Health Technology Assessment: introducing a vacuum-based preservation system for biological materials in the anatomic pathology workflow

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Key words
Health Technology Assessment • Histopathology • Under-vacuum sealing • Tissue specimens • Fixatives

Summary
Introduction. The objective of this work is to assess the implementation of a newly introduced medical equipment technology for the vacuum-based preservation of biological materials within an Anatomic Pathology service.

Methods. The approach selected for the analysis is the Health Technology Assessment (HTA), a comprehensive evaluation method based on relevant scientific evidence and designed to support healthcare decision makers in purchasing, replacing or disposing of technologies. The analysis focused on specific domains such as Technology, Organization, Safety and Economy.

Results. The study proves that the use of such technology ensures the biological specimen to be suitably preserved (up to 72 hours), both reducing the amount of fixative being employed in the diagnostic process (30% to 55%) and resulting, in the particular context under examination, in savings of 93%.

Discussion. The HTA reported no significant drawbacks related to the use of the technology being examined. Nonetheless, the workflow for managing the transfer of biological materials from the Operating Room to the Anatomic Pathology department needs to be redefined – in terms of handling, processing, storage and disposal. Other elements concerned the monitoring of storage temperature, fresh tissue handling and especially fixative amount reduction, which positively impacts on the operators’ safety with regard to chemical hazards.

Reference context
Immunological and molecular diagnostic techniques have become increasingly effective. As a result, histological surveys have improved over the years, allowing for enhanced morphological diagnoses at subcellular level. In order to ensure the accuracy, standardization and reproducibility of diagnostic tests, it has thus become necessary to perform the best possible preservation of protein components and nucleic acids, which is obtained by means of fixatives of various compositions working as stabilizers 12.

However, special attention should be paid to some of the critical elements which can be highlighted in the anatomic pathology workflow, namely tissue storage times and methods prior to fixation, fixation duration and specimen transfer conditions on the way to the Anatomic Pathology laboratory 3. Moreover, the carcinogenicity and/or mutagenicity of the fixatives that are generally in use constitute a risk factor for the operators 45.

These considerations lead the scientific community to search for alternative solutions, both aimed at minimizing any molecular alterations and morphological modifications of biological materials due to hypo- or hyper-fixation and ensuring improved operational safety 6.

Within this framework, a HTA study has been conducted in collaboration with the Anatomy and Histopathology Department of the “Nuovo Ospedale di Prato”, run by USL 4 of Prato. Its objective was to assess possible implications for the introduction of a vacuum-based transport and preservation system for biological specimens as an alternative to the current procedure, which provides for immersion in a glyoxal-based fixative.

Acknowledgements
It is a pleasure to thank Milestone S.r.l., A. Menarini Diagnostics S.r.l., Kaltek S.r.l. and Rivac S.r.l for their collaboration and support.

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HealtH tecHnology assessment

The HTA model

The introduction of a vacuum-based, temperature controlled preservation system for biological materials has implications of different nature which encompass multiple aspects. HTA was identified as the most appropriate tool to thoroughly review the many outlooks offered by the use of the technology. Each result was supported by scientific evidence.[7–9]

This study was conducted through a preliminary planning phase, directly involving the decision maker, where the specific needs and the peculiarities of the technology’s new context were to be identified. Particular attention was paid to the analysis of Prato’s histopathological workflow and to determining volumes of activity (number of specimens/year), as well as annual fixative consumption and its related costs, both with respect to purchase and disposal.

The policy question constituting the central idea of the whole evaluation process was formulated as follows: “Assessing the potential impact of the introduction of a vacuum-based preservation system for biological materials, followed by an automated insertion of formalin, in an anatomic pathology service workflow”. The policy question is substantiated by research questions as specified in Table I. In order to identify and select the scientific evidence answering these questions, a research protocol has been developed by determining a priori which strategy should be adopted to review the literature and the study enrollment from databases and topic-specific search engines (HTA-Engine, PubMed, NICE, The Cochrane Library, NHS-EED, CRD and so on). The technology has been recently introduced in the medical equipment industry, so its diffusion is still quite limited among healthcare services and diagnostic processes. Assuming a low num-

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Tab. I. Research questions.

