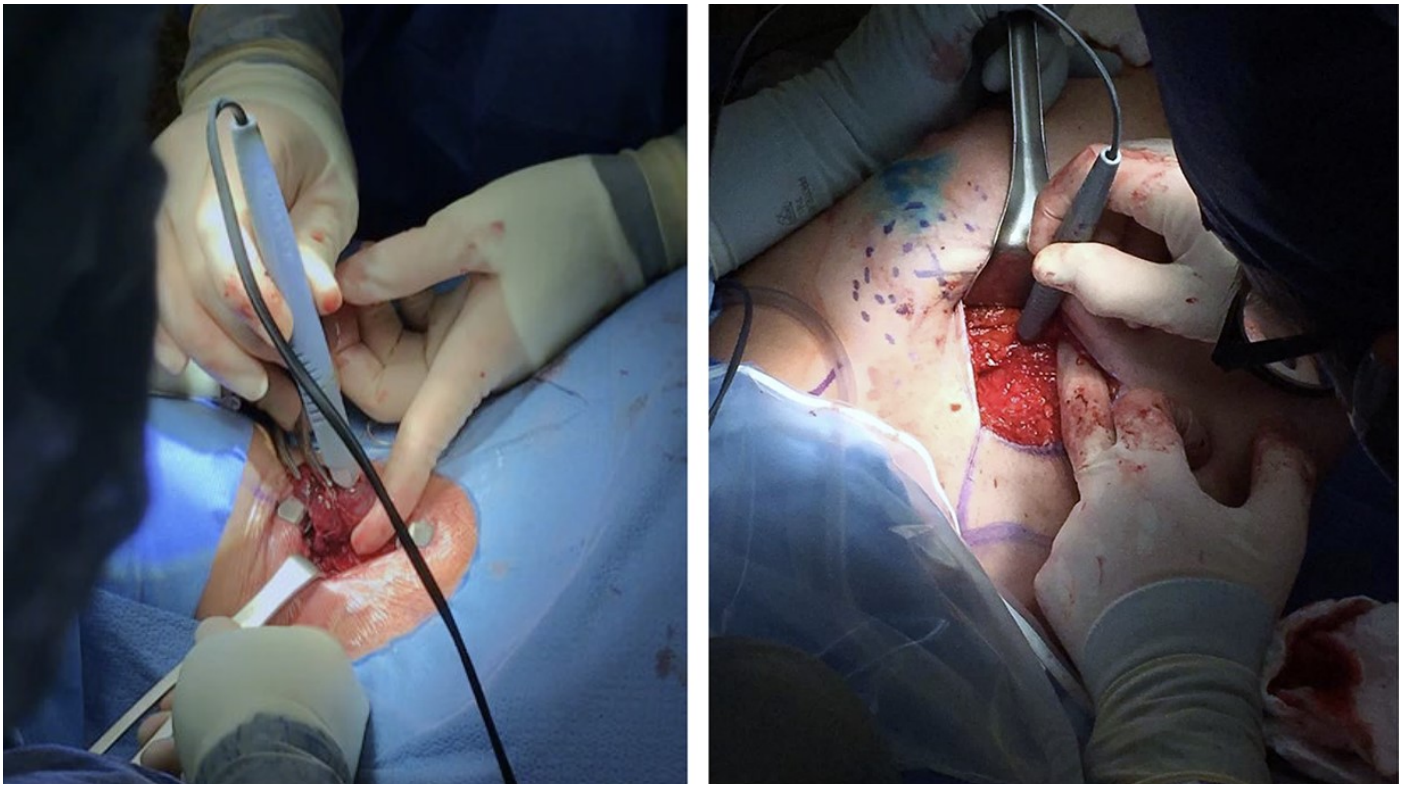


The MasSpec Pen, shown in use during cancer surgery (left: thyroidectomy, right: breast lumpectomy), provides real-time feedback to surgeons, eliminating the need for immediate histopathology consultation. Credit: J. Zhang, M. Sans, et al./American Association for Clinical Chemistry. (2021, Clinical Chemistry)[1]

The MasSpec Pen: A "Touch" of Genius for Cancer Surgeries

Researchers at the University of Texas suggest mass spectrometers in operating rooms might change the way we perform surgeries, for the better. **By Tim Huygelen**

All quotes in this technology feature are taken from a Q&A session with Dr Livia Eberlin, hosted by the American Chemical Society[2]. Although an attempt was made to secure a separate interview with the team specifically for this article, their scheduling constraints prevented it from taking place.

