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ORIGINAL ARTICLE

Cell block practices in European cytopathology laboratories

Irena Srebotnik Kirbis PhD[1] | Ivana Kholova MD, PhD[2] | Heini Huhtala MSc[3] | Massimo Bongiovanni MD[4] | Margareta Strojan Flezar MD, MIAC, PhD[1] | Chantell Hodgson MSc[5] | Beatrix Cochand-Priollet MD, MIAC, PhD[6]

[1]Institute of Pathology, Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

[2]Pathology, Fimlab Laboratories and Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[3]Faculty of Social Sciences, Tampere University, Tampere, Finland

[4]Medisyn Pathology, Sonic Healthcare, Lausanne, Switzerland

[5]United Kingdom National External Quality Assessment Service for Cellular Pathology Technique, Newcastle upon Tyne, UK

[6]Department of Pathology, Cochin Hospital, University Paris, Paris, France

Correspondence
Irena Srebotnik Kirbis.
Email: irena.srebotnik-kirbis@mf.uni-lj.si

Abstract

Background: There are numerous methods and procedures described for the preparation of cell blocks (CBs) from cytological samples. The objective of this study was to determine current practices and issues with CBs in European laboratories.

Methods: A link to an online survey, with 11 questions about CB practices, was distributed to cytology laboratories via participants of United Kingdom National External Quality Assurance Service for Cellular Pathology Techniques and national representatives in the European Federation of Cytology Societies.

Results: A total of 402 laboratories responded completely (337/402, 84%) or partially (65/402, 16%) to the survey by February 4, 2022. The most common CB practice is embedding cell pellets using plasma and thrombin (23.3%), agar (17.1%), Shandon/Epredia Cytoblock (11.4%), HistoGel (7.9%), and Cellient (3.5%). Other methods such as CytoFoam, albumin, gelatin, Cytomatrix, and collodion bags are rarely used (1.0%, 0.7%, 0.7%, 0.3%, and 0.2%, respectively). CBs are also prepared from naturally occurring clots or tissue fragments (29.5%) and cells scraped from unstained or prestained smears (4.4%). The most frequent issues with the CBs in a daily cytology practice are low cellularity (248/402, 62%) and dispersed cells (89/402, 22%), regardless of the CBs preparation method or how the samples for embedding were selected.

Conclusions: There is a great variability in CB practices in European laboratories with low cellular CBs as the main issue. Additional studies are mandatory to evaluate and improve performance and cellular yield of CBs.

KEYWORDS
cell blocks, cytopathology, immunocytochemistry, molecular cytology, quality

INTRODUCTION

Cytological samples embedded into paraffin or so called cell blocks (CBs) are one of the tools to prepare cytological samples for microscopic evaluation, beside direct smears, Cytospins, and liquid-based cytology (LBC) preparations. The main advantages of CBs are preservation of potential architectural features, easy archiving for future studies, and application of ancillary diagnostic tests already validated for FFPE tissue samples.[1–4] However, preparation of CBs significantly increases laboratory workload, cost, and turn-around time.[1,3] Besides, there is no standardized and optimized method for CB preparation or guidelines for good laboratory practice.[5] Moreover, as first revealed by Crapanzano et al., inconsistent and suboptimal cellularity of CBs might be an issue with the application of CBs in a daily practice.[6]

To evaluate daily practices and potential issues with the CBs in a wide range of European laboratories, an online survey in collaboration between European Federation of Cytology Societies (EFCS) and United Kingdom National External Quality Assurance Service (UK NEQAS) for Cellular Pathology Techniques (CPT) was designed and performed.

MATERIALS AND METHODS

An online survey with 11 questions was designed using the web-based SurveyMonkey platform (https://www.surveymonkey.com/) and approved by members of the EFCS working group and members of UK NEQAS CPT. An invitation letter with a link to the survey was distributed to cytology departments via the official national representatives of all cytology societies affiliated with the EFCS and UK NEQAS CPT–registered participants. The number of laboratories that received the invitation to the survey was not monitored.

All questions with predetermined, multiple-choice answers are shown in Table 1. All the participants' answers were collated. In some questions, multiple responses were allowed. The frequencies of responses in each category were calculated.

Differences in frequencies for CB issues were evaluated for the following groups of CB preparation methods - automated (Cellient), gelling (agar, gelatin, HistoGel, plasma-thrombin), naturally occurring clots and visible tissue fragments, foams and matrix (Cyto Foams, Cytomatrix), commercially available kits (Shandon/Epredia) and other methods, using Fisher exact test. A p value ≤ 0.05 was considered statistically significant.

RESULTS

Responses

Of 511 responses received, 402 (79%) were included in the present analysis as being answered completely (337/402, 84%) or partially (65/402, 16%). Responses with answers to only general questions (country and participation in UK NEQAS CPT) were excluded from the analysis (109/511, 21%). Not all laboratories provided responses to every question. The number of laboratories that responded to a specific question is indicated correspondingly.