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Tab. III. Study Enrollment.

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<th>Authors - Publication</th>
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<tr>
<td>Tissue transfer to pathology labs: under vacuum is the safe alternative to formalin</td>
<td>C. Bussolati, et al. Virchows Archiv</td>
<td>2008</td>
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<td>Histologic validation of vacuum sealed formalin-free tissue preservation and transport system</td>
<td>R.J. Zarbo, et al. Pathology and Laboratory Medicine of the Henry Ford Health System, Detroit, Michigan, USA</td>
<td>2012</td>
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<td>Evaluation of tissue preservation using a vacuum-based refrigeration system for specimen transfer from theatre to laboratory</td>
<td>D.P. Boyle, et al. Department of Pathology, Royal Group of Hospitals Trust, Belfast, Northern Ireland</td>
<td>Not available</td>
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<td>Analyse qualitative et quantitative d’échantillons tissulaires par le procédé TissueSafe® en vue d’analyses morphologiques et moléculaires. Evaluation sur une série de 10 cas</td>
<td>M. Caly, et al. Service de Pathologie et Centre de Ressources Biologiques (CRB), Institut Curie, Paris, France</td>
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ber of supporting scientific evidence, no tight restrictions were set to include publications in the review. Table II shows the key terms used for research, which has been conducted continuously during six months. The selected studies (Tab. III) provide suitable answers to the research questions and constitute the baseline for analyzing HTA domains.

**HTA domain assessment**

**The Technology domain**

*Technology*

Stemming from the food industry, the technology pertains to the field of in vitro diagnostic medical devices (Directive 98/79/CE). A market analysis has been conducted to identify the most relevant manufacturers of such systems worldwide: *Milestone S.r.l.*, *Kaltek S.r.l.* and *Rivac S.r.l.* For this purpose, the technical and commercial materials made available on public channels by manufacturers, suppliers and institutional research centers has been taken as reference. Therefore, the main system manufacturers and suppliers were contacted. The key elements of the technology can be summarized as follows:

- vacuum type;
- specimen container type;
- temperature monitoring system;
- automated filling with fixative;
- traceability system.

As regards the vacuum type, the market offers systems that can completely extract air from the specimen container (*Tissue Safe* and *Seal Safe* by Milestone S.r.l., *Tissue Vacuum* by Kaltek S.r.l. and *VM-VAC Med Series* by Rivac S.r.l.) as well as protective atmosphere solutions, which can compensate oxygen with an inert gas – generally nitrogen (*Tissue Vacuum Plus* by Kaltek S.r.l. and *T-Filler* by Rivac S.r.l.). In the former case (Figs. 1-3), bags are used for preserving biological materials, available in different sizes and made of gas-impermeable materials. Their vacuum level can be selected and suited to a specific biological tissue type from the control panel, so that the chance of causing damage or shocks, which might make the tissue useless for diagnostic purposes, will be reduced. In the latter case (Figs. 4-5), the containers intended for preservation are quite similar to those used in traditional procedure, where nitrogen proves to be a proper filler as it prevents the container from imploding and therefore the contained materials from being squeezed.
Clinical effectiveness

The analysis of scientific evidence relied on a constant comparison with the traditional procedure. In terms of diagnostic effectiveness, this was found to be substantially equivalent to vacuum-based preservation. According to reference bibliography, the assessment focused on biopsies that were bigger than 2 cm – to which the technology being examined fully applies – omitting the histopathological transfer of small tissue specimens (< 2 cm), which are collected into containers previously filled with fixative.

The introduction of the vacuum-based preservation technique allows fresh tissues to be properly preserved in the Operating Room in respect of morphological and biomolecular properties. Scientific literature provides evidence of an optimal preservation of tissues for a time span varying from a few hours to 72 hours, if vacuum-sealed at 4°C. In doing so, the next fixation step can be optimized, since the anatomic pathologist is the only one in charge of monitoring times and standardizing methods besides having biological materials available for tissue banking or molecular surveys. Nevertheless, in this context it should be considered that operators may initially object to handling a higher amount of fresh tissues, which have a different consistency compared to fixated biological materials.

