on shallow surfaces; (iii) intraoperative applications[2].

Pathology is one of the cornerstones of modern medicine and particularly of cancer medicine. The evaluation of tumor specimens by an experienced pathologist represents the basis for clinical cancer medicine and a key step in the decision to treat or not a patient. Pathology tumor evaluation remained in its basic approach largely unchanged for many years.

The digital revolution promoted the development of digital pathology which emerged as a potential new standard of care where glass slides are digitized into whole slide images using digital slide scanners[4]. The digitalization of images provided the unique opportunity to support the image classification tasks by deep learning techniques, whose development was promoted by studies of artificial intelligence mimicking the capacity of human mind to learn by visual perception and to make decisions according to this learning[5]. This approach promoted the development of computational pathology which offers a unique opportunity of support to clinical activity by improving diagnostic quality, by helping the clinicians to develop optimal, individualized plans of treatment for patients[4][6].

In a recent study published on Scientific Reports, Maktabi et al. reported the exploration of hyperspectral imaging for histological evaluation of 95 oesophageal adenocarcinoma (EAC) specimens[7]. EAC specimens were stained with hematoxylin and eosin and were analyzed by HIS in the spectral range of 500-1000 nm; tumor regions corresponding to the normal (squamous epithelium) and the tumor (EAC cells and tumor stromal cells) were analyzed for their spectral transmittance properties[7]. The analysis of the transmittance spectra at 500-570 nm and at 650-750 nm showed the existence of remarkable differences in tumor areas enriched in squamous epithelium or esophageal adenocarcinoma cells: cancer cells due to their higher nucleus to plasma rate have a stronger staining than squamous epithelium, since these cells undergo nuclear loss during epithelium stratification and are less stained by eosin[7]. The combination in hyperspectral imaging with a machine learning technology based on a multi-layer perceptron (MLP) was used to analyze the spectra values generated by optical imaging and allowed to classify three different histopathological features of esophageal adenocarcinoma specimens (squamous epithelium cells, esophageal adenocarcinoma cells, and tumor stromal cells) with an accuracy comprised between 78 and 80%[7]. The tumor grading and the anti-tumor treatment affected the spectral properties of EAC cells: the spectra of EAC cells and of tumor stromal cells showed significant differences following the pTNM-categories and grading; the highest predictivity of HIS analysis was related to patients in a metastatic condition; the classification test based on HIS analysis in patients without neoadjuvant treatment showed a higher performance than in patients with neodjuvant treatment[7].

Future studies will be required to improve EAC detection and classification by HIS though acquisition of more spectral data, the inclusion of balanced datasets, the implementation of HIS with microscopy and the development of a more robust, sensitive, and accurate algorithm will be required for routine application of HIS. Furthermore, future studies should address the problem of the identification and differential diagnosis of precancerous lesions and carcinoma *in situ* by HIS. In this context, it is of interest to note that multispectral light scattering endoscopic imaging (MSLSEI) displayed a promising capacity to detect precancerous esophageal lesions; in fact, Qiu et al. in a double-blind that characterized the system's ability as a screening tool, showed that MSLSEI was able to diagnose 55 out of 57 patients[8]. A comparison of multispectral data with subsequent pathology showed an accuracy of 90% in detecting individual locations of dysplasia[8]. Importantly, another study showed that spectral endoscopy significantly sensitive to detect changes in neovascularization during the progression of esophageal lesions from Barrett's esophagus to dysplastic lesions and to carcinoma *in situ*: non-dysplastic and neoplastic Barrett's esophagus displayed a higher blood volume compared to normal squamous esophageal epithelium and vessel size appeared higher in dysplatic/neoplastic compared to non-dysplastic Barrett's esophagus[9]. Importantly a deep learning algorithm was able to distinguish and classify the spectra of neoplastic lesions compared to non-dysplastic Barrett's esopahgus with an accuracy and sensitivity of about 84% and a sensitivity of

85.5%[9].

Other recent studies have shown the consistent potentialities of hyperspectral imaging in the study of pathology tumor specimens.

Ishikawa et al have reported the hyperspectral imaging pathological tissues microarrays of human pancreatic tissue using a combination of microscopy and hyperspectrum camera. Data of the spectral range from 420 to 750 nm were used for analysis of the spectrum profile of these tissues. 19 hematoxilin-eosin-stained tumor specimens were analyzed in this study and achieved a sensitivity of 91% and an accuracy of 94% and a 14% improvement over the standard RGB images[10]. In this study, spectral data were interpreted and classified using a support vector machine classifier.