The highest number of responses included in analysis were from the United Kingdom (123/402, 31%), followed by Italy (55/402, 14%), Turkey (33/402, 8%), Germany (23/402, 6%), Portugal (18/402, 4%), the Netherlands (18/402, 4%), Switzerland (17/402, 4%), and France (15/402, 4%). Responses received from some overseas and non-European countries (18) were grouped as Other. Three respondents did not indicate country of origin (Figure 1).

Cytology samples embedded into cell blocks

Slightly more than half of laboratories (52%) prepare more than 400 CBs annually (Table 2) and for the majority of responding laboratories (74/101, 73%), preparation of CBs represents a minor portion of the workload (up to 25%).

Cell blocks are prepared from all cytology samples in 113/399 (28%) laboratories, whereas just 1 specific sample was processed in CBs in 42/399 (11%) of responding laboratories. The rest of the laboratories prepare CBs from different combinations of cytology samples (244/399, 61%).

Cell blocks are most frequently prepared from body cavity fluids (37%), followed by respiratory samples (26%), fine-needle aspiration (FNA) needle washings (19%), cyst contents (15%), LBC samples (14%), and cells scraped from stained smears (2%) (Figure 2).

Methods for CBs preparation

Cell pellets are most frequently embedded using plasma and thrombin method (23.3%) followed by agar (17.1%), Shandon/Epredia Cytoblock (11.4%), HistoGel (7.9%), and Cellient (3.5%). Other methods such as CytoFoam, albumin, gelatin, Cytomatrix, and collodion bags are rarely used (1.0%, 0.7%, 0.7%, 0.3%, and 0.2%, respectively), whereas none of the participating laboratories reported application of the recently described methods BioInnovation and AFFECT (Figure 3). Beside cell pellets, laboratories also embedded naturally occurring clots and/or tissue fragments (29.5%), whereas cells scraped from unstained or prestained smears are rarely embedded (4.4%).

In the majority of laboratories, one or two methods are used for CB preparation (373/395, 94%), whereas three or four different methods are used in 6% (22/395) of laboratories (for all combinations of different CBs preparation methods, see Table S1).

Sample triage for CB preparation

Selection of cytology samples for CB processing is most frequently based on microscopic evaluation (29%), followed by macroscopic

TABLE 1 Questions and predefined answers included in the web-based survey.

Question	Predefined answers
What sample types are cell blocks prepared from?	All cytology samples
	Body cavity fluid
	Respiratory samples
	Fine-needle aspiration needle washings
	Scraped material from fine-needle aspiration slides
	Cyst contents
	Liquid-based cytology specimens
	Other
Which of the following method(s) are routinely used to prepare cell blocks from cytology specimens?	AFFECT
	Agar
	Albumin
	BioInnovation
	Cell scrape
	Cellient
	Collodion
	Gelatin
	HistoGel
	Naturally occurring clots/tissue fragments
	Plasma and thrombin
	Shandon
	Other
What fixative(s) is routinely used for cell blocks?	Buffered formalin
	10% formalin
	Alcohol
	Alcohol followed by buffered formalin
	Alcohol followed by 10% formalin
	Other
Are cell blocks processed using standard histopathology programs?	Yes
	No
If cell blocks are NOT processed using standard histopathology programs, what steps are different?	Fixation times
	Rapid processing schedule
	Other
What is the main reason for cell block production in your laboratory?	As a complement to morphological diagnosis
	To perform immunocytochemistry ancillary testing
	To perform molecular testing
	To store the material for future tests
	Other
Which laboratory personnel request cell block production?	Standard laboratory procedure
	Supervisory scientist
	Technologist
	Consultant pathologist
	Clinician/other
How are samples triaged/selected for cell block preparation?	No triage, cell blocks are prepared from all samples
	Rapid on site evaluation
	Anamnestic and clinical data
	Cell count
	Macroscopic evaluation
	Microscopic evaluation
	Visual assessment of tissue fragments
	Other
How many cell blocks per year do you routinely produce?	0–50
	51–100
	101–200
	201–300
	301–400
	>400
What percentage of your routine cytology laboratory workload is cell blocks?	<5
	6–10
	11–25
	25–50
	>50
What are the main issues with cell blocks in your laboratory?	Low cellularity
	Dispersed cells
	Inconsistent results of immunocytochemistry/fluorescence in situ hybridization/special staining
	Poor morphology
	Antigenicity loss
	Not enough sections obtained from cell blocks
	Other

