AMBIENT MS PROFILING OF MENINGIOMAS: INTRAOPERATIVE ONCOMETABOLITE-BASED MONITORING

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The primary method of initial treatment of meningiomas is radical neurosurgical intervention. Various methods of intraoperative diagnostics currently in development aim to improve resection efficiency; we focus on methods based on molecular profiling using ambient ionization mass spectrometry. Such methods have been proven effective on various tumors, but the specifics of the molecular structure and the mechanical properties of meningiomas raise the question of applicability of protocols developed for other conditions for this particular task. The study aimed to compare the potential clinical use of three methods of ambient ionization in meningioma sample analysis: spray from tissue, inline cartridge extraction, and touch spherical sampler probe spray. To this end, lipid and metabolic profiles of meningioma tissues removed in the course of planned neurosurgical intervention have been analyzed. It is shown that in clinical practice, the lipid components of the molecular profile are best analyzed using the inline cartridge extraction method, distinguished by its ease of implementation and highest informational value. Analysis of oncometabolites with low molecular mass is optimally performed with the touch spherical sampler probe spray method, which scores high in both sensitivity and mass-spectrometric complex productivity.

Keywords: mass spectrometry, ambient ionization, electrospray ionization, meningioma, lipids, oncometabolites

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Compliance with ethical standards: the study was approved by the Ethics Committee of N. N. Burdenko National Medical Research Center of Neurosurgery (protocols №40 of 12 April 2016 and №131 of 17 July 2018) and conducted in accordance with the Declaration of Helsinki (2000 and subsequent revisions). All patients signed a voluntary informed consent form to participate in the study with use of biomaterials for research purposes.

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ПРЯМОЕ МАСС-СПЕКТРОМЕТРИЧЕСКОЕ ПРОФИЛИРОВАНИЕ МЕНИНГИОМ: ИНТРАОПЕРАЦИОННЫЙ МОНИТОРИНГ НА ОСНОВЕ ОНКОМЕТАБОЛИТОВ

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Основным методом лечения менингиом на первом этапе является нейрохирургическое вмешательство с максимальной радикальностью. Для повышения полноты резекции в настоящее время разрабатывают различные подходы интраоперационной диагностики, в частности, опирающиеся на принципы молекулярного профилирования. Основанные на масс-спектрометрии с прямой ионизацией, подобные методы демонстрируют свою эффективность на различных видах опухолей, однако особенности молекулярного строения и механические характеристики менингиом не позволяют напрямую транслировать протоколы, разработанные для других нозологий. Целью работы было провести сравнение возможностей применения трех методов прямой ионизации для исследования образцов менингиом: метода прямого спрея с ткани, метод картриджной экстракции и метода ионизации с поверхности сферического пробоотборника. Для этого анализировали липидный и метаболический профиль тканей менингиом, иссеченных в ходе планового нейрохирургического вмешательства. Было показано, что для анализа липидных компонент молекулярного профиля оптимальным для клинического применения оказывается метод картриджной экстракции, отличающийся наиболее простой реализацией и максимальной информативностью. Для анализа онкометаболитов с малой молекулярной массой лучшим выбором является метод ионизации с поверхности сферического пробоотборника, обеспечивающий высокую чувствительность и наилучшую производительность масс-спектрометрического комплекса.

Ключевые слова: масс-спектрометрия, прямая ионизация, электрораспылительная ионизация, менингиома, липиды, онкометаболиты

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Of all the meningeal tumors of the central nervous system (CNS), meningiomas are the most clinically significant. These brain tumors commonly occur in adults and account for over 36% of the total number of newly diagnosed CNS tumors [1, 2]. They are predominantly discovered by chance, i. e. the disease develops asymptomatically at the initial stage, but clinical symptoms can be observed in 15% of cases. Incidence of meningiomas increases with age; in addition, they are unusually common in females of reproductive age (~3 : 1 female predominance in this age group) [3]. This may be due to the peculiarities of the hormonal profile of women. Clinical symptoms are highly variable and depend on the location of the tumor. As with other intracranial tumors, meningiomas may present with manifestations of intracranial hypertension in the form of headache, nausea, vomiting, and reduced visual acuity [4].