Hu et al investigated 30 gastric cancer patients and used data of the spectral range from 410 to 910 nm and developed a deep-learning model-based analysis method[11]. The experimental results showed an accuracy of the proposed model for normal and cancer gastric tissue model of 97.5%; the deep-learning model used in this study was based on the Convolutional Neural Network[11].

Ma et al have investigated hyperspectral microscopic imaging and machine learning methods for automatic detection of squamous cell carcinoma of head and neck on histologic slides[12]. They developed a method for nuclei segmentation from hyperspectral images based on principle component analysis, allowing to extract nuclei in hyperspectral images without extracting other subcellular components[12]. Both spectra-based support vector machine (SVM) and patch-based convolutional neural network were used for nuclei classification: the average accuracy of spectra-based SVM classification and of the HIS patch-based CNN classification were 68% and 82%, respectively[12]. Another study reported the analysis of 10 head and squamous cell carcinomas based on the incorporation of polarized hyperspectral imaging with machine learning for automatic detection on hematoxylin and eosin stained tissue slides; several machine learning algorithms, including support vector machine, random forest, Gaussian naïve Bayes, and logistic regression were applied to the collected images for the automated detection of tumor cells: SVM was the best classifier for the classification of the spectral images[13].

Ortega et al. reported the study of 13 glioblastoma specimens using hyperspectral imaging and deep learning techniques[14]. In this study, a hyperspectral microscope with a spectral range from 400 to 1000 nm was used; using a convolutional neural network, glioblastomas were automatically detected within the pathological slides with sensitivity and specificity values of 88% and 77%, respectively[14]. These results represented an improvement of 7% and 8%, respectively, as compared to the results obtained using RGB[14].

Van Vilet-Pérez et al. have performed a pilot study for evaluating the feasibility of hyperspectral imaging for epithelial ovarian cancer detection in *ex vivo* tissue samples; a linear support vector machine (SVM) was used for classification of normal and tumoral tissue[15]. Using this approach, tumor tissue was classified with a sensitivity of 81% and a specificity of 71%[15].

Complete tumor removal during surgery remains challenging because in many instances visualization of the tumor is difficult and the lack of accurate techniques for intraoperative evaluation of tumor margins to provide a rapid indication whether tumor resection is incomplete. A promising new approach for the intraoperative evaluation of tumor margins is represented by hyperspectral imaging. Recent studies have reported some promising results of hyperspectral imaging in tumor surgeries, such as head and neck cancer surgery[16][17], glioblastoma tumor surgery[18][19] and breast-conservative

surgery[20][21]. These studies were based on the evaluation of intraoperatory fresh tumor specimens. Particularly relevant was the study carried out by Kho et al evaluating the use of hyperspectral imaging for tumor detection in fresh human breast tissue specimens; this study showed a high diagnostic performance of this technique on sliced breast tissue specimens[20]. Importantly, hyperspectral imaging was significantly faster compared with currently available margin assessment techniques. Finally, other studies were focused to gastrointestinal tumors and showed promising results supporting hyperspectral endoscopic or intraoperative tumor analysis for either supporting early tumor diagnosis or for evaluating the surgical transection margin[22][23][24][25].

In conclusion, the study by Maktabi et al[7], as well as the other studies here analyzed, strongly support further development of hyperspectral imaging techniques for improving tumor diagnosis, by both microscopic and endoscopic techniques, for better guiding tumor biopsy and for providing a better intraoperative evaluation of tumor margins. A major challenge in the future developments of hyperspectral tumor imaging is related to the absolute need of standardization of the methods used and to study larger sets of patients allowing to carefully evaluate the contribution of HIS over current techniques of tumor imaging.

