Research autopsy programmes in oncology: shared experience from 14 centres across the world


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Abstract

While there is a great clinical need to understand the biology of metastatic cancer in order to treat it more effectively, research is hampered by limited sample availability. Research autopsy programmes can crucially advance the field through synchronous, extensive, and high-volume sample collection. However, it remains an underused strategy in translational research. Via an extensive questionnaire, we collected information on the study design, enrolment strategy, study conduct, sample and data management, and challenges and opportunities of research autopsy programmes in oncology worldwide. Fourteen programmes participated in this study. Eight programmes operated 24 h/7 days, resulting in a lower median postmortem interval (time between death and start of the autopsy, 4 h) compared with those operating during working hours (9 h). Most programmes (n = 10) succeeded in collecting all samples within a median of 12 h after death. A large number of tumour sites were sampled during each autopsy (median 15.5 per patient). The median number of samples collected per patient was 58, including different processing methods for tumour samples but also non-tumour tissues and liquid biopsies. Unique biological insights derived from these samples included metastatic progression, treatment resistance, disease heterogeneity, tumour dormancy, interactions with the tumour micro-environment, and tumour representation in liquid biopsies. Tumour patient-derived xenograft (PDX) or organoid (PDO) models were additionally established, allowing for drug discovery and treatment sensitivity assays. Apart from the opportunities and achievements, we also present the challenges related with postmortem sample collections and strategies to overcome them, based on the shared experience of these 14
programmes. Through this work, we hope to increase the transparency of postmortem tissue donation, to encourage and aid the creation of new programmes, and to foster collaborations on these unique sample collections.

Keywords: research autopsy; tissue donation; metastatic cancer; tumour model; liquid biopsy

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Introduction

Metastatic disease is the main cause of death from cancer and is currently almost always incurable [1]. The multi-step progression from early to metastatic cancer has been described for some tumour types (reviewed in [2–5]). However, many of the steps in the cascade are still poorly understood from a biological point of view [2]. Additionally, inter- and intra-patient tumour heterogeneity is increasingly being described at the (epi)genomic, transcriptomic, phenotypic, and micro-environmental levels [6–11], and complicates the clinical management of metastatic disease [12].

A better biological understanding of metastatic cancer is key to advancing the clinical management of cancer patients. The goals of research include the discovery of features shared by all metastases that are efficiently targetable, of ways to reduce intra-tumour heterogeneity, or of mutually exclusive mechanisms that can be targeted through combination strategies. This requires comprehensive studies of multiple samples per patient at multiple points in time. Unfortunately, obtaining a biopsy from a metastatic site is often not possible due to their anatomical localisation and the invasiveness of the procedure. Even when technically feasible, the biopsy may not be representative of the full tumour profile. Liquid biopsies, such as blood samples, can represent an elegant way of sampling a more complete tumour profile, but to what extent different metastases contribute has so far been studied only in small cohorts [13–15].

Research autopsies, aimed at collecting multiple patient samples within a short timeframe after death for the specific purpose of translational research, constitute an invaluable answer to this problem. Also termed rapid autopsy or postmortem tissue donation programmes, they importantly differ from clinical autopsies not only in their goals but also in their organisation [16–20]. The concept is not new and has been of great value in areas of research in which access to samples is problematic.
Shared experience from 14 research autopsy programmes in oncology worldwide

During life, such as neurological [21–25] and chronic (infectious) diseases [26,27]. More recently, research autopsies have also been used to help to understand organ damage from COVID-19 [19,28–30]. In oncology, multiple excellent autopsy programmes have been developed and have described their structure and logistics of approach [11,16–18,31–38]. Most publications are, however, single programme reports and do not compare methodologies across locations in a structured way [16,32,38]. The research autopsy as a method of enhancing access to tissue samples is also still under-utilised. This study evaluated 14 research autopsy programmes in oncology worldwide to identify commonalities, important logistical aspects of tissue donation, and ethical considerations. Experience gained in these studies may be informative for increasing transparency, enhancing worldwide interdisciplinary collaborative research, as well as for the initiation of new programmes and expansion of existing programmes.

Materials and methods

Ethics approval statement

Each programme has its respective ethics approval and patient consent for participation. A questionnaire with over 150 questions on five topics (study design, patient enrolment, study conduct and tissue donation procedure, sample and data management, and challenges and opportunities) was designed for this study (supplementary material, Table S1). Research autopsy programmes in oncology were identified based on literature reviews, clinical trial databases, and professional networks. Programmes temporarily on hold were eligible, while programmes for paediatric patients (which generally have distinct inclusion procedures) or pure clinical autopsy programmes were excluded. Programmes were contacted via e-mail, and follow-up meetings after questionnaire completion were conducted to clarify uncertainties and to ensure data completeness across the topics. No ethical approval was needed for this study. Information was retrieved between December 2022 and May 2023. The results are presented in a descriptive manner.

