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Identification of Breast Tumors from Diathermy Smoke by Differential Ion Mobility Spectrometry.

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Abstract

Introduction: Breast cancer is the most frequent cancer in women worldwide. The primary treatment is breast-conserving surgery or mastectomy with an adequate clearance margin. Diathermy blade is used extensively in breast-conserving surgery. Surgical smoke produced as a side product has cancer-specific molecular features. Differential mobility spectrometry (DMS) is a rapid and affordable technology for analysis of complex gas mixtures. In our study we examined surgical smoke from malignant and benign breast tissue created with a diathermy blade using DMS.

Material and methods: Punch biopsies of 4 mm diameter from breast cancer surgical specimens were taken during gross dissection of fresh surgical specimen and placed in a well plate. The measurement system is a custom-built device called automatic tissue analysis system (ATAS) based on a DMS sensor. Each specimen was incised with a diathermy blade and the surgical smoke was analyzed.

Results: We examined 106 carcinoma samples from 21 malignant breast tumors. Benign samples (n = 198) included macroscopically normal mammary gland (n = 82), adipose tissue (n = 88) and vascular tissue (n = 28). The classification accuracy when comparing malignant samples to all benign samples was 87%. The sensitivity was 80% and the specificity was 90%. The classification accuracy of carcinomas to ductal and lobular was 94%, 47%, respectively.

Conclusions: Benign and malignant breast tissue can be identified with ATAS. These results lay foundation for intraoperative margin assessment with DMS from surgical smoke.

Keywords:

Breast cancer, Differential ion mobility spectrometry, Surgical smoke, Surgical margin, Electrosurgery

Abbreviations:

1. Radiofrequency (RF)
2. Optical coherence tomography (OCT)
3. Rapid evaporative mass spectrometry (REIMS)
4. Differential mobility spectrometry (DMS)
5. Field asymmetric ion mobility spectrometry (FAIMS)
6. *Automatic tissue analysis system* (ATAS)
7. Linear discriminant analysis (LDA)
8. *Forward sequential feature selection* (FSFS)
9. 10-fold cross validation (10-f-CV)
10. Receiver operating characteristic (ROC)
11. The area under the curve (AUC)

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1. Introduction

Breast cancer is the most frequent cancer among women; it affects nearly 1.7 million women worldwide each year and is the fifth most common cause of cancer death in women [1]. The surgical treatment of breast cancer consists of the removal of the tumor by either breast-conserving surgery or mastectomy, accompanied with sentinel node biopsy and in select cases, removal of the axillary lymph nodes [2]. According to recent data, 60% of breast cancer is treated with breast-conserving surgery, while 80% of breast cancer patients are eligible to breast-conserving surgery, suggesting that although patient choice and logistics affect the choice of treatment, the practice may still be too radical [3,4]. Acquiring adequate margin clearance is a key challenge in breast-conserving surgery. A positive margin increases the risk of local recurrence in both invasive breast cancer and ductal carcinoma *in situ* (DCIS), warranting reoperation. [5,6] According to the Society of Surgical Oncology guidelines on margins in breast-conserving surgery, no ink on tumor consensus appears adequate for stage I and II invasive breast cancer, but for DCIS use of 2 mm margin should be the standard [7,8]. According to recent data, up to 30% of patients requires reoperation due to inadequate clearance margins after breast-conserving surgery [9-11]. No-ink-on-tumor consensus has led to a decrease in reoperation rates and an increase in the popularity of breast-conserving surgery [9].

Due to costs associated with reoperations, several methods have been developed for the intraoperative evaluation of margins. An intraoperative histological examination of resected tissue by frozen section analysis can be used in suspicious areas but the entire surgical margin cannot be evaluated [12]. The diagnostic accuracy of frozen section analysis is good [13] and routine use of frozen section analysis in breast-conserving surgery has been shown to significantly reduce the reoperation rate [12,14]. Imprint cytology of specimen surfaces has been shown to have the highest performance in evaluating surgical margins of breast cancer patients [15]. The challenges of frozen section analysis include the added duration and disruption of the operation, transportation of samples and the costs of the contribution of the pathologist.