References

1. ^*M. Halicek, I. Fabelo, S. Ortega, G. M. Callico, B. Fei. (2019). In-vivo ande x-vivo tissue analysis through hyperspectral imaging techniques: revealibng the invisible features of cancer. Cancers. 11(576).*
2. a, b, c *Y. Zhang. (2020). Applications of hyperspectral imaging in the detection and diagnosis of solid tumors. Transl Cancer Res. 9:1265–1277. doi:10.21037/tcr.2019.12.53*
3. ^*S. Ortega, M. Halicek, H. Fabelo, M. allico, B. Fei. (2020). Hyperspectral and multispectral imaging in digital and computational pathology: a systematic review. Biomed Opt Express. 11:3195.*
4. a, b *G. Campanella. (2019). Clinical-grade computational pathology using weakly supervised deep learning on whole slide images. Nat Med. 25:1301–1309. doi:10.1038/s41591-019-0508-1*
5. ^*Y. Le Cun, Y. Bengio, G. Hinton. (2015). Deep learning. Nature. 521:436–444. doi:10.1038/nature14539*
6. ^*M. Cui, D. Y. Zhang. (2021). Artificial intelligence and computational pathology. Lab Invest. 101:412–422. doi:10.1038/s41374-020-00514-0*
7. a, b, c, d, e, f *M. Maktabi. (2022). Tumor cell identification and classification in esophageal adenocarcinoma specimens by hyperspectral imaging. Sci Rep. 12:4508. doi:10.1038/s41598-022-07524-6*
8. a, b *Qiu. (2018). Multispectral light scattering endoscopic imaging of esophageal precancer. Light Sci Amp Appl. 7:17174. doi:10.1038/lsa.2017.174*
9. a, b *D. J. Waterhouse. (2021). Spectral endoscopy enhances contrast for neoplasia in surveillance of Barrett's esophagus. Cancer Res. 81:3415–3425. doi:10.1158/0008-5472.can-21-0474*
10. ^*M. Ishikawa. (2019). Detection of pancreatic tumor cell nuclei via a hyperspectral analysis of pathological slides based on stain spectra. Biomed Opt Express. 10:4568–4592. doi:10.1364/boe.10.004568*
11. a, b *B. Hu, J. Duy, Z. Zhang, Q. Wang. (2019). Tumor tissue classification based on micro-hyperspectral technology and deep learning. Biomed Opt Express. 10:6370–6389. doi:10.1364/boe.10.006370*

12. [a, b, c]*L. Ma, M. Halicek, X. Zhou, J. Dormer, B. Fei. (2020). Hyperspectral microscopic imaging for automatic detection of head and neck squamous cell carcinoma using histologic image and machine learning. John E. Tomaszewski, Aaron D. Wardeditors. Med Imaging 2020 Digit Pathol. 11320:113200W. doi:10.1117/12.2549369*
13. [^]*X. Zhou. (2020). Automatic detection of head and neck squamous cell carcinoma on pathologic slides using polarized hyperspectral imaging and machine learning. Med Imaging 2021 Digit Pathol. 11603. doi:10.1117/12.2582330*
14. [a, b, c]*S. Ortega. (1911). Hyperspectral imaging for the detection of glioblastoma tumor cells in H&E slides using convolutional neural networks. Sensors. 20. doi:10.3390/s20071911*
15. [a, b]*Van Vliet-Pérez S.M. (2022). Hyperspectral imaging for tissue classification after advanced stage ovarian cancer surgery – a pilot study. Cancers. 14:1422. doi:10.3390/cancers14061422*
16. [^]*G. Lu. (2017). Detection of head and neck cancer in surgical specimens using quantitative hyperspectral imaging. Clin Cancer Res. 23:5426–5436. doi:10.1158/1078-0432.ccr-17-0906*
17. [^]*B. Fei. (2017). Label-free reflectance hyperspectral imaging for tumor margin assessment: a pilot study on surgical specimens of cancer patients. J Biomed Opt. 22, 1:1. doi:10.1117/1.jbo.22.8.086009*
18. [^]*H. Fabelo. (2018). An intraoperative visualization system using hyperspectral imaging to aid in brain tumor delineation. Sensors. 18:430. doi:10.3390/s18020430*
19. [^]*F. Manni. (2020). Hyperspectral imaging for glioblastoma surgery: improving tumor identification using a deep spatial-spectral approach. Sensors. 20:6955.*
20. [a, b]*E. Kho. (2019). Hyperspectral imaging or resection margin assessment during cancer surgery. Clin Cancer Res. 25:3572–3580.*
21. [^]*E. Kho. (2019). broadband hyperspectral imaging for breast detection using spectral and spatial information. Biomed Opt Express. 10:4496–4515.*
22. [^]*C. L. Tsai. (2021). Hyperspectral imaging combined with artificial intelligence in the early detection of esophageal cancer. Cancers. 13:4593. doi:10.3390/cancers13184593*
23. [^]*B. Jansen-Winkeln. (2021). Comparison of hyperspectral imaging and fluorescence angiography for the determination of the transection margin in colorectal resections-a comparative study. Int J Colorectal Dis. 36:283–291. doi:10.1007/s00384-020-03755-z*
24. [^]*T. Collins. (2021). Automatic recognition of colon and esophagogastric cancer with machine learning and hyperspectral imaging. Diagnostics. 11:1810. doi:10.3390/diagnostics11101810*
25. [^]*S. Hennig. (2022). Novel intraoperative imaging of gastric tube perfusion during oncologic esophagectomy-A pilot study comparing hyperspectral imaging (HSI) and fluorescence imaging (FI) with indocyanine green (ICG. Cancers. 14:97. doi:10.3390/cancers14010097*