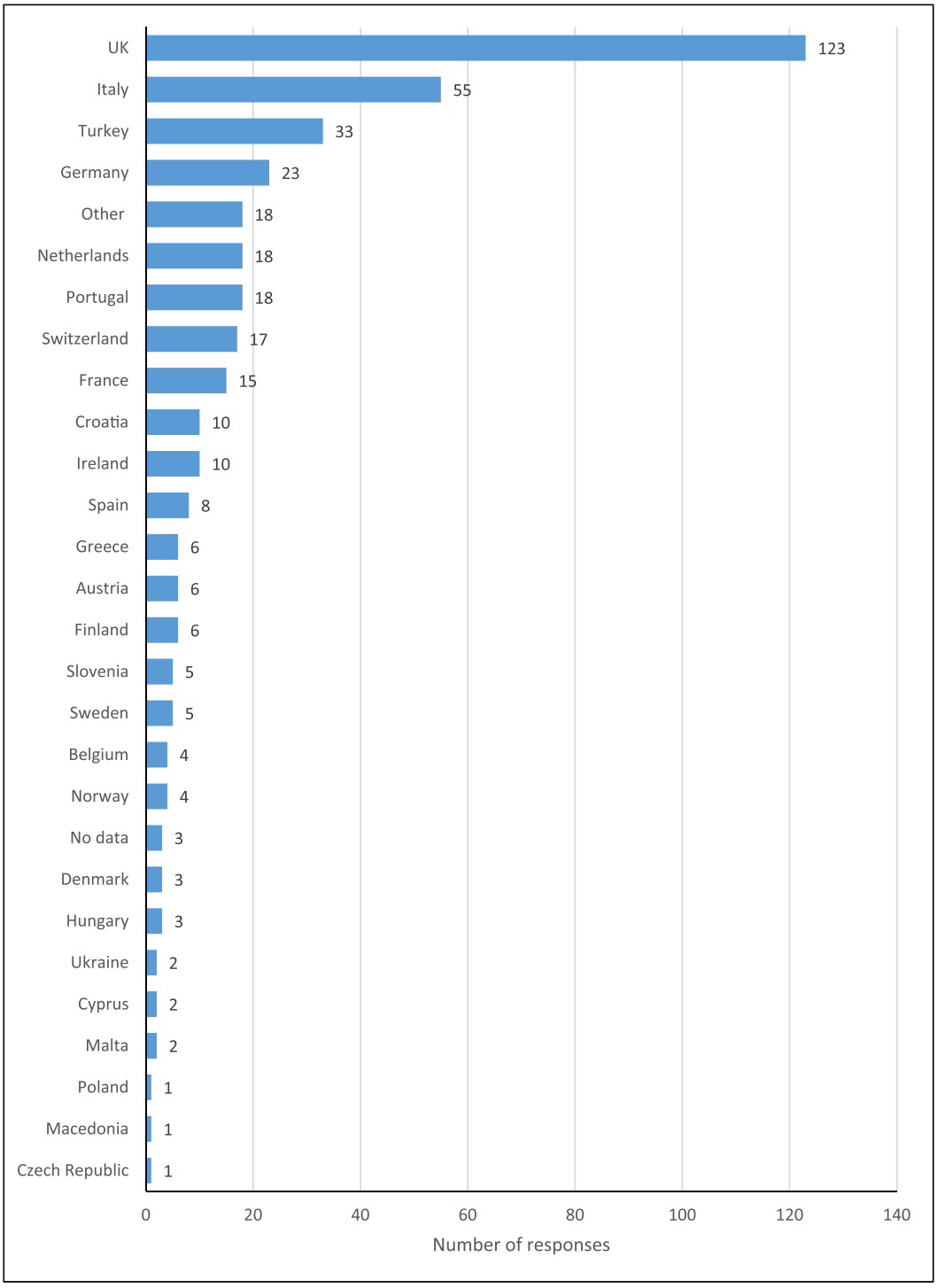

FIGURE 1 Number of responses to the cell block online survey received from different countries.

sample evaluation (21%) and rapid onsite evaluation of sample adequacy (13%). Anamnestic data, defined as information received at specimen referral is used less frequently (10%) whereas cell count, in which number of cells in a sample is determined, is only rarely used (2%). CBs are done without any triage in 17% of responses/cases (Figure 4).

Fixation and CB embedding

The majority of laboratories use formalin-based fixatives for CBs (69%) or fixation with ethanol followed by formalin (16%). Standard histopathology programs for CB embedding are used by 90% of participants.

Satisfaction with the CBs

The highest frequency of always satisfied with the CB quality was found in laboratories preparing CBs using albumin (1/4, 25%), followed by plasma and thrombin (27/117, 23%), Shandon/Epredia (10/51, 19%), HistoGel (7/39, 18%), cell scraping (4/24, 17%), and other methods (5/37, 13%). However, the lowest frequency of always satisfied laboratories was found for laboratories embedding naturally occurring clots and/or tissue fragments and CBs prepared with Cellient or agar (17/153, 11%, 2/18, 11% and 8/82, 10%, respectively) (Figure 5).