Treatment of symptomatic meningioma begins with radical microsurgical or endoscopic removal of afflicted tissue [5, 6]. Although many brain tumor visualization methods have been developed in recent time, tumor delimitation is not performed in real time in most clinical cases. MRI methods, applied primarily prior to the operation, are presently employed in both diagnosis and operation navigation. As of other clinically relevant methods, use of fluorescent molecular imaging [7] is limited mainly by the specificity and sensitivity of the study being performed, and intraoperative ultrasound is not applicable if tumor density is close to that of intact tissue. Histopathological methods are the gold standard in tumor assessment and provide diagnostic information during surgery within half an hour, but they are usually limited to one segregated sample (or a small number thereof) from each operation and are not used to delimit tumors.

Various intraoperative diagnostic methods currently in development aim to increase the efficiency of surgical intervention [8, 9], enabling control over composition of the excised tissue; some methods are based on molecular profiling [10–13]. For example, gangliosides are used to differentiate astrocytoma [14]. Lipid profiles, oncometabolites, and specific neurometabolites such as n-acetylaspartate (NAA) are also used to delimit tumors [15, 16].

Ambient MS allows to analyze excised tissues almost in real time. The registered molecular profiles contain information both on the metabolic profile of tissues and on the change in the ratio of various lipids, which makes it possible to facilitate automatic classification by presence and proportion of malignant cells in the test sample [17, 18]. Thus, using rapid extraction of lipids and metabolites from tissue [13, 17, 19] or touch spray ionization [15, 20, 21], methods have been developed to differentiate various tumors from intact tissue. However, choice of a direct ionization method that is optimal for further development of methods for intraoperative meningioma monitoring is non-trivial due to the specifics of the molecular structure of meningeal tumors. The aim of this work was to compare three methods of mass spectrometric profiling and determine their applicability for solving the problems of differentiating afflicted and intact tissue in patients with meningioma.

METHODS

Histologically annotated and anonymized samples of meningiomas were provided by the N. N. Burdenko National Medical Research Center of Neurosurgery. All samples were obtained as part of planned operations for resection of pathological brain tissue.

Three methods of molecular profiling have been applied to the samples: spray from tissue (SFT) [22, 23], inline cartridge extraction (ICE) [17], and touch spherical sampler probe spray (SSP) [21].

To analyze meningioma samples using SFT [22, 23], a sample about 2 mm in size is placed on the tip of a disposable injection needle located at a distance of 10 mm from the vacuum interface of the mass spectrometer (Fig. 1).

The solvent is fed through a fused silica capillary with a flow rate of 3 μl/min directly onto the surface of the sample to extract lipids and metabolites. The molecules are ionized immediately after extraction by a voltage of up to 4–6 kV applied to the injection needle (selected empirically based on the geometric parameters of the sample), which ensures the formation of a Taylor cone and electrospray at the end of the needle.

To implement ICE [17], a disposable cartridge with a sample is inserted into the solvent supply line using common HPLC fittings for supplying solutions (Fig. 2).

The cartridge is a stainless steel tube with an internal diameter of 1.8 mm. A sample sized approximately 1 mm^2 is placed in the cartridge. The molecules from the sample are extracted by the solvent flowing through the solvent supply line at 2 μl/min. To connect to the line, two short sections of PEEK (polyether ether ketone) capillary are inserted into the tube and crimped to prevent leaks. The glass fiber filter in the cartridge prevents macroscopic parts of the sample from entering the line and blocking it. A standard commercially available electrospray ion source is installed at the end of the line after the cartridge. The voltage on the ion source is 3 kV in the positive-ion mode and 4 kV in the negative-ion mode.

SSP [21] uses fibrous samplers of spherical shape followed by electrospray ionization directly from their surface. A sampler is a rod of cleaned and pressed polymer fibers (specifically polyethylene terephthalate) 10 mm long, 2 mm in diameter. A sample is taken through a swab touch using the aforementioned porous sampler. The sampler is then fixed in a special ion source, where the solvent (80 μl) and high voltage (5 kV) are supplied for electrospraying.

