Confocal microlaparoscope for imaging the fallopian tube

Tzu-Yu Wu
Andrew R. Rouse
Setsuko K. Chambers
Kenneth D. Hatch
Arthur F. Gmitro
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Tzu-Yu Wu,a,b Andrew R. Rouse,a,b,c Setsuko K. Chambers,c,d Kenneth D. Hatch,c,d and Arthur F. Gmitroa,b,c,*

Abstract. Recent evidence suggests that ovarian cancer can originate in the fallopian tube. Unlike many other cancers, poor access to the ovary and fallopian tubes has limited the ability to study the progression of this deadly disease and to diagnosis it during the early stage when it is most amenable to therapy. A rigid confocal microlaparoscope system designed to image the epithelial surface of the ovary in vivo was previously reported. A new confocal microlaparoscope with an articulating distal tip has been developed to enable in vivo access to human fallopian tubes. The new microlaparoscope is compatible with 5-mm trocars and includes a 2.2-mm-diameter articulating distal tip consisting of a bare fiber bundle and an automated dye delivery system for fluorescence confocal imaging. This small articulating device should enable the confocal microlaparoscope to image early stage ovarian cancer arising inside the fallopian tube. Ex vivo images of animal tissue and human fallopian tube using the new articulating device are presented along with in vivo imaging results using the rigid confocal microlaparoscope system. © The Authors. Published by SPIE under a Creative Commons Attribution 3.0 Unported License. Distribution or reproduction of this work in whole or in part requires full attribution of the original publication, including its DOI. [DOI: 10.1117/1.JBO.19.11.116010]

Keywords: confocal; microlaparoscope; fallopian tube; ovarian cancer; fiber bundle.

Paper 140501PR received Aug. 1, 2014; accepted for publication Oct. 21, 2014; published online Nov. 20, 2014.

1 Introduction

Ovarian cancer is a devastating disease with an overall high morbidity and low 5-year survival rate.1 Unfortunately, there are no known early detection strategies that have resulted in either earlier stage diagnosis or improved survival.2,3 As a consequence, many high-risk women choose to undergo prophylactic surgical removal of their ovaries and fallopian tubes to prevent future ovarian cancer. Although this procedure prevents ovarian cancer in 95% of the cases, there are significant downsides in terms of early menopause and cardiovascular disease in addition to removing the patient’s ability to have children.4–7 Clearly, providing women in the high-risk population the option to undergo prophylactic surgery would be beneficial if the imaging procedure had sufficient diagnostic sensitivity and specificity.

Although ovarian cancer was long thought to originate in the epithelial surface of the ovary, no precancerous or intraepithelial lesions have been identified in the ovary. New evidence suggests that ovarian and fallopian tube cancers derive instead from cells of Mullerian origin and there is strong evidence that many cancers in the ovary in fact arise from cells originating in the fallopian tube.5–11 We have previously demonstrated a rigid confocal microlaparoscope system for imaging the epithelial surface of the ovary12–16 and our results as well as the findings of several other groups17–20 demonstrate that the high resolution en face images obtained with confocal microendoscopes can be used for diagnosing disease.

To demonstrate the potential for confocal microendoscopy applied to the fallopian tubes, we first used our previously developed rigid clinical confocal microlaparoscope to image the fimbriae of the fallopian tubes. The preliminary in vivo and ex vivo images show potential to identify pathologic changes in the fallopian tubes, but the rigidity and the diameter of the confocal microlaparoscope make it difficult to image beyond the exposed surfaces of the fimbria. In order to obtain better access to the fallopian tube itself, we modified the rigid confocal microlaparoscope to include a small diameter articulating distal tip. The new articulating confocal microlaparoscope employs a bare fiber optic imaging bundle that is capable of visualizing cellular morphology and subcellular detail such as nuclear size and shape. In the following section, we briefly review the instrumentation of the rigid confocal microlaparoscope and present preliminary ex vivo and in vivo images of human fallopian tube images obtained with that system. The new articulating tip confocal microlaparoscope is described in Sec. 3 along with ex vivo images of fallopian tubes obtained using the new system. A discussion and conclusions of the work are presented in Sec. 4.

2 Imaging Fallopian Tubes Using the Rigid Confocal Microlaparoscope

2.1 Optical Scan Unit General Description

Both the rigid clinical system and the new articulating bare fiber system connect to the same optical scan unit. A detailed description of this confocal slit-scanning system can be found in previous publications.15,21 Briefly, a laser source provides an excitation wavelength of 488 nm. A cylindrical lens transforms the collimated laser beam into a line illumination profile that is scanned across the proximal end of an imaging fiber bundle by a
scan mirror. Induced fluorescence from the exogenously labeled tissue is collected back through the fiber, de-scanned by the scan mirror, and imaged onto a fixed confocal slit aperture, which rejects light emitted from out-of-focus planes within the tissue. A second scan mirror and a camera lens image the signal onto a two-dimensional (2-D) CCD camera. The two scan mirrors synchronously scan the excitation line of illumination across the proximal end of the fiber bundle and map the emission light onto the CCD to produce a 2-D en face confocal image of the sample. The confocal images are read out of the camera at 30 frames per second and displayed on a monitor for the surgeon to view in the operating room.