In the delicate field of cancer surgery, where precision is critical, researchers at the University of Texas have introduced the MasSpec Pen, a significant innovation that uses mass spectrometry coupled with a 3D-printed pen-like device to transform cancer resection[3]. Upon contact with tissue, the pen emits a water droplet, capturing molecular data for quasi-instant cancer cell identification, improving surgical accuracy and reducing risks. This advancement not only simplifies tumour detection, but also makes surgery less invasive, marking a significant step forward in improving patient care and surgical outcomes.

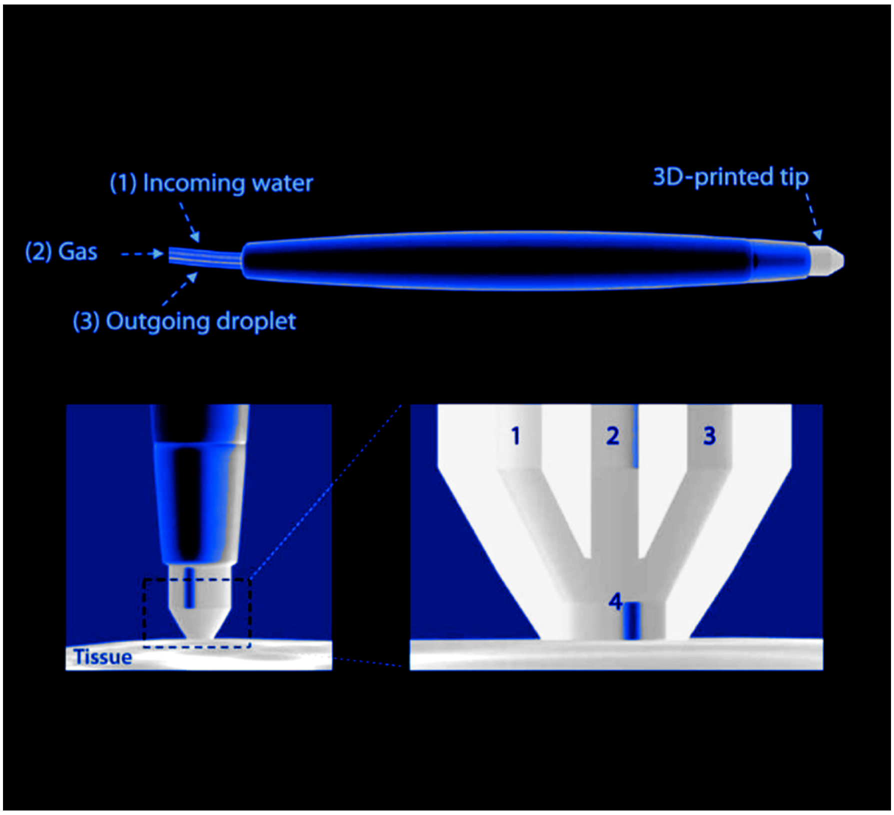
Mass spectrometry, the key technology behind the MasSpec Pen, works by ionising chemical compounds to produce charged molecules and then measures their mass-to-charge ratios. These tools can precisely determine the molecular signature of a sample, which the MasSpec Pen uses to make its predictions.

The Complex Challenges of Histopathology

Surgical procedures, which are complex in themselves, are further complicated by the need for accurate detection of cancer margins. Traditional histomorphological techniques, including frozen section, imprint cytology and cavity scraping, are invasive and time-consuming. These methods require the removal of tissue - often healthy tissue alongside cancerous tissue - and can take up to 30 minutes to complete[4]. Frozen section and imprint cytology require the presence of a specialist histopathologist for accurate interpretation. On the other hand, in the absence of a histopathologist, excisional surgery involves the surgical removal of tissue around the margins of the tumour, with the aim of completely removing the cancer cells but resulting in the loss of significant amounts of healthy tissue. The effectiveness of this method varies, with sensitivities and specificities ranging from 55-80% and 70-100% respectively[4].