Several methods are being developed for assessing breast cancer margins intraoperatively *in vivo* or *ex vivo* besides imaging and histological assessment. Use of radiofrequency (RF) spectroscopy analysis for the detection of surgical margins (MarginProbe®) might reduce the number of reoperations due to inadequate clearance margins [16,17]. In the study by Schnabel et al. the sensitivity and specificity of the device were 75% and 46%, respectively [17]. However, RF spectroscopy disrupts the workflow of the surgeon and might compromise the orientation of the tumor leading to challenges in re-excision. Specimen radiography is used especially for nonpalpable tumors and can be a factor to consider for predicting tumor margins [18]. Intraoperative ultrasound can offer additional information on surgical margins in breast-conserving surgery [19]. Breast specimen radiography and large specimen MRI can offer additional information on the diameter of the invasive carcinoma, but for example the detection of DCIS is challenging [20]. Optical coherence tomography (OCT) has shown potential for intraoperative margin assessment in breast-conserving surgery with a sensitivity varying from 100% to 58.8% and specificity from 82% to 81% in studies [21,22].

Electrosurgery is used extensively in breast surgery [23]. It cuts tissues by heat-induced evaporation, producing surgical smoke [24]. Rapid evaporative mass spectrometry (REIMS) studies show that the molecular composition of surgical smoke has cancer-specific features with an accuracy of over 95%

for discriminating malignant tissues from benign ones [25,26]. Currently, the disadvantage of mass spectrometry technology is the excessive cost and complexity, preventing adoption outside research facilities. Differential mobility spectrometry (DMS) or synonymous field asymmetric ion mobility spectrometry (FAIMS) have been extensively studied in medical applications [27]. DMS is a variant of ion mobility spectrometry: a stream of gas is first ionized, then an asymmetric radiofrequency electric field is applied to the sample gas, enabling the differentiation and filtering of ions to discriminate and analyze the molecular composition of the sample and present it as a dispersion plot. The advantage of DMS is its lower cost, complexity and maintenance requirements compared to systems based on mass spectrometry. We have demonstrated that DMS discriminates porcine tissues by surgical smoke [28]. To date, there is no data on discrimination of benign and malignant tissues.

In our study we examined surgical smoke created with a diathermy blade using DMS. We analyzed fresh malignant breast tissue, normal mammary gland and adipose tissue *ex vivo*. Our goal was to demonstrate the capability of DMS in this application, paving way for real-time margin assessment.

2. Material and Methods

2.1 Study material

This study has been approved by the Ethical Committee of Tampere University Hospital (TAUH) (code R17007). The tissue material consisted of breast cancer surgical specimens of which surgery were performed in TAUH and Hatanpää County Hospital between June 2017 and November 2017. All patients included in the study underwent standard diagnostic workup and pre-operative tumor board. Tissue samples were collected by two breast pathologists (J.H. and T.T.) from Fimlab Laboratories, which is the principal pathology laboratory in the TAUH region.

Punch biopsies of 4 mm diameter were taken during the gross dissection of fresh surgical specimen. Tissues included in the study were: palpable breast carcinoma preliminarily assessed as clinical tumor stage (cT) ≥ cT2, macroscopically normal mammary gland > 2 cm apart from the malignant tumor, fat and vascular structures. Several samples, usually five, were taken from each category per patient. Vascular specimens were collected only when clearly visible on grossing. The accuracy of sample site for cancerous punch biopsies were histologically verified in 20 cases (Fig. 1). The samples were covered with a gauze moisturized with saline to prevent dehydration and stored at +4 ˚C until analysis at Tampere University of Technology within the same or following day in most cases. For the analysis, a custom-made well plate was made to control the sampling process.

The well plate contained 40 rounded wells (5.5 mm diameter, 5.75 mm depth). To prevent the diathermy knife from short-circuiting due to direct contact with the well plate, the wells were covered with a thin protective layer of agar. Agar was a suitable material for the protective layer, since it produces unnoticeable DMS response, when subjected to electrosurgery. The surgical smoke analyses were performed in random order. Measurements of poor quality due to incomplete production of smoke, defective sample preprocessing or malfunctions in the DMS analysis were excluded from the study. The selection criteria for technically failed measurements are presented in Fig. 2. The number of measured and excluded samples for each measurement day can be seen in the supplementary material (Table S1). The full reports of the cases (structured histopathology report and a prognostic panel including estrogen receptor (ER), progesterone receptor (PgR), Ki-67, Her2 IHC and dual ISH) were gathered from patient records after analysis.