Results

Presentation of the included programmes

Twenty-eight programmes were identified, of which 23 were contacted after revision of inclusion criteria (supplementary material, Figure S1). Of these, 14 provided us with their data within the set timeframe. Though a majority (n = 9) were based in the USA (Figure 1A), others from the United Kingdom, Belgium, Hungary, Australia, and Japan (n = 1 in each country) were included. The main characteristics of the respective programmes are listed in supplementary material, Table S2. Of note, none of the 23 identified programmes were in South America or Africa.

All principal investigators (n = 14) had academic positions. The programme set-up was led by a research team in eight, a clinical team in two, and a combination of both in four programmes. Most programmes followed institutional ethics committee-approved research protocols as required by their legal and ethical framework for research on deceased patients. Some studies formalised their protocol after conducting sporadic research autopsies at patients’ requests (n = 6). Others spent a median of 12 months (range 6–48 months) of logistic and administrative preparatory work before any autopsy was performed. The legal framework influenced the establishment and conduct of some of the autopsy programmes. The PEACE (Posthumous Evaluation of Advanced Cancer Environment) programme, for example, experienced autopsy delays due to strict regulations regarding the signature of death certificates. The UPTIDER (UZ/KU Leuven Program for Tissue Donation to Enhance Research), Genitourinary Cancer Biorepository, Legacy Project for Rapid Tissue Donation, and CASCADE (Cancer tISue Collection After DEath) programmes operated in regions where assisted dying was or became authorised, enabling pre-planning of the autopsy if the patient chose euthanasia (which occurred in 25%, <10%, 8%, and 3% of patients in these programmes, respectively). The programmes primarily focused on collecting metastatic and non-tumour tissues to allow diverse lines of research. Research objectives built on this focused on cancer heterogeneity, tumour evolution, tumour micro-environment, mechanisms of treatment response/resistance, representability of liquid biopsies, and creation of experimental tumour models. Additionally, some programmes supported research in other diseases or areas, through the sharing of samples or of experience for the creation of other programmes.

All programmes adopted a multidisciplinary approach with high involvement of the Departments of Pathology and General Medical Oncology (in n = 14 and n = 13 programmes, respectively). Of note, the number of pathologists involved varies according to the programme: most have a pool of three or four pathologists on rota, while others have dedicated pathologists in the programme or are (co)-led by pathologists. Many programmes additionally collaborated with other clinical and academic partners, both within their institution and externally.

Patient inclusion and follow-up

Six programmes enrolled patients with any primary cancer type (Figure 1B and supplementary material, Table S2). Three adopted a focused multi-cancer approach including only tumour types with established collaborations for maximal sample utilisation. The remaining five programmes allowed up to two primary tumour types: breast in Legacy to Life, Hope for OTHERS (Our Tissue Helping Enhance Research & Science), the UNC Breast
Tumour Donation program, and UPTIDER; and prostate and bladder cancer in the Genitourinary Cancer Biorepository. Of note, the multi-cancer programme CASCADE had a sister project focusing on breast cancer only (BROCADE), which will be discussed separately only if significantly differing from CASCADE.

Most programmes \( (n = 12) \) allowed patients dying at home to participate but put restrictions on distance from...
the programme hospital. Patient referral was allowed in eight programmes, on the condition of registration in one of the enrolling centres. Patients of particular research interest due to clinical features of their cancer, i.e. genetic predisposition or specific treatments, were sometimes targeted for enrolment. However, this was never an official inclusion criterion. Most programmes \((n = 11)\) did not accept patients with known communicable diseases, either chronically or acutely present at the time of death. In the other programmes, appropriate equipment and measures were used to ensure that autopsies were safely performed in these high-risk settings \([19]\).

Informed consent was required in all programmes, signed either obligatorily by the patient \((n = 1)\), by the next-of-kin/family \((n = 6)\), by both \((n = 1)\), or by either of the two \((n = 6)\). Treating-oncologists usually first approached patients and/or their families but sometimes found it difficult to discuss end-of-life matters in their role as healthcare providers. In response to this, some programmes have allowed first conversations by psychosocially trained members of the research team. Occasionally, patients touched on the subject themselves, especially in regions where assisted dying was legal. Leaflets in hospital waiting rooms, information on the institution’s website, or articles in the general press could enhance self-referral \((ten \text{ programmes used this})\). We have listed tips for best wording to introduce and discuss the topic in Table 1.

Three inclusion strategies emerged from our survey, with corresponding timelines presented in Figure 