Sometimes satisfied with the CBs quality was laboratories preparing CBs with collodion (1/1, 100%), gelatin (1/4, 25%), and Cellient (4/18, 22%).

Rarely or never satisfied with the quality of CBs was laboratories using other methods for CB preparation (1/37, 3%) plasma and thrombin (2/117, 2%), agar (1/82, 1%), and naturally occurring clots and tissue fragments (2/153, 1%).

The highest frequency of always satisfied with the CBs' quality was found for laboratories using cell count as a triage method (4/14, 29%), whereas for all other triage methods, the frequencies of always satisfied varied from 12% to 18% (Figure 6).

TABLE 2 Annual number of prepared CBs.

CBs per year	No (%) of laboratories
0–50	30 (9)
51–100	21 (6)
101–200	39 (11)
201–300	43 (12)
301–400	33 (10)
400+	181 (52)

Abbreviation: CBs, cell blocks.

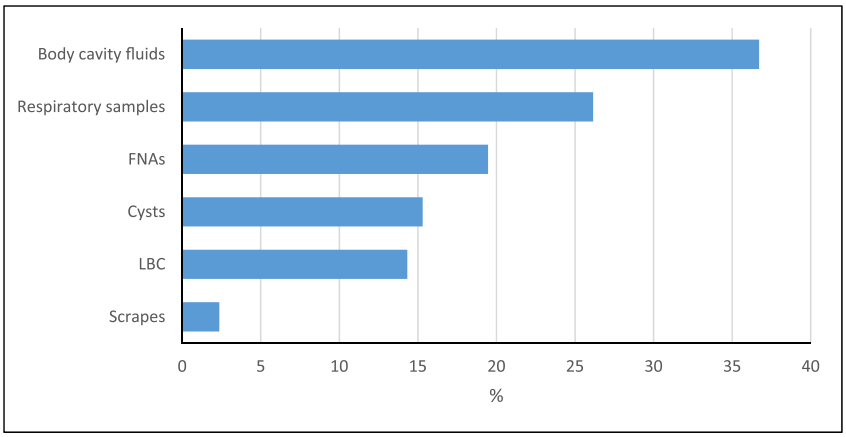

FIGURE 2 Cytology samples used for CBs preparation. FNAs indicates fine-needle aspiration samples; LBC, liquid-based cytology.

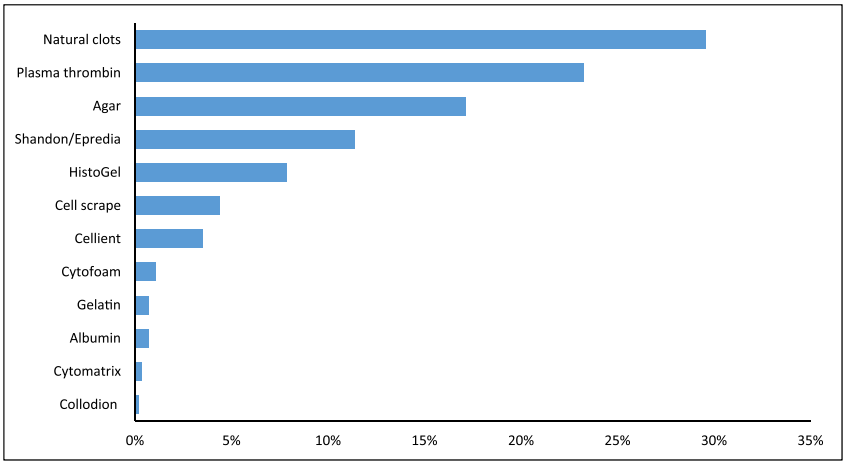

FIGURE 3 Frequencies of different methods used for cell block preparation.

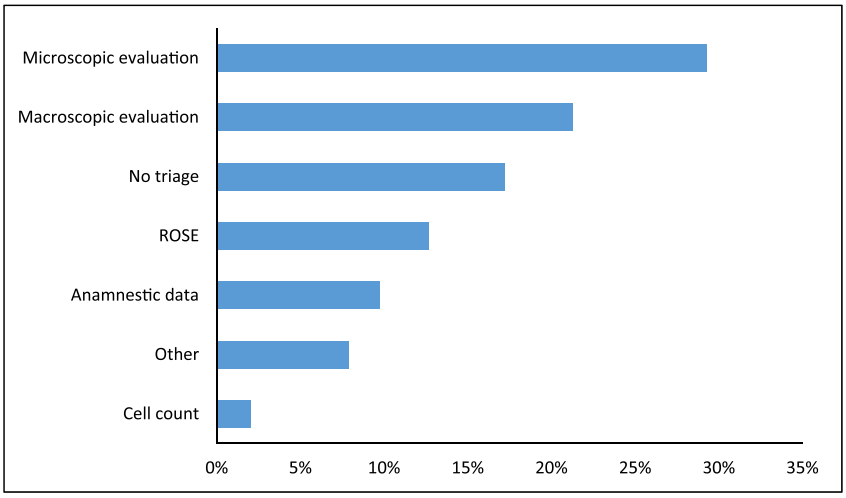

FIGURE 4 Methods used for cell block sample triage. ROSE indicates rapid on-site evaluation.