2.2 Rigid Confocal Microlaparoscope

The rigid confocal microlaparoscope probe has a 5-mm diameter and 30-cm-long rigid tip on a handle that connects to the optical scan unit through a cable containing the fiber bundle and electrical wires that control the operation of the instrument. The rigid confocal microlaparoscope incorporates a 30,000 element fiber-optic imaging bundle with 4-μm center-to-center spacing, which transfers the scanned line illumination profile to the distal end of the probe. The fiber bundle has an imaging diameter of 720 μm, a minimum bending radius of 40 mm, and an NA of 0.35. A miniature achromatic objective lens images the distal end of the fiber bundle into the tissue. A focus mechanism in the handle of the microlaparoscope allows the user to focus from 0 to 200 μm below the surface of the tissue. During a laparoscopic procedure, the rigid catheter is inserted through a trocar and routed to the ovary under guidance by a conventional wide-field laparoscope. The microlaparoscope is placed in contact with the ovary and fluorescent contrast agent is topically delivered to the tissue at the imaging site.

2.3 Imaging Results Using the Rigid Confocal Microlaparoscope

To evaluate whether we can identify pathologic changes in fallopian tube using confocal microendoscopy, we used the current rigid microlaparoscope to examine excised human fallopian tube samples. In addition, we were able to test the concept of in vivo fallopian tube imaging during several surgeries where the surgeon was able to manipulate the fallopian tube and position the 5-mm rigid tip of this microlaparoscope on the fimbriated end of the fallopian tube.

Figure 1 shows two ex vivo images of human fallopian tube stained with acridine orange and imaged with the rigid confocal microlaparoscope. The figure includes corresponding histology images taken from the regions where the confocal images were obtained. The diagnosis in both cases was normal fallopian tube. Images taken from the rigid confocal microlaparoscope have a full field-of-view of 0.45 mm in tissue space. Figure 2 shows in vivo images taken with the rigid microlaparoscope. As stated, the rigidity and diameter of this system make it hard to image inside the fallopian tube but the surgeon was able to image the fimbriae. Figures 2(a) and 2(b) were taken from a patient whose histologic diagnosis revealed normal tissue. Figures 2(c) and 2(d) were obtained from a patient who had a visible mass attached to

Fig. 1 Ex vivo confocal microlaparoscope images and corresponding histologic images of excised normal human fallopian tube stained with acridine orange. Images (a) and (b) are from a similar location on one patient. Images (c) and (d) are from a similar location on another patient. The confocal images (a) and (c) have a full field-of-view of 0.45 mm.

Fig. 2 In vivo images of human fallopian tube stained with acridine orange and imaged during open surgery with the rigid confocal microlaparoscope system. Images (a) and (b) are from a patient with healthy tubes and ovaries. Images (c) and (d) are from a patient diagnosed with high grade serous carcinoma in the fallopian tube and no ovarian involvement. The full field-of-view of images is 0.45 mm.
the fimbriated end of the fallopian tube. The mass was imaged \textit{in vivo} with the rigid confocal microlaparoscope system and then diagnosed via frozen section as high grade serous carcinoma. Interestingly, the ovary associated with this fallopian tube had no evidence of cancer on pathologic examination. This particular fallopian tube tumor would have been visually detected and biopsied without the need for a high resolution imaging system. However, this case does call attention to the benefit of a high resolution imaging system to help diagnosis cases where fallopian tube pathology is less clinically evident.

These imaging results suggest that the confocal microlaparoscope has sufficient resolution to differentiate cellular structures in the fallopian tube. One can certainly visualize significant differences between the two \textit{in vivo} cases in Fig. 2, presumably stemming from morphological changes in the cancerous tissue.

3 Imaging Fallopian Tubes Using the New Articulating Confocal Microlaparoscope Catheter

3.1 New Articulating Confocal Microlaparoscope Catheter

To enable better \textit{in vivo} access to fallopian tubes, we designed and built a prototype laparoscopic imaging probe. This probe is a bare fiber bundle imaging system (i.e., no miniature objective lens), which has a thin 2.2-mm-diameter articulating distal tip. The fiber bundle has the same specifications as the one used in the rigid system. Since it is a bare fiber probe, the focal plane is static such that only the tissue in contact with the tip of the fiber bundle is imaged by the confocal instrument. The new articulating microlaparoscope catheter incorporates a dye channel to deliver exogenous contrast agent to the tissue. The smaller diameter distal tip and the ability to control the angle of the tip provide the size and flexibility needed to image inside the curved and delicate structure of the fallopian tube.