As concerns those systems relying on a protective atmosphere, there has been no evidence from publications. Probably, this is because they have recently been introduced in the market and some dedicated studies have likely been started or will be carried out in the near future. Furthermore, the reviewed literature provided no evidence that under-vacuum sealing and the preservation in a protective atmosphere share an equivalent clinical effectiveness.

Temperature monitoring

Reviewing the literature has stressed another significant topic: vacuum prevents tissues from drying, thus facilitating their cooling, delays autolysis processes owing to the lack of air insulation, as well as facilitates transport and optimizes storage. However, it should not be deemed to be an alternative to cooling as a preservation method for histological tissues. This being said, it becomes increasingly important to monitor and maintain the preservation temperature of histological materials at constant values, i.e. about 4°C, so as to ensure adequate preservation. For instance, this requirement becomes essential in the event of a prolonged transfer into cool bags, with the Operating Room and the Anatomic Pathology laboratory being reasonably far apart.

The solutions found on the market range from using temperature sensors (Kaltek S.r.l., Rivac S.r.l.) to data loggers based on RFID technology (Milestone S.r.l.). Recorded data can be transmitted to a computer where the management software is installed, then they can be used to create reports summarizing the most relevant information. In this way, it is possible to monitor and furnish detailed proof of the transport conditions of tissue materials, which will constitute the baseline for a standardizable and reproducible fixation protocol.

Automated filling with fixative

Some of the systems observed throughout the market analysis phase provide for the automated filling of specimen containers with fixative. Such systems are able to utilize the right amount of fixative liquid, which is calculated by suitable sensors on the basis of the weight or volume of tissue specimens.

Systems such as T-Filler by Rivac S.r.l. and Seal Safe by Milestone S.r.l. give the opportunity to select the most appropriate program to meet specific needs, so that it can be used with a high degree of flexibility in different workflow steps. Seal Safe allows for the vacuum-sealing of specimen bags. Moreover, it adds the advantages of vacuum to the
automated filling with fixative: by creating a microenvironment saturated with fixative, for which tissue penetration is facilitated, vacuum assures preservation and uniform fixation. Specifically, it is possible to opt for four preset programs which differ according to their specimen weight/fixative weight ratio (1:1, 1:2, 1:2.5, 1:3). As a result, fixative consumption is significantly reduced. The T-Filler system provides the opportunity to perform an automated formalin-filling cycle into the specimen container, thus optimizing the amounts needed for proper fixation (volume ratio 1:10). Besides, the specimen containers can be packed following, if need be, an inert gas empty and/or fill cycle. The Tissue Filling Plus system produced by Kaltek S.r.l. is currently being placed on the market. Hence, no proper assessment has been made due to a lack of relevant information.

The introduction of such a system in Prato’s context has a major impact on the fixative type being used and provides the basis for replacing glyoxal with formalin throughout the histopathological routine. Nonetheless, methods need to be validated and all different working protocols, as well as the detection systems of histopathological and immunohistochemical surveys, require further examination. Such a change is perfectly consistent with the needs expressed by the decision maker: the use of a fixative that is well-established within most international contexts appears to be an important requisite in a field such as Anatomic Pathology, where prospective quality control, second opinion and external advice are mostly essential. Along with the proven potential of vacuum-based preservation for molecular pathology, this could set the ground for performing a broader test panel at Prato’s Anatomy and Histopathology Department, where biomolecular trials would provide for useful diagnostic insights.

The Organization domain

Workflows redefinition

Over the years the histopathological workflow phase concerned by the technology has experienced no significant modifications and the human factor still plays a crucial role. Thus, any change needs to be taken into account and assessed by considering its potential impact on the organizational context and workflows, as well as according to the staff being involved.

As far as operators are concerned, scientific studies give evidence of a high degree of satisfaction with the use of the technology, both in terms of occupational ergonomics and safety. By introducing specimen bags, transport operations have been optimized owing to volume and weight reduction. On the other hand, the transport method is partially optimized when containers are used for protective atmosphere preservation (Modified Atmosphere), as only weight is reduced – yet not the overall size. Such aspects are more or less relevant depending on the hospital ward structure and the distance between the Operating Rooms and the Anatomic Pathology laboratory, which might cause trouble in transferring containers filled with fixative liquid.