2.2 Measurement system

The measurement system used in this study is an advanced model of a custom-built device that we have previously described as the *automatic tissue analysis system* (ATAS). The system comprises a

computer-controlled electrosurgical sampling stage, a gas sample pre-processing unit, and the ENVI-AMC® DMS device (Environics Oy, Finland). [28]

In this study, the DMS analysis produced an output *dispersion plot* of 1620 values that represent the ion spectrum of the measured surgical smoke sample. A schematic illustration of the measurement system and an example output dispersion plot are presented in Fig. 3.

Sampling protocol

Each sample was cut individually in an automated measurement sequence. The depth (3 mm) and duration (1.5 s) of the electrosurgical cut was kept constant to stabilize the concentration of the created surgical smoke. The duration of DMS was one minute, after which the system cleaned itself with dried purified air for another minute to prevent carry-over in the subsequent measurement.

2.3 Classification Models and Statistical Analysis

The DMS data from the measured surgical smoke was processed with cross-validated linear discriminant analysis (LDA) classification algorithms created in MATLAB (The MathWorks Inc., U.S.A). The basic principle of LDA classification is presented in the supplementary material (Fig. S1). The LDA classification models were cross-validated with 10-fold cross validation (10-f-CV). To exclude the possible overfitting bias from the classification, an additional holdout classification with randomly selected 70% of the data used as the train set and the remaining 30% used as the test set, was also conducted.

The LDA classification of the samples was first done by using the full raw data matrix (1620 values) of the dispersion plots. The analysis was continued with a process called *forward sequential feature selection* (FSFS) to locate the key areas in the dispersion plots of the tissue types. In FSFS, subsets

of the data matrices are selected until the classification accuracy does not improve significantly by the addition of new features [29]. A block diagram explaining the principle of FSFS is presented in the supplementary material (Fig. S2). The most relevant pixels in the dispersion plots were chosen for further analysis by performing 1000 cycles of FSFS each with new dataset partitions for 10-f-CV.

Using the FSFS-selected features, a receiver operating characteristic (ROC) curve was also plotted to visualize the diagnostic properties of the differentiation of carcinoma and all measured benign tissues. The ROC curve was plotted using the bootstrap method with 1000 repetitions.

3. Results

3.1 Characteristics of study samples

In total we examined 106 surgical smoke samples from 21 malignant breast tumors and 198 samples from benign tissues including macroscopically normal mammary gland (n = 82), adipose tissue (n = 88) and vascular tissue (n = 28). No benign breast tumors were included in the study. Clinical characteristics of carcinomas are presented in Table 1. Histopathological analysis was done for all tumors.

3.2 Classification results

With the raw data, our 10-f-CV LDA model achieved a classification accuracy of 86.5% when comparing carcinoma samples to all benign samples. The sensitivity was 80.1% and specificity 89.9%. The results of the binary classification are presented in Table 2. With the holdout method, the classifier achieved an overall classification accuracy of 84.9%, a sensitivity of 77.1% and a specificity

of 89.1%. In total, we measured 350 samples, out of which 304 were used in the final analysis. The exclusion criteria for the raw data can be seen in Fig. 2.

The classification accuracy of breast cancer to ductal (n = 69), lobular (n = 32) and invasive micropapillary (n = 5) was 94%, 47%, and 100%, respectively. The total classification accuracy by cancer type was 80.2%. The confusion matrix of the classification results is presented in the supplementary material (Table S2).

After the breast cancer classification with all 1620 pixels of the dispersion plot, the thousand FSFS cycles were performed. The process revealed that by average, 7 pixels from the dispersion plot were used in the feature selective classification of carcinoma and benign tissues. The average classification accuracy was 82.4% with a standard deviation of 1.8%. With the seven most frequently selected pixels, a ROC curve for the classification between carcinomas and benign tissue was plotted (Fig. 4). The area under the curve (AUC) value for the classification was 0.895 with 95% confidence bounds of 0.850 and 0.923.

4. Discussion

DMS coupled with ATAS achieves high performance in discrimination of benign and malignant breast tissue. The analysis of raw DMS data achieved a high discrimination rate of 86.5%. Similar performance was retained with only seven selected features of the dispersion plots and with the holdout validation. These results demonstrate the feasibility of intraoperative margin assessment with DMS from surgical smoke.

The inherent advantage of surgical smoke analysis is that if the surgeon uses electrocautery to excise the whole tumor, the whole surface of the cavity is sampled without additional stages in the surgery.

Furthermore, the orientation is easy to maintain and real-time analysis would allow the surgeon to excise positive margins accurately without resorting to larger resections such as shaving the whole cavity.