To compare the effectiveness of the various direct ionization methods, we analyzed three meningioma samples obtained from three patients. Each meningioma sample was divided into three parts and analyzed by each of the proposed methods. The results of the study were validated on samples of meningiomas obtained from three different patients. The experiments were performed using an LTQ XL Orbitrap ETD hybrid mass spectrometer (ThermoFisher; USA) in full scan mode with m/z 100–2000. Mass spectra were obtained using both low resolution mass analyzers (LTQ XL ion trap in “normal” scan mode) and high resolution mass analyzers (Orbitrap with 30,000 FWHM resolution at m/z = 400). The temperature of the heating capillary at the entrance to the mass spectrometer was 220°C. The extraction solvent consisted of methanol (MeOH, > 99.9% HPLC; Merck KgaA; Germany), isopropanol (i-PrOH, > 99.9% HPLC; Merck KGaA, Germany), acetonitrile (ACN, > 99.9% HPLC; Merck KgaA, Germany), and deionized water (H_2O, $\rho \geq 17$ MΩ × cm) in a ratio of 3 : 3 : 3 : 1 (vol.), with the addition of 0.1% (vol.) acetic acid (CH_3COOH, >99%; Merck KgaA, Germany), which is optimal for extraction of lipid molecules and metabolites from soft fabrics, as well as suitable for use in electrospray ionization sources.

The most intense peaks were additionally annotated with exact mass readings using the LipiDex software [24], and with isotopic distribution using the Xcalibur™ software (Thermo Scientific-Jose; USA).

RESULTS

For all three methods (SFT (Fig. 3), ICE (Fig. 4A) and SSP (Fig. 4B)), the high-resolution mass spectra in the positive-ion mode are

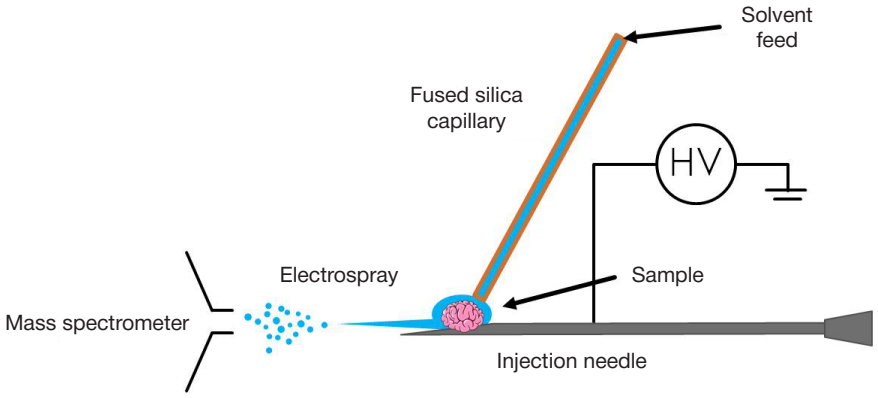

Fig. 1. SFT installation diagram

characterized by similar composition and relative intensity of the spectra of ions associated with lipids (600 < m/z < 900. Positive ions are registered in the form of protonated ions or ions cationized with sodium or potassium. The ICE and SSP spectra showed an additional intense group of peaks (1450 < m/z < 1650), where two groups of peaks (one characteristic of cardiolipins, the other for membrane lipid dimers) superposed. While the SFT and ICE spectra exhibit close signal-to-noise ratios, the same indicator is two to four times lower for SSP spectra, complicating discovery and analysis of low-intensity peaks.

Low resolution in the positive-ion mode yields similar spectra. SFT spectra additionally revealed an approximately 2.5 times higher intensity of lipid peaks (Fig. 5A), and, accordingly, a lower relative (but not absolute) intensity of peaks in m/z 100–400 in comparison with the ICE spectra (Fig. 5B). SSP spectra showed a reduced intensity in the region of the spectrum characteristic of lipids, but an increased intensity and diversity of peaks in low masses, where metabolites were recorded (Fig. 5C).

Characteristic lipid peaks were detected in all high-resolution spectra in the negative-ion mode (Figs. 6 and 7). The signal intensities of molecules of different classes vary between the three methods to a much lesser extent than in the positive-ion mode. However, only two methods of direct ionization (ICE and SSP) registered ions corresponding to the NAA neurometabolite, characteristic of intact nervous tissue [25, 26], in the spectra. The presence of this metabolite indicates that the studied samples were taken from the border of the tumor. The low-resolution spectra in the negative-ion mode are similar to each other in terms of the lipid ions (the results are completely identical to the corresponding high-resolution mass spectra and are not presented here). However, NAA could not be identified in any of the spectra obtained in this mode.