Dr Livia Eberlin, who was instrumental in the development of the MasSpec pen, explains the challenges faced in current practice: "There are areas of sub-specialty, not all hospitals have a pathologist that's a specialist in certain cancer type and it's also a lengthy process." Longer operation times mean that the patient has to stay under anaesthetic for a greater length of time, leading to prolonged recovery times. "With the MasSpec pen division we want to empower the surgeons to be able to do that analysis themselves in the operating room."

A comparative study has also highlighted the drawbacks of conventional biopsy and histopathology methods. Although effective, they often prolong the duration of surgery and increase the risk to the patient. In contrast, intraoperative mass spectrometry techniques have proven to be a much faster and more accurate alternative, allowing patients to recover more quickly, minimising the likelihood of further surgery and sparing healthy tissue[3].



Cross-sectional diagram of the MasSpec Pen which has 3 inner channels connected to plastic tubes. Adapted from J. Zhang, J. Rector, et al./ Sci Transl Med. (2017, American Association for the Advancement of Science)[3]

Breaking New Ground

In the quest to overcome the limitations of traditional surgical techniques, a solution emerged in 2013 with the development of the iKnife by Dr Júlia Balog and her team[5]. The iKnife was the first to successfully develop a point-based mass spectrometry tool for surgical procedures. Used as a cauterisation device during surgery, the iKnife works by releasing smoke from the cauterised tissue. This smoke is then suctioned into a mass spectrometer where its composition is analysed to determine the presence of cancer cells. Within moments of cauterisation, surgeons are alerted by a combination of visual light signals and audible beeps indicating whether the tissue is cancerous or not. This immediate feedback mechanism facilitates decision making in the operating room and ensures rapid and accurate cancer detection[5].

"With the MasSpec pen division we want to empower the surgeons to be able to do that analysis themselves in the operating room."

However, this approach is not without its drawbacks. The cauterisation process, which is essential to the iKnife's operation, inherently causes tissue damage. Surgeons therefore face the challenge of needing to use the iKnife cautiously to minimise damage to healthy tissue, as excessive cauterisation could damage the healthy tissue the surgeons are trying to preserve using the iKnife[3, 5].

The MasSpec Pen

Inspired by the iKnife, Dr Eberlin's team set out to use 3D printing technology to improve surgical safety. Their innovation, the MasSpec Pen, combines the precision of mass spectrometry with 3D printing to provide real-time analysis of live tissue during surgery. Unlike traditional methods, this pen uses a breakthrough technique to evaporate moisture on the tissue, which is then analysed by the mass spectrometer. This process ensures that the tissue is not damaged and represents a significant advancement in surgical procedures[3].

The effectiveness of the MasSpec Pen was initially validated through tests on ex-vivo human cancer tissue and in-vivo experiments in mice, demonstrating its potential to accurately identify cancer cells. Subsequent clinical trials in a variety of cancers, including pancreatic[6] and breast cancer[7], confirmed its accuracy and utility for a wide range of cancers. The device's software uses the Lasso method to analyse mass spectrometry data, differentiating between cancerous and non-cancerous tissue with high accuracy and can theoretically differentiate between types of healthy tissue as well[3].

Dr Eberlin highlights the speed of the mass spectrometry analysis: "The mass spectrometer we used is an Orbitrap mass spectrometer... we can get a mass spectrum in milliseconds. Most of the 15-second analysis time is spent administering the water, holding the pen on the tissue long enough to pick up the metabolites, and sending the sample through the tubes to the mass spectrometer. The design of the MasSpec Pen, with three distinct channels for sample delivery, evaporation and aspiration, was designed to preserve tissue integrity. The use of water as a solvent was a deliberate choice, emphasising the device's commitment to non-invasiveness and compatibility with living tissue.

Overcoming Obstacles

When using the MasSpec Pen in live surgeries, the surgical teams faced several challenges, none of which affected the success of the surgery. Increased noise levels and the need for occasional system restarts were noted, but these did not affect surgical outcomes. A significant adaptation was the decision to mount the system on wheels to improve its manoeuvrability within the hospital. This modification was critical for the use of a sophisticated mass spectrometer, which is essential for the pen's accuracy[1]. Dr Livia Eberlin, pivotal in this breakthrough, highlights, "the mass spectrometer is in a rolling table so we roll it into the surgical room and we have it actually installed there running full time during the periods of our study." This choice avoided the need for a smaller, potentially less accurate mass spectrometer, in the hope that future technological advances will allow the use of smaller spectrometers without sacrificing performance.