The performance of ATAS is close to the reported performance of REIMS, which achieved sensitivity and specificity of 100% in a proof-of-principle study with 16 patients. The discrimination seems to result from different glycerophospholipid profiles. [26] Although the performance of REIMS is impressive, the costs and maintenance needs of mass spectrometry technology remain a major obstacle for clinical adoption. As a more economical option, DMS may achieve the optimal compromise of cost and performance.

Our results compare favorably to existing margin assessment methods. RF spectroscopy, which has been shown to reduce the re-excision rate in breast-conserving surgery in two studies [16,17], has shown comparable performance in detection of benign breast tissue and carcinoma with a sensitivity and specificity of 90% and 91%, respectively [30]. RF spectroscopy can cover an area large enough to be practical but can currently only be performed *ex vivo*, leading to challenges of accurate orientation of the resected tumor. If the margin is positive, a larger re-excision is needed to achieve negative margins because the orientation of elastic breast tissue is difficult to maintain. OCT has been applied for intraoperative breast cancer margin evaluation with a sensitivity of 100% and a specificity of 82% [21]. It yields a histologic view of the tissue, which requires human interpretation and thus significant training for the surgeon. Nolan et al. addressed this issue by developing a decision support system for studying axillary lymph nodes in breast cancer surgery with a low sensitivity of 58.8% and mediocre specificity of 81.4% [22]. The results imply that in skilled hands, the specificity of OCT is similar to ATAS. However, the results concerning the sensitivity of OCT are inconclusive. Both RF and OCT require an additional stage of analysis in the surgery, which prolongs the anesthesia and interrupts the workflow.

Our protocol was designed to minimize bias. In addition to cancerous tissue, benign samples were collected from the patients as reference. Samples were collected within hours of the operation, stored fresh and analyzed shortly after gathering. The collection of samples was done by two experienced pathologists. The analysis of surgical smoke was done in a standardized pattern in a controlled environment. Hence, the analyses done on separate occasions are comparable and the risk for day-to-day bias is low. Punch biopsies of cancerous tissue were histologically verified in 20 cases. Biopsies from one large lobular carcinoma (T3) were not verified, but due to the macroscopic extend of the carcinoma it is likely that all punch biopsies consisted of cancerous tissue. From the 20 carcinomas that were histologically verified, punch biopsies from 18 cases consisted entirely of cancerous tissue. Punch biopsies from two carcinomas were only partially cancerous tissue in the histological assessment: in total 10 punch biopsies classified as malignant tissue may contain benign tissue. When the samples from the unverified lobular carcinoma and the samples from the two carcinomas of which punch biopsies were only partially cancerous tissues were excluded from the study, the accuracy (87%), sensitivity (84%) and specificity (89%) remained unchanged suggesting insignificant bias. Therefore, the samples remained included in the study. Benign punch biopsies were not histologically verified. However, all benign punch biopsies were collected by experienced pathologists by macroscopic judgement from a distance of 2 cm from the tumor. Should some of the benign contain malignant tissue, it would cause negative bias and would underestimate the performance of DMS.

All carcinomas that were preliminarily assessed as clinical tumor stage were included in the study. Despite the preliminary estimation a portion of tumors were classified as pT1c (n = 4). One of the tumors was micropapillary carcinoma and consequently the number of micropapillary carcinoma samples analyzed was small compared to other carcinomas. Micropapillary and ductal carcinoma samples were analyzed on the same day: all micropapillary samples were classified correctly and only one ductal carcinoma sample was classified as invasive micropapillary. The performance of the classification could be more balanced with additional measurements to strengthen classification of

carcinomas by their key features or by separating the benign classes. Weighting coefficients could also be implemented for further improving the diagnostic properties.

Even though the results of this study were comparable to previous studies, limitations of the design must be acknowledged. The key issues in the study were the challenges relating to the function of the ATAS system, variations in the study material, and the duration of the measurements. The system-related limitations led to occasional failed measurements that could not be used in the result analysis. The causes for failed measurements were 1) sample adherence to the diathermy, which prevented smoke production, 2) data communication delay between the sampling system, and 3) malfunctions of the pre-processing unit or the DMS device. Even with the exclusion of technically failed measurements, responses of especially vascular tissue specimens exhibited high variation. The heterogeneity of the tissue pieces and the resulting variation in the dispersion plots can explain the relatively low sensitivity of the binary classification. In our classification models, the benign tissue class was heterogenous with distinct dispersion plots from adipose tissue, macroscopically normal mammary gland and vascular tissue. This makes the classification criteria more complex and reduces the performance in small samples. The dispersion plots of the malignant tissues were more homogenous, leading to a more uniform malignant class. In addition, the benign class consisted of almost twice as many samples compared to the malignant class, which may bias the classification algorithm to favor the larger group in unsure cases, resulting in high specificity, but low sensitivity.