The articulating microlaparoscope, shown pictorially in Fig. 3, incorporates an ergonomic lightweight handle. The distal tip articulates by flexing the handle relative to the direction of the rigid portion of the laparoscope probe. A ball and socket mechanism in the front portion of the handle serves as the pivot point. The flexible distal tip of the laparoscope is composed of 20 metal links that stack on top of each other. Four metal wires extend from a component aligned with the socket, through the ball, down a 30-cm-long rigid metal tube, through four small holes on the rims of the 20 metal links, and finally connect to the distal tip of the probe. As the surgeon changes the angle between the handle and the metal tube, the change in tension on the four internal drive wires causes articulation of the distal tip in a manner similar to that of a traditional flexible endoscope. Roughly 45 deg of angle between the handle and the rigid tube provides nearly 90 deg of distal tip articulation.

The design also incorporates an articulation lock that allows the surgeon to set and maintain a specific angle at the distal tip. A single multipurpose button allows the surgeon to save still frames with a short press and deliver a predetermined amount of contrast agent with a long press. Video can be recorded via the computer-based controls on the optical scan unit. A small figure illustrating the handle of the articulating tip confocal microlaparoscope probe is shown in Fig. 4. The design incorporates an articulation lock that allows setting and maintaining a specific angle at the distal tip. A multipurpose button on top of the probe allows the operator to deliver contrast agent and grab static images.

Fig. 3 The articulating confocal microlaparoscope. An internal motor controls the delivery of contrast agent through a hypodermic dye line to the imaging site. A single-multipurpose button is used to save still frames and delivery contrast agent. An articulation lock located on the underside of this design allows the clinician to fix the distal tip at a specific angle.

Fig. 4 The handle of the articulating tip confocal microlaparoscope probe. The design incorporates an articulation lock that allows setting and maintaining a specific angle at the distal tip. A multipurpose button on top of the probe allows the operator to deliver contrast agent and grab static images.
syringe loaded with 0.2 cc of contrast agent is inserted into a Luer Lock connector in a recessed cavity that guides the fluid down a 21 gauge hypodermic tube to the distal tip. The articulation mechanism was inspired by commercial instruments that are designed to overcome the limitations imposed by rigid laparoscopic instruments. The probe has a symmetrical design that allows for both left-handed and right-handed usage. The mechanical design for the new catheter was done in SolidWorks and then made using a rapid prototyping Objet350 Connex 3D printer. A photograph of the prototype device is shown in Fig. 4 and a demonstration of the articulating distal tip is provided in Fig. 5.

3.2 Imaging Results Using the New Articulating Confocal Microlaparoscope

The spatial resolution of this bare fiber system is ∼7-µm lateral and 20-µm axial measured in water with a full field-of-view of 0.72 mm. The imaging performance of the prototype articulating tip probe was demonstrated using excised animal tissue as well as excised human fallopian tube tissue. Figure 6 shows preliminary ex vivo fluorescent confocal images obtained from a mouse [Figs. 6(a) and 6(b)] and a rat [Figs. 6(c) and 6(d)]. The articulating bare fiber probe was placed in contact with the tissue surface after acridine orange was topically applied through the contrast agent delivery channel. Figure 7 shows ex vivo images from human fallopian tube stained with acridine orange. Figures 7(a)–7(c) were obtained when the articulating distal tip was placed in contact with the fimbriae. Figure 7(d) was taken when the articulating distal tip was inserted inside the lumen of the fallopian tube. The corresponding histological diagnosis for the fallopian tube tissue in Figs. 7(a)–7(c) was postmenopausal normal fimbria. A histologic diagnosis for the tissue shown in Fig. 7(d) was not obtained since it was difficult to correlate the image location to the tissue site while the tip was inside the lumen of the fallopian tube. The images shown in Figs. 6 and 7 are high resolution and high contrast, and clearly demonstrate the powerful imaging capabilities of this new microlaparoscope probe. During ex vivo imaging, we found that the thin articulating tip can be inserted 2 cm beyond the fimbriated end of the fallopian tube relatively easily. Although the new articulating tip probe has not yet been tested in vivo, we expect that it will provide better access to the fallopian tubes and an image quality...
4 Discussion and Conclusions