One of the paramount concerns transitioning from lab-based experiments to clinical application was the potential interference of blood in the analysis. Dr Eberlin addresses this, stating, "One of our major concerns going to the clinic was blood...but the beauty of mass spectrometry is that the resolution is so high and we have such high level of chemical specificity that we can still detect all of our other compounds."

Despite initial concerns about ion-optic contamination and blood interference, the functionality of the MasSpec Pen has been robust, tested in 100 surgeries and on 177 organs. Feedback from surgical teams was overwhelmingly positive, highlighting the efficiency of the device and its seamless integration into the surgical workflow without causing intra- or post-operative complications[1].

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Production of the MasSpec Pen

The MasSpec pen, with its 3D printed construction, opens up new possibilities for surgical precision and customisation. This innovative approach allows the pen to be manufactured virtually anywhere, providing the flexibility to adapt its design to meet different surgical needs. However, the production process has its own challenges, notably the high cost associated with 3D printing and the need for sterility in surgical environments. This requires the pens to be disposed of regularly, adding to the cost of ownership[3]. The ideal solution would be to mass produce these pens and the associated mass spectrometry equipment, which would not only ensure their widespread availability, but also significantly reduce costs through economies of scale.

The Road Ahead

Since the introduction of the MasSpec Pen, there have been several notable advancements that have further expanded the scope of intraoperative mass spectrometry. These include Spidermass, a novel technology that uses laser desorption mass spectrometry for tissue analysis[8]. This technique, which eliminates the need for a water droplet by using a laser to evaporate the inherent moisture in tissue. While particularly useful for application on skin, its application requires precise handling to avoid direct tissue contact, which presents challenges for surgical use, where the device would need to be cleaned regularly[4,8].

This collaboration has resulted in a custom-designed pen that perfectly complements the capabilities of the robotic system, demonstrating the potential of 3D printing to tailor surgical tools to specific surgical needs. The design of the pen was specifically redesigned to fit seamlessly onto one of the robot's arms. This integration has shown promising results in a porcine surgical trial and was possible due to the flexibility of 3D-printed designs[9].

Going Industrial

Intraoperative mass spectrometry technology, embodied in innovations such as the iKnife[5], MasSpec Pen[3] and SpiderMass[8], is at the forefront of surgical precision and has demonstrated remarkable accuracy and utility in the hands of surgeons. Despite their proven effectiveness, there is potential for improvement, particularly through the integration of advanced machine learning algorithms for more nuanced analysis of specimens[4]. Addressing system efficiency, as well as challenges related to device positioning and cleanliness, could further refine these technologies.

However, the real breakthrough lies not only in refining these technologies, but in making them widely available to surgeons worldwide. The current limitation is not the lack of innovation, but the scarcity of these advanced tools in the surgical community. A decisive shift towards mass production, particularly for devices such as the 3D-printed MasSpec pen, could democratise access without compromising environmental sustainability. This approach, while economically viable, would have a greater environmental impact and should encourage the development of reusable and easily sterilisable components.

The cost of high-precision instruments such as Orbitrap mass spectrometers, used in conjunction with the MasSpec Pen, is a significant barrier. These instruments, which can cost upwards of half a million dollars, also have significant ongoing costs for maintenance, calibration and consumables, compounded by their energy requirements. A move towards more affordable mass spectrometry solutions could catalyse the wider adoption of intra-operative mass spectrometry technologies, making these ground-breaking tools a staple in surgeries worldwide. Environmental sustainability remains a key consideration and efforts are underway to develop the MasSpec pen with reusable components to minimise waste.

Extending the Impact

Dr Livia Eberlin's vision extends beyond the medical field, the group has been working on applications in forensics[10] and research on live animals[11]: "We have used the MassSpec Pen to analyse drugs in various samples in forensic applications, pesticide analysis and agricultural applications... we can analyse a living animal and not cause any damage to the organism." This expansive potential underscores the potential of these new mass spectrometry implementations, going far beyond the operating room.

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