In this pilot study with the focus on the proof-of-concept, we used a high-resolution dispersion plot and a long cleaning period to maximize the data from the samples. This results in 1-minute duration of the measurement with an additional 1-minute for cleaning period. However, the FSFS classification models revealed that the whole spectrum of 1620 pixels is needlessly large for accurate differentiation of carcinoma and benign breast tissues. By concentrating on the selected areas of the dispersion plot, the combined measurement and recovery time is reduced to seconds, making it feasible for real-time

use. This model will be validated in future work, taking a step further towards the intraoperative cancer margin analysis.

5. Conclusions

The results demonstrate the ability of DMS to differentiate malignant and benign breast tissues based on surgical smoke in a laboratory setting. In the future, a rapid analysis model should be validated and the automatic tissue analysis system should be further developed for robust operation.

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7. References

[1] J Ferlay, I Soerjomataram, R Dikshit, S Eser, C Mathers, M Rebelo, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int.J.Cancer. 136 (2015) E359-86.

[2] E Senkus, S Kyriakides, S Ohno, F Penault-Llorca, P Poortmans, E Rutgers, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 26 (2015) 8-30.

[3] J Fajdic, D Djurovic, N Gotovac, Z Hrgovic. Criteria and procedures for breast conserving surgery. Acta inform.med. 21 (2013) 16-19.

[4] CE DeSantis, CC Lin, AB Mariotto, RL Siegel, KD Stein, JL Kramer, et al. Cancer treatment and survivorship statistics, 2014, CA Cancer.J.Clin. 64 (2014) 252-271.

[5] N Houssami, P Macaskill, ML Marinovich, M Morrow. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann.Surg.Oncol. 21 (2014) 717-730.

[6] ML Marinovich, L Azizi, P Macaskill, L Irwig, M Morrow, LJ Solin, et al. The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma In Situ Treated with Breast-Conserving Therapy: A Meta-Analysis, Ann.Surg.Oncol. 23 (2016) 3811-3821.

[7] M Morrow, KJ Van Zee, LJ Solin, N Houssami, M Chavez-MacGregor, JR Harris, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery with Whole-Breast Irradiation in Ductal Carcinoma In Situ. [Review], Ann.Surg.Oncol. 23 (2016) 3801-3810.

[8] MS Moran, SJ Schnitt, AE Giuliano, JR Harris, SA Khan, J Horton, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Int.J.Radiat.Oncol.Biol.Phys. 88 (2014) 553-564.

[9] M Morrow, P Abrahamse, TP Hofer, KC Ward, AS Hamilton, AW Kurian, et al. Trends in Reoperation After Initial Lumpectomy for Breast Cancer: Addressing Overtreatment in Surgical Management. JAMA Oncol. 3 (2017) 1352-1357.

[10] LE McCahill, RM Single, EJ Aiello Bowles, HS Feigelson, TA James, T Barney, et al. Variability in reexcision following breast conservation surgery. JAMA. 307 (2012) 467-475.

[11] MT van Leeuwen, MO Falster, CM Vajdic, PJ Crowe, S Lujic, E Klaes, et al. Reoperation after breast-conserving surgery for cancer in Australia: statewide cohort study of linked hospital data. BMJ Open. 8 (2018) e020858.

[12] JM Jorns, D Visscher, M Sabel, T Breslin, P Healy, S Daignaut, et al. Intraoperative frozen section analysis of margins in breast conserving surgery significantly decreases reoperative rates: one-year experience at an ambulatory surgical center. Am.J.Clin.Pathol. 138 (2012) 657-669.

[13] St John,Edward Robert B.Sc, M.R.C.S., RBS AlKhudairi, HMRCS Ashrafian, TFECTS Athanasiou F.R.C.S., Z Takats, DJMP Hadjiminas F.R.C.S., et al. Diagnostic Accuracy of Intraoperative Techniques for Margin Assessment in Breast Cancer Surgery: A Meta-analysis, Ann.Surg. 265 (2017) 300-310.