DISCUSSION

Rapid tissue analysis using ambient mass spectrometry is currently in consideration as a tool for molecular diagnosis of CNS tumors. While the idea of embedding molecular profiling methods in a surgical instrument [11, 19] is indeed attractive, its implementation is associated with disadvantages similar to those of intraoperative tomography. The need to equip each operating room with an expensive mass spectrometer, in addition to the complexity of certification of such complexes, makes it difficult to introduce them into clinical practice. At the same time, offline analysis methods [13, 17], in which a tissue sample is taken *in vivo* during resection and then analyzed *ex vivo* in a pathological laboratory, can be easily integrated into routine practice, which provides quick feedback to the surgeon and enables precise tumor excision. When integrated as a standard practice in rapid histological examination of clinical images, molecular profiling provides information on excised tissue within minutes, where the primary rate-limiting factor is the time required for transit of the sample between the operating room and the laboratory.

Each of the presented methods of ambient ionization of tumor tissues has a set of characteristic features. SFT

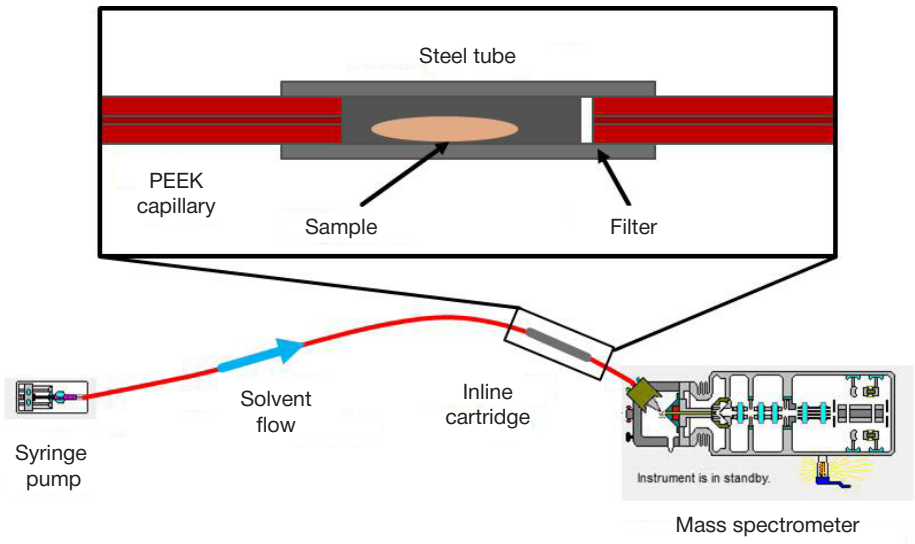

Fig. 2. ICE installation diagram

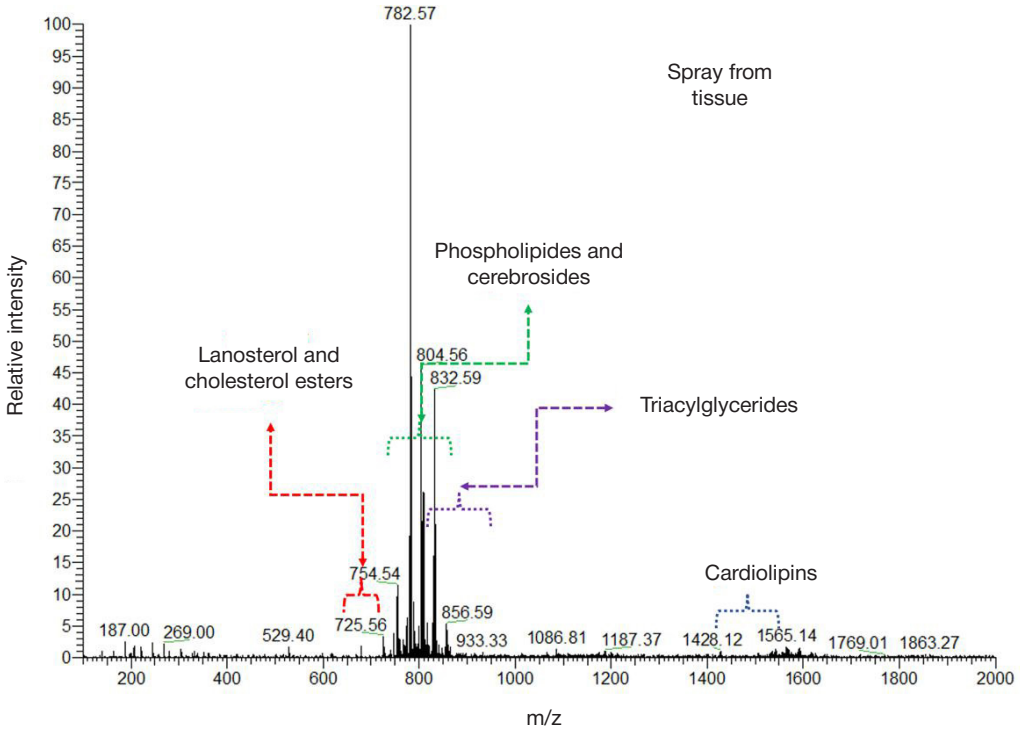

Fig. 3. Positive-ion high-resolution mass spectra of meningioma samples: SFT

completely eliminates the possibility of cross-contamination (i.e., the presence of residual molecules of the previous sample in the analysis of the current one, and their effect on the mass spectrum), since the only elements of the ion source that come into contact with the analyzed image completely disposable. However, the stability of ionization, which is important for obtaining reliable and repeatable