The storage of unprocessed materials, which are designed to be disposed of after reporting, could also benefit from utilizing bags with a vacuum-based packing system. Particularly, those tissue specimens that are already fixated can be stored under vacuum, if need be with a low fixative amount: this can produce about 50% of storage space reduction. The impact on waste management is also significant: the collection and disposal procedures can become easier as separating biological materials from fixative is no longer needed.

The manufacturers commit to identifying various solutions and flexible configurations so as to enable the decision maker to opt for the best arrangement for the specific context. Once the most appropriate configuration was found, the workflow – as shown in Figure 6 – was therefore proposed to and shared with Prato’s Hospital, in order to define the work streams and the division of roles and activities.

Traceability

To ensure the traceability of biological materials, it is essential to assign a univocal identification code from the Operating Room, which allows to follow them throughout the whole process and track their position. In this connection, the solutions available on the market (Rivac S.r.l., Milestone S.r.l.) are equipped with the following elements:

- barcode printer;
- barcode optical scanner;
- data management software.

To implement such a traceability system, the information system of the Operating Room should be integrated with the management software used at the Anatomic Pathology laboratory. In doing so, information would be shared both effectively and efficiently.

The Safety domain

This domain was assessed by paying special attention to the implications of the technology use and those concerning the safety of the operators involved, so the analysis was focused on the chemical hazard related to the use of fixatives. In Prato’s histopathological practice, the first contribution in terms of safety consists in replacing glyoxal-based fixative (mutagenic\(^a\)) with formalin (carcinogenic\(^b\)). Moreover, scientific literature provides evidence of the positive impact of the vacuum-based procedure.

As regards risk assessment, adverse events are remarkably less likely to occur as the use of fixative is limited to histopathological laboratories, where it is safely handled under exhaust hoods. In fact, its use in Operating Rooms has strongly decreased (up to 70-90%),


\(^b\) The International Agency for Research on Cancer (IARC) classifies formalin as carcinogen Group 1.
thus allowing to reduce exposure related to the manual filling of containers. As a result, accidental fixative spillages during transfer operations are also reduced, as well as the formation of toxic vapors when opening histological containers in reduction rooms or storing post-sampling residual materials. Furthermore, an additional reduction of chemical hazard is made possible by the automated filling of specimen containers with fixative, because operators are less likely to be exposed to the source of danger.

Conversely, biological hazard requires some considerations: with the introduction of vacuum-based technology, most surgical biotic specimens are fresh rather than submerged in fixative liquid when they reach the Anatomic Pathology laboratory, which is likely to increase such hazard. However, literature analysis did not offer any information concerning the increase/decrease of the biological risk related to the use of the new procedure. Indeed it is true that, according to the colloquial evidence provided by clinicians, operators’ safety is
properly ensured by the adoption of adequate preventive measures as well as personal and collective protective equipment – which are normally used in laboratories.

**THE ECONOMY DOMAIN**

Being duly contextualized in Prato’s framework, the economic assessment rests on a comparison between the traditional management of biological materials (current scenario) and their vacuum-based management. As regards market supply, offering systems that are designed to be used in Operating Rooms and Anatomic Pathology, the two following scenarios (A and B) have been postulated and developed for the comparison:

- current scenario – immersion of the biological specimen in glyoxal-based fixative, immediately after being taken in the Operating Room;
- scenario A – introduction of the technology in the Operating Room: transfer of fresh, under vacuum biological specimen, then fixation in formalin by the traditional procedure;
- scenario B – similar to the previous one, with the vacuum-based technology being introduced in Anatomic Pathology, too: transfer of fresh, under vacuum biological specimen, then fixation in formalin by using the technology.