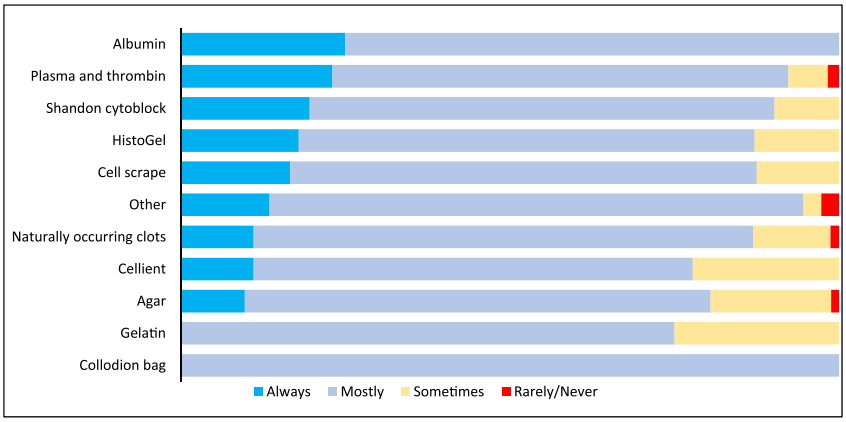

FIGURE 5 Satisfaction with cell block quality regarding the preparation method.

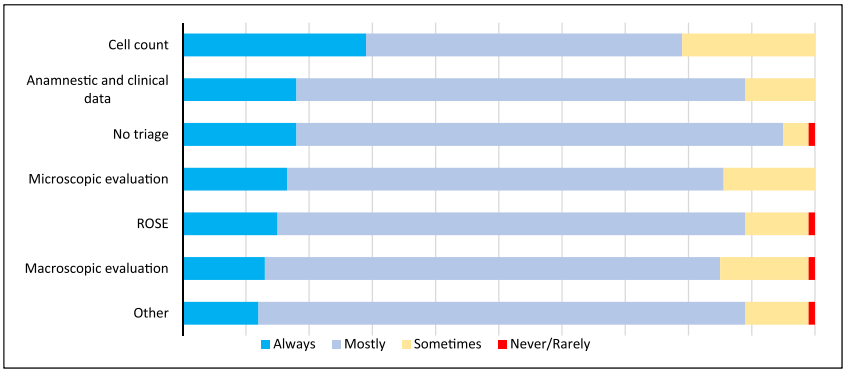

FIGURE 6 Satisfaction with cell block quality regarding the sample triage. ROSE indicated rapid onsite evaluation.

Cell block issues

The most frequent issues of using CBs in a daily practice for laboratories that participated in this survey was low cellularity (248/402, 62%), followed by dispersed cells (89/402, 22%), not enough sections obtained from CB (61/402, 15%), inconsistent results obtained on CBs (41/402, 10%), poor morphology (33/402, 8%), and other reasons (6/402, 1%).

The frequency of low cellular CBs for different individual CB preparation methods included in the survey varied from the lowest 50% for CBs prepared with albumin (2/4) and Cytomatrix (1/2) to 75% for CBs prepared with gelatin (3/4). The highest frequency (1/1, 100%) of low cellularity was found for CBs prepared with collodion bag; however, this method is biased because it was used only in 1 laboratory. The highest frequency of cells dispersed throughout hematoxylin and eosin sections was found for CBs prepared with Cytofoam (2/2, 100%), followed by albumin and gelatin with 50% (both 2/4). The frequency of inconsistent results varied from 4% for agar (4/98) to 25% for albumin (1/4), whereas no issues with inconsistent results were reported for collodion (0/1), Cytofoam (0/6), Cytomatrix (0/2), and gelatin (0/4). The highest frequency of poor morphology and/or antigenicity loss was found for CBs prepared with albumin (2/4, 50%), followed by cell scrape (7/25, 28%) and Cellient (3/20, 15%). The frequency of not enough sections varied from 11% for HistoGel (4/45) to 28% for cell scrapes (7/25), whereas no issues with not enough sections was reported for collodion (0/1), CytoFoam (0/6), Cytomatrix (0/2), and gelatin (0/4) (Figure 7).