[14] JCFACS Boughey, TJFACS Hieken, JWFACS Jakub, ACFACS Degnim, CSFACS Grant, DRFACS Farley, et al. Impact of analysis of frozen-section margin on reoperation rates in women

undergoing lumpectomy for breast cancer: Evaluation of the National Surgical Quality Improvement Program data, Surgery. 156 (2014) 190-197.

[15] M Bakhshandeh, SO Tutuncuoglu, G Fischer, S Masood. Use of imprint cytology for assessment of surgical margins in lumpectomy specimens of breast cancer patients. Diagn.Cytopathol. 35 (2007) 656-659.

[16] TM Allweis, Z Kaufman, S Lelcuk, I Pappo, T Karni, S Schneebaum, et al. A prospective, randomized, controlled, multicenter study of a real-time, intraoperative probe for positive margin detection in breast-conserving surgery. Am.J.Surg. 196 (2008) 483-489.

[17] F Schnabel, SK Boolbol, M Gittleman, T Karni, L Tafra, S Feldman, et al. A randomized prospective study of lumpectomy margin assessment with use of MarginProbe in patients with nonpalpable breast malignancies. Ann.Surg.Oncol. 21 (2014) 1589-1595.

[18] C Mazouni, R Rouzier, C Balleyguier, L Sideris, F Rochard, S Delaloge, et al. Specimen radiography as predictor of resection margin status in non-palpable breast lesions. Clin.Radiol. 61 (2006) 789-796.

[19] NS Ivanovic, DD Zdravkovic, Z Skuric, J Kostic, N Colakovic, M Stojiljkovic, et al. Optimization of breast cancer excision by intraoperative ultrasound and marking needle - technique description and feasibility. World Journal of Surgical Oncology. 13 (2015) 153.

[20] H Abe, A Shimauchi, X Fan, JN River, H Sattar, J Mueller, et al. Comparing post-operative human breast specimen radiograph and MRI in lesion margin and volume assessment. J.appl.clin.med.phys. 13 (2012) 3802.

[21] FT Nguyen, AM Zysk, EJ Chaney, JG Kotynek, UJ Oliphant, FJ Bellafiore, et al. Intraoperative evaluation of breast tumor margins with optical coherence tomography. Cancer Res. 69 (2009) 8790-8796.

[22] RM Nolan, SG Adie, M Marjanovic, EJ Chaney, FA South, GL Monroy, et al. Intraoperative optical coherence tomography for assessing human lymph nodes for metastatic cancer. BMC Cancer. 16 (2016) 144.

[23] FC Meeuwsen, ACP Guedon, EA Arkenbout, M van der Elst, J Dankelman, JJ van den Dobbelsteen. The Art of Electrosurgery: Trainees and Experts. Surg.Innov. 24 (2017) 373-378.

[24] I Bruske-Hohlfeld, G Preissler, K Jauch, M Pitz, D Nowak, A Peters, et al. Surgical smoke and ultrafine particles. J.occup.med.toxicol. 3 (2008) 31.

[25] J Balog, T Szaniszlo, K Schaefer, J Denes, A Lopata, L Godorhazy, et al. Identification of biological tissues by rapid evaporative ionization mass spectrometry. Anal.Chem. 82 (2010) 7343-7350.

[26] J Balog, L Sasi-Szabo, J Kinross, MR Lewis, LJ Muirhead, K Veselkov, et al. Intraoperative tissue identification using rapid evaporative ionization mass spectrometry. Science Translational Medicine. 5 (2013) 194ra93.

[27] JA Covington, MP van der Schee, ASL Edge, B Boyle, RS Savage, RP Arasaradnam. The application of FAIMS gas analysis in medical diagnostics, Analyst. 140 (2015) 6775-6781.

[28] A Kontunen, M Karjalainen, J Lekkala, A Roine, N Oksala. Tissue Identification in a Porcine Model by Differential Ion Mobility Spectrometry Analysis of Surgical Smoke. Ann.Biomed.Eng. (2018).

[29] H Liu, Feature Selection. In: Sammut C., Webb G.I. (eds) Encyclopedia of Machine Learning. , Springer, Boston, Ma, 2011,.

[30] Z Kaufman, H Paran, I Haas, P Malinger, T Zehavi, T Karni, et al. Mapping breast tissue types by miniature radio-frequency near-field spectroscopy sensor in ex-vivo freshly excised specimens. BMC med.imaging. 16 (2016) 57.