Scientific evidence has shown that the introduction of vacuum-based technology in the Operating Room (Scenario A) would engender a fall in fixative consumption – implying a reduction of its purchase and disposal costs – which varies between 30% and 50%. A further consumption reduction would add to these values (25-30%) by utilizing tools in the Anatomic Pathology department that combine vacuum with automated filling with fixative; this situation (Scenario B) would determine a total reduction varying from about 55% to 80%. Another significant feature of the economic analysis deals with using a fixative other than the one in use in Prato today (current situation), in case the technology is adopted (Scenario A or Scenario B): the purchase cost of glyoxal is about ten times higher than that of formalin. As far as the disposal cost is concerned, then, choosing a different fixative does not affect the expenditure as this hinges on the waste amount that needs to be managed.

In order to link these percentage values to an actual economic value, the annual fixative consumption was calculated for the considered scenarios (Fig. 7). As regards scenarios A and B, the amounts were estimated by considering the worst case, which entails a fixative consumption reduction of 30% and 55%, respectively. It was calculated that the use of a new fixative would produce a lower annual expenditure (around 84%), which is due to both purchase and disposal costs.

After integrating the results obtained from previous analyses, the estimated total savings vary from 89% to 93%, which correspond to scenario A and scenario B, respectively (Fig. 8).

Nevertheless, emerging costs should be also taken into account, namely new costs that would arise following the decision of a technological renewal (e.g. equipment purchase, technical assistance, staff training, installation operations).

A number of expenditure items that are able to generate savings should be also taken into account as they can modify the above-mentioned percentage values, although they are hardly quantifiable. Vacuum-based technology allows to strongly reduce the risk of accidental fixative spillages and therefore any costs related to the management of emergency situations which might occur (e.g. closing an Operating Room, cleaning a fixative spillage). Moreover, with an extremely low amount of formalin, the vacuum-sealing of post-sampling residual materials would imply a limitation of fixative-generated vapors inside the ventilated cabinets, allowing to change filters less frequently. Other savings should be also taken into consideration in respect of space optimization and storage volume reduction: a limited overall size involves a lower expenditure for archive management. Lastly, an easier waste management of post-sampling residual materials would certainly constitute another cost-saving solution.

An approximate assessment was made to determine a possible way to recover the investment costs, so as to identify the years needed to attain economic balance with regard to the initial costs that were covered to purchase the technology. In particular, for the two scenarios
being considered the investment will be recovered from the first half and the second half of the fifth year, respectively, since the purchase of the technology.

Conclusions

The HTA study allowed to analyze the impact of introducing the technology for the preservation and the vacuum-sealed transfer of biological materials throughout the workflow of the Anatomy and Histopathological Department of the “Nuovo Ospedale di Prato”, run by the USL 4 of Prato. The assessment was formulated from a multidisciplinary perspective, going into a variety of aspects which might be influenced by the technology implementation and emphasizing its potential as an alternative to the gold standard, i.e. immersion in fixative. Generally speaking, the results obtained show a good degree of consistency, in terms of morphological and biomolecular preservation, between the traditional management and transport procedure applied to biological specimens longer than 2 cm and their transfer under vacuum at low temperatures.

On one side, some tools are able to add the automated filling with fixative to the benefits of vacuum-sealing, which allows to reduce the use of fixative liquids in the Operating Room and to obtain safer handling operations in the Anatomic Pathology department. On the other side, in Prato’s specific context, it implies that glyoxal is replaced with formalin. This appears to be a favorable change as it would foster the interaction between the laboratory and regional/national services, allowing also to participate in international quality control programs. Nonetheless, such a choice would require further examination of the working protocols of histopathological and immunohistochemical surveys. Beside the benefits of diagnostic effectiveness, from an organizational point of view some interesting prospects also arise with respect to the whole workflow traceability and the optimization of the transport, storage and disposal of post-sampling residual materials. In economic terms this is highly cost-saving, considering the reduction of fixation consumption related to the introduction of the technology. The main critical elements can be attributed to the necessary adaptation – or redefinition, if need be – of safety procedures and the organizational setting of the Anatomic Pathology workflow following the introduction of the technology. Other short- or long-term benefits might foreshadow a scenario that is consistent with the hypothetical increase in analytical activities, resulting in a richer test panel performed through molecular pathology procedures. Moreover, a role redefinition of the Anatomic Pathology service could be envisaged, since the technology would allow to evolve to reorganization models that are moving towards a higher service integration.

References