There are no statistically significant differences in frequencies of individual CB issues among CB preparation methods classified in the following groups: automated (Cellient), commercially available kit (Shandon/Epredia), foams and matrix (CytoFoams, CytoMatrix), gelling (agar, gelatin, HistoGel, plasma-thrombin), naturally occurring clots, and visible tissue fragments and other methods (Table 3).

The lowest frequency of low cellular CBs was reported in laboratories using cell count as a triaging method (50%), whereas all other triaging methods frequencies for low cellular CBs varied from 58% to 72% (Figure 8).

Dispersed cells are most frequently reported in laboratories using cell count as triaging (57%), whereas for other triaging methods the frequencies of dispersed cells are between 19% to 28%.

The main reason for CBs preparation is to perform immunocytochemistry (ICC; 91%), followed by molecular testing (61%), to

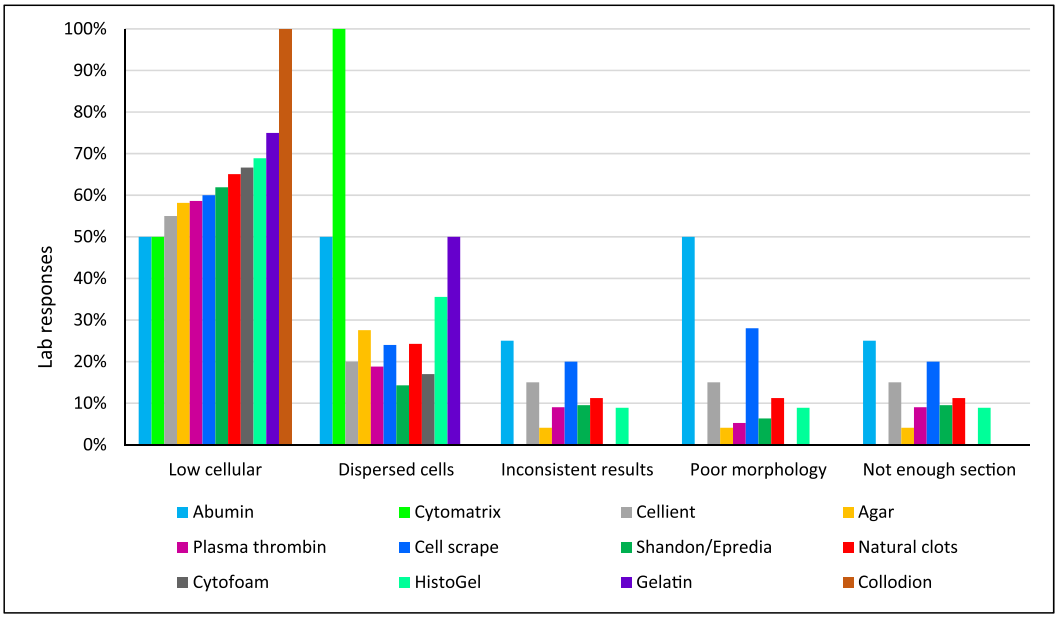

FIGURE 7 Frequency of issues for cell blocks prepared with different methods.

TABLE 3 Frequencies of individual CB issues for different groups of CB preparation methods.

	Groups of CBs preparation methods						
	Automated $n = 20$	Foams/matrix $n = 9$	Gelling $n = 284$	Natural clots $n = 169$	Other $n = 42$	Shandon/Epredia kit $n = 63$	
CBs issues	%	%	%	%	%	%	*p* value
Low cellular	55.0	66.7	60.2	65.1	76.2	61.9	0.413
Dispersed cells	20.0	22.2	25.4	24.3	26.2	14.3	0.571
Inconsistent results	15.0	0.0	7.4	11.2	11.9	9.5	0.507
Poor morphology	15.0	0.0	6.0	11.2	16.7	6.3	0.076
Not enough sections	15.0	0.0	15.0	16.6	16.7	15.9	0.875