test results, depends on the shape of the analyzed tissue sample. Since meningeal brain tumors generally have low mechanical rigidity and high plasticity, it is difficult to control the shape and size of the sample; therefore, additional adjustment of the voltage in the ion source is required for each sample, which reduces efficiency and requires additional staff qualifications.

ICE enables a highly stable ionization process due to the use of a standard mass spectrometer electrospray source. Ion sources of this type are widespread and are used to analyze various biological molecules, including those used in medical diagnostics. However, the need to flush the ion source between samples reduces performance of the method, since insufficient cleaning of the ion source can lead to cross-contamination between samples and, consequently, erroneous identification of oncometabolites in the test sample.

SSP, which employs disposable samplers, eliminates the problem of sample cross-contamination, which is characteristic of ICE, and simplifies the analysis process in comparison with SFT. The spherical shape of the rigid samplers ensures the geometry of the ion source is constant and simplifies the sampling process, which consists only of touching the sample with the tip of the sampler. The inertness of the materials from which the sampler is made also makes it possible to use it for sampling directly in the operating room, if appropriate certification is carried out. Despite these advantages, SSP is less efficient for the analysis of the lipid component of the molecular profile in the positive-ion mode. Importantly, this includes phosphatidylcholines and other components of cell membranes, which change significantly in the process of malignancy. However, in the negative-ion mode in the spectrum of the lipid component, phosphatidylserines in particular are