A confocal microlaparoscope with a small diameter articulating distal tip was successfully developed to image inside the fallopian tube. The instrument is intended to allow the detection of early stage ovarian cancer arising in the fallopian tube. In this pilot study, tissues were topically stained with the fluorescent contrast agent acridine orange, which readily crosses the cell membrane and intercalates with DNA in the cell nucleus and RNA in the cytosol. Our work has shown significant promise in the identification of ovarian cancer using acridine orange and we have an investigational new drug approval from the US Food and Drug Administration (FDA) to test acridine orange in patients whose tissue is being surgically removed subsequent to imaging. However, there are concerns about the potential mutagenicity of acridine orange. For in vivo clinical use, we are investigating several FDA approved contrast agents including fluorescein sodium, methylene blue, and indocyanine green. The new articulating catheter can be used with any of these alternative contrast agents. The development of a safe and effective contrast agent for in vivo detection of ovarian cancer is a fundamental goal of our on-going research.

The results of ex vivo and in vivo imaging of human fallopian tube using our previously developed rigid clinical confocal microlaparoscope suggest the potential of the proposed confocal imaging technique, but access to the fallopian tube is limited by the geometry of the 5-mm-diameter rigid device. The new lightweight ergonomic confocal microlaparoscope with its articulating distal tip, will enable access to the distal end of the fallopian tube during laparoscopic surgery. The ability to image inside of the fallopian tubes up to a few centimeters past the fimbria is a significant advantage of this new instrument. Although the 7-μm lateral resolution of the articulating tip probe is less than the 4.5-μm lateral resolution of the rigid clinical microlaparoscope probe, the performance is sufficient to resolve subcellular structures, such as cell nuclei, and the important microstructural features relevant to ovarian cancer detection. In addition, the overall sensitivity of the bare-fiber articulating design is quite similar to that of the miniature objective–based rigid system. The bare-fiber system collects less light because it eliminates the miniaturization objective, which has 15 optical surfaces.

Overall, the images obtained with this bare fiber-bundle imaging system are of comparable quality to images of ovarian tissue collected with the rigid clinical system. Ultimately, this articulating tip device may allow surgeons to image ovarian cancer arising inside the fallopian tube and to provide a means to detect the disease at an earlier stage when it is more amenable to effective treatment. In vivo clinical evaluation of the new articulating microlaparoscope system is the next step in demonstrating the potential of this instrumentation.

Acknowledgments

This research work has been supported by a Better Than Ever Grant from the University of Arizona Cancer Center and a grant from the National Cancer Institute CA115780. The authors would like to thank the Center for Gamma-ray Imaging’s Rapid Prototype 3-D Printer Team for their assistance with printing the catheter, and Dr. Wenxin Zheng, Professor of Pathology, Obstetrics, and Gynecology at the University of Arizona, College of Medicine, for his collaboration on this project.

References


Tzu-Yu Wu is a PhD candidate in the College of Optical Sciences, at the University of Arizona. Her research is focused on the development of high-resolution imaging devices that provide rapid detection of early stage cancer through a minimally invasive procedure. Her interests include optical system design, opto-mechanics, and biomedical optics. She is enthusiastic about bench to bedside translation where researchers transform ideas into clinically viable instruments and ultimately translate that research into practice.

Andrew R. Rouse is a research assistant professor in the Department of Medical Imaging and College of Optical Sciences at the University of Arizona. He has a long track record in the field of biomedical optics with a focus on small minimally invasive catheter-based...
medical imaging systems. He has experience in the design, testing, and use of miniature lens assemblies appropriate for thin in vivo catheter system.

Setsuko K. Chambers is a professor of gynecologic oncology and the Bobbi Olson Endowed Chair in Ovarian Cancer Research at the University of Arizona. She received an MD from Brown University in 1980 and completed a residency in obstetrics and gynecology at Yale University in 1984. In addition to her clinical duties as section head of gynecologic oncology, she is actively involved in basic research of the molecular factors that influence ovarian cancer carcinogenesis, growth, and metastatic spread.

Kenneth D. Hatch is a professor in the Department of Obstetrics and Gynecology at the University of Arizona. He has been president of the Society of Gynecologic Oncologists, the Society of Pelvic Surgeons, and the American Society of Colposcopy and Cervical Pathology. He is a fellow of the American College of Obstetricians and Gynecologists and the American College of Surgeons. His main research is on development of advanced laparoscopic surgical treatment of women with ovarian cancer.

Arthur F. Gmitro is the Fenton Maynard Chair in Cancer Imaging and professor of medical imaging and optical sciences at the University of Arizona. He received his PhD in optical sciences from the University of Arizona in 1982. Before joining the UA faculty, he was an assistant professor of diagnostic radiology at Yale University from 1982 to 1987. His major areas of research include magnetic resonance imaging and biomedical optical imaging, and continues to work on development of these technologies.