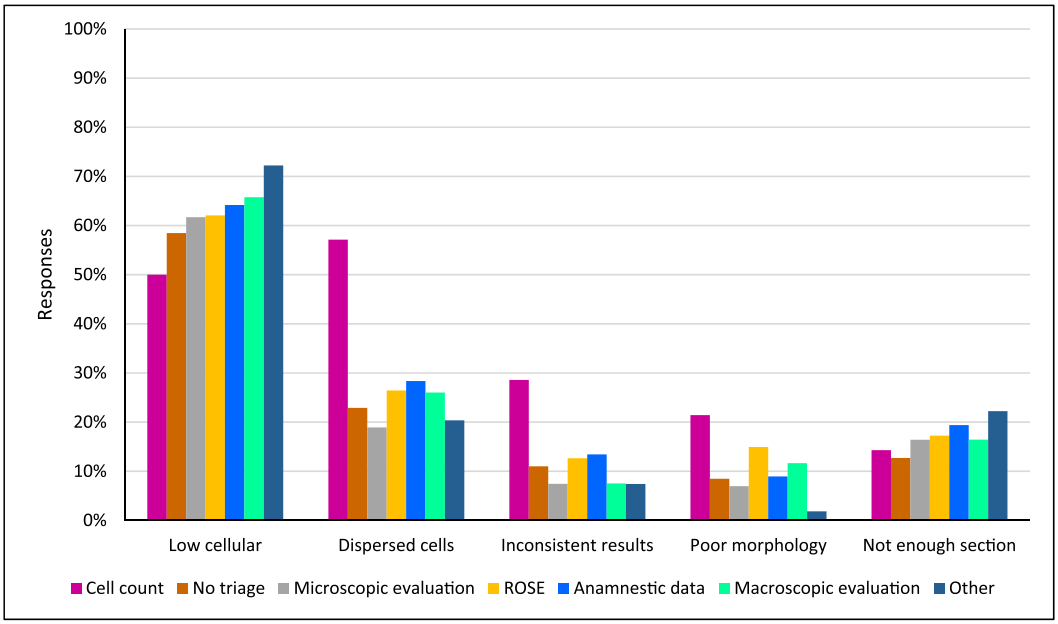

FIGURE 8 Frequency of issues for cell blocks with different triage methods. ROSE indicates rapid on-site evaluation.

complement morphological diagnosis (59%) and to store material for future studies or testing (33%).

DISCUSSION

Our survey demonstrated for the very first time that CB practices vary widely among European laboratories and, most importantly, that low cellularity is the main problem with CBs in daily cytology practice, regardless of the CB preparation method used.

The interest for CBs in diagnostic cytopathology is constantly increasing as reflected by the number of publications on PubMed. From only 30 articles having CB in the title or abstract published in 2000, there were 176 such articles published in 2020. However, application of CBs in a daily cytology practice is still limited and represents a minor workload (up to 25%) in the majority of European laboratories as shown in our survey.

Most probable reasons for this discrepancy are lack of standardization in CB preparation as well as inconsistency and inadequate cellularity of CBs.[5]

There are several very different approaches how to collect and embed cells from cytological samples with advantages and disadvantages already well presented by several authors.[1–4]

The most basic CB preparation method is embedding visible tissue fragments or naturally occurring clots that are simply transferred from the sample or objective slide directly to the tissue cassettes without any additional processing steps. This appears to be the only reasonable way to prepare them for microscopic evaluation. Cellularity of these CBs is obviously affected only by the cellularity of the fragments or clots.

On the other hand embedding cell pellets from primary or secondary cell suspensions is a much more demanding and variable process. There are already at least 10 different methods described for concentrating and embedding cell pellets into paraffin[1–3] and yet plasma and thrombin remain the most popular CB preparation method globally[6,7]; this was also confirmed in our survey.

The first report about using plasma and thrombin for embedding cytological samples was published in 1948[8] and has now various modifications.[2] The method is regarded as cheap, simple, convenient, and efficient for daily practice.[2,3,9] However, there are several reasons why this method should no longer be used in a modern cytology practice. First, plasma contains cell-free DNA,[10] which might be a source of DNA contamination and can lead to a false-positive or false-negative results of molecular analysis.[11] Moreover, thrombin reagents might contain contaminant extraneous cells,[7] and this could also interfere with the results of molecular or immunocytochemical analysis.[7,10] Second, sources of plasma and thrombin are not standardized and vary not only between laboratories but also in each individual laboratory over time. Pooled and expired plasma usually used for the CB preparation has variable clotting abilities, which might also deteriorate over time. Moreover, anticoagulation or other therapies can alter clotting abilities of plasma.[3]

Beside plasma and thrombin, other gelling agents such as agar, albumin, gelatin, and HistoGel are also used. As shown in our survey, in European laboratories, agar is more frequently used than HistoGel (17.1% and 7.9%, respectively), but is much more common in the United States (27%).[6] Albumin and gelatin as gelling agents are rarely used (0.7%) in European laboratories.

The main problem with agar and agarose is high melting temperature (85°C and 95°C, respectively), which might compromise cell morphology[1] and immunoreactivity. HistoGel is hydroxyethyl agarose with a low melting and low gelling temperature (65°C and 26°C, respectively) and probably the most appropriate gelling agent for CB preparation. Commercially prepared HistoGel is easy to store

and enables time-efficient CB preparation.[3] The main problem with HistoGel CBs is inconsistent cellular yield.[3] However, appropriate optimization of HistoGel processing steps will most probably improve the quality and performance of HistoGel CBs. In our recent study, we demonstrated that immediate centrifugation after adding 3 to 5 drops of melted HistoGel to the cell pellet is crucial for achieving consistent cellularity of CBs, even from a low cellular sample. Moreover, orientation of a congealed cell pellet in the tissue cassette seems very important as well. Simply putting a congealed HistoGel button in a tissue cassette in a concave orientation yielded much lower number of serial hematoxylin and eosin sections with great variability in number and the distribution of cells than longitudinally sectioned HistoGel button (data not yet published). Both of these improved preparation steps would most probably improve consistency of CB cellularity also in case of other gelling agents.