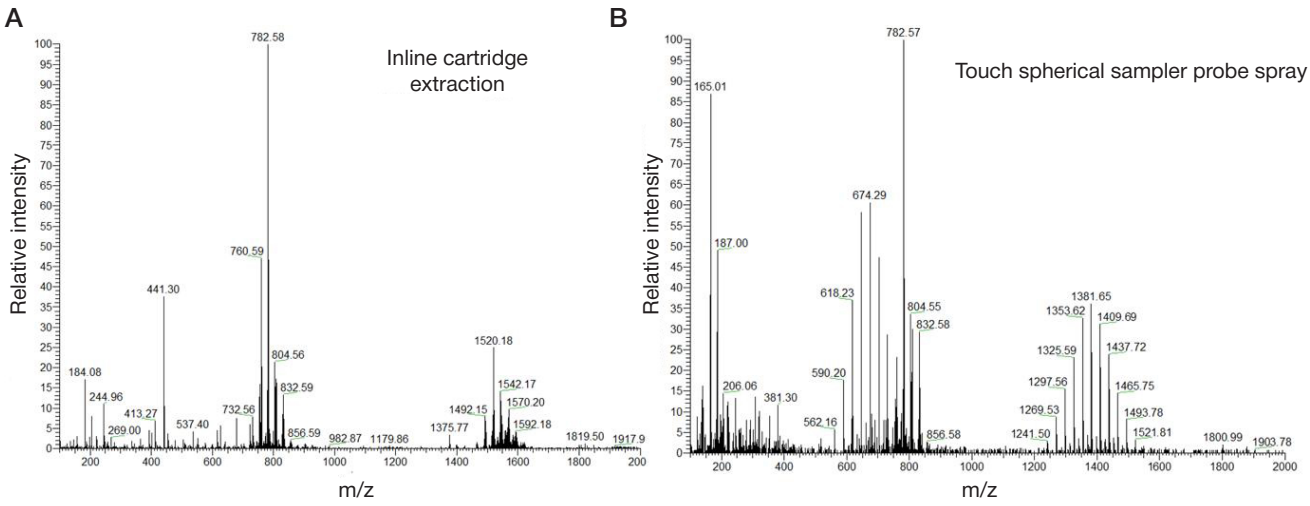

Fig. 4. Positive-ion high-resolution mass spectra of meningioma samples: ICE (**A**) and SSP (**B**)

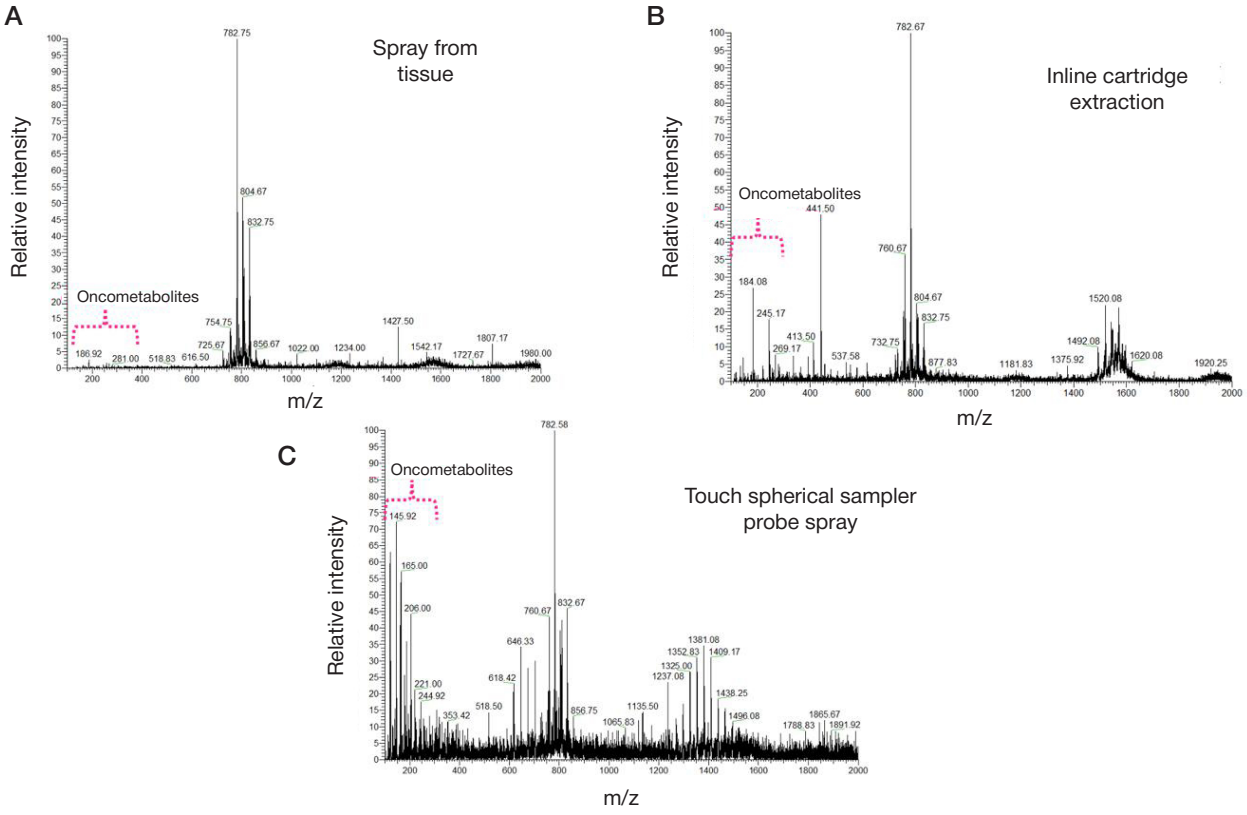

Fig. 5. Positive-ion low-resolution mass spectra of meningioma samples: SFT (**A**), ICE **(B)**, and SSP (**C**)

observed, which make up a significant proportion of lipids in the cell membranes of intact brain tissue, which makes it possible to use SSP to differentiate tumor and intact tissue using molecular profiling data.