Among nongelling methods of preparing CBs, Shandon/Epredia Cytoblock kit is the most frequently used in some European laboratories, namely in the United Kingdom (20/61, 33%), France (9/61, 15%), Netherlands (6/61, 10%), Switzerland and Turkey (both 5/61, 8%), and in Germany (4/61, 6%). However, it is only sporadically used in other countries. According to the studies on thyroid[12] and salivary gland[13] FNAs, the Shandon/Epredia Cytoblock kit more often yields insufficient CBs than plasma and thrombin or in-house CB preparation methods.

Cellient is the only automated system for CB preparation and is not common in US (8%)[6] or European laboratories (3.5%). The main disadvantages of this method are high cost and adjustment, optimization, and revalidation of all ICC protocols because of a methanol-based fixation.[14–17]

CytoFoams,[18–20] CytoMatrix,[21,22] and collodion bags[23,24] were reported for their efficient embedding of cytological samples, but are rarely used in the European laboratories.

Low and inconsistent cellularity of CBs was already reported in the individual studies, where approximately 60% of CBs were unsuitable for ancillary methods because of low cellularity.[5,25] Actually, it seems that low cellularity is the common and main issue with CBs in a daily cytology practice, as already shown by Crapanzano et al. in US laboratories[6] and was also demonstrated on a larger scale in our survey of the European laboratories. In addition, our survey demonstrated that low cellularity of CBs is a key issue regardless of CB preparation method and sample triage. This important finding in our survey would be worth exploring in another sample-based study. For efficient evaluation of a true performance and a cellular yield of different CBs preparation methods, low cellular samples (with approximately 0.5×10^6 cells) might be used, as shown at our recently performed CB workshop (results not yet published). On the other hand, it is necessary to evaluate whether the cells are getting lost during processing and at which step or they are just dispersed on different layers throughout the CB. Perhaps we need to carefully set criteria for samples suitable/eligible for embedding to improve cellularity. As shown in one of our previous studies, good CB cellularity can be expected only when we have a sample with at least 1×10^6 cells.[26]

Laboratories will soon be challenged with accreditation requirements such as those from International Organization for Standardization 15189 Medical Laboratories Requirements for Quality and Competence[27] and new European In Vitro Diagnostic Medical Devices regulation[28] in which all reagents that can affect the quality of examinations have to be thoroughly identified, documented, and evaluated before use. This will take great effort and much additional work, especially in case of using pooled, expired plasma with variable and unstable clotting abilities and thrombin with potential contaminants affecting tests results. At a minimum, accurate tracking and documentation of each plasma source in the pooled mixture, including history of anticoagulant and other therapies, will be required. Before use, any new plasma-thrombin mixture will need to be evaluated for the presence of cell-free DNA and contaminating foreign cells as well as clotting ability. An additional challenge for laboratories using CBs in general will also be risk management and actions for assuring adequate cellularity of CBs. Laboratories will have to identify risks for low cellular CBs for each specific preparation method and find opportunities for improvements.

In a conclusion, routine preparation of CBs significantly increases laboratory workload, operating cost, and sample turnaround time.[1] By using a suboptimal preparation method, precious samples can be compromised and made unavailable even for a basic morphological evaluation.

Additional studies are recommended to evaluate, improve, optimize, and standardize performance and cellular yield of CBs.

AUTHOR CONTRIBUTIONS

Irena Srebotnik Kirbis: Conceptualization, methodology, data curation, visualization, formal analysis, and writing the original draft. **Ivana Kholova**: Conceptualization and review and editing of the manuscript. **Heini Huhtala**: Data curation, statistics, and visualization. **Massimo Bongiovanni**: Supervision and review and editing of the manuscript. **Margareta Strojan Flezar**: Supervision and review and editing of the manuscript. **Chantell Hodgson**: Data curation and resources. **Beatrix Cochand-Priollet**: Project administration, supervision, review, and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

There are no financial disclosures from any of the authors.

ORCID

Irena Srebotnik Kirbis https://orcid.org/0000-0003-0934-0469
Ivana Kholova https://orcid.org/0000-0003-4089-0450

Heini Huhtala https://orcid.org/0000-0003-1372-430X
Massimo Bongiovanni https://orcid.org/0000-0001-9846-6682

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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