In contrast to the lipid component, the efficiency of ionization of low-mass metabolites ionized in the m/z range 100–400 turned out to be comparable for all ionization methods. However, the metabolic profile obtained using SFT

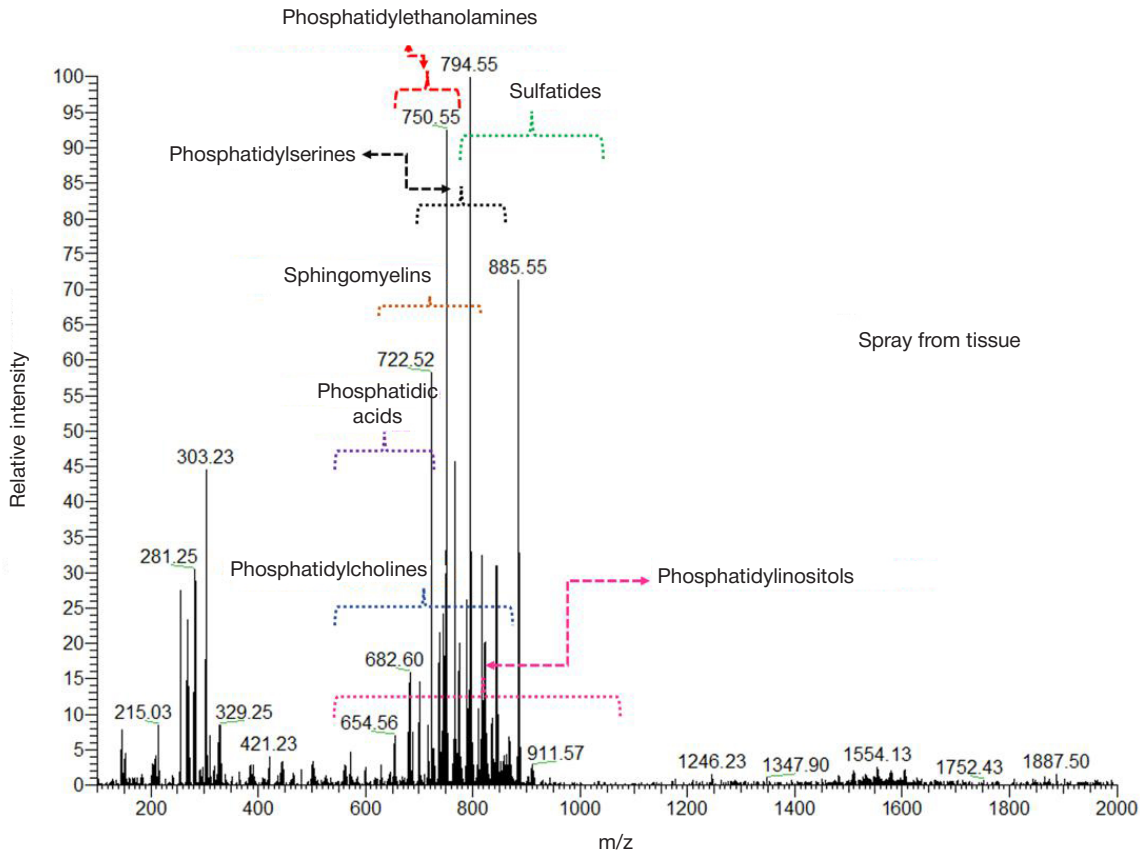

Fig. 6. Negative-ion high-resolution mass spectra of meningioma samples: SFT

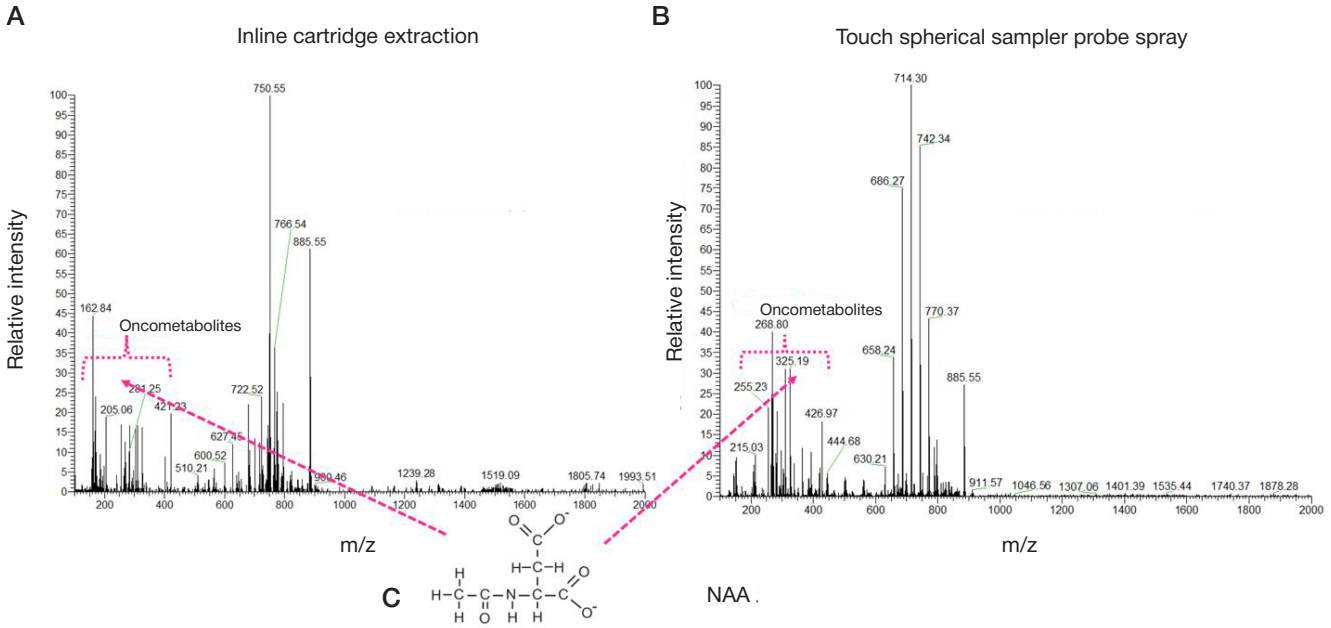

Fig. 7. Negative-ion high-resolution mass spectra of meningioma samples: ICE (**A**) and SSP (**B**). **C**. Structural formula of the neurometabolite NAA

was less diverse, as it showed less mass-spectrometric peaks. Significantly, none of the experiments using this method detected NAA, which was registered when these samples were simultaneously examined using other ionization methods. This result is likely associated with lower efficiency of extraction of water-soluble metabolites from a whole tissue sample by washing the sample with a solvent during ionization compared to a more complete cartridge-aided extraction, or to efficient transfer of moderately hydrophobic analytes to the surface of a fibrous sampler.

SSP in the negative-ion mode, in turn, appears promising for express surgical evaluation of the tumor resection margin. Due to the relatively high ion intensity in this range, it seems possible to detect an oncometabolite, in particular NAA, and provide an assessment of tumor infiltration, which is of paramount importance when trying to maximize glioma resection (a favorable prognostic factor for patients with glioma).

CONCLUSIONS

The use of various ambient ionization methods for studying CNS meningeal tumor samples makes it possible to obtain a molecular profile sufficiently intense to be suitable for differentiating tumor tissues from intact ones, as was previously demonstrated for glial tumors. Spray from tissue is a highly productive method of obtaining spectra of the lipid component of tissues. Inline cartridge extraction is the simplest to implement, but has the lowest analysis productivity. Touch spherical sampler probe spray has limited application in analysis of the lipid fraction, but it is suitable for detection of onco- and neurometabolites, and is likewise easy to implement. The choice of an ionization method for clinical use thus directly depends on the requirements for ease of implementation and analysis performance imposed on the laboratory, and on the set of classes of biological molecules, lipids or water-soluble metabolites that best characterize a particular condition, accounting for its degree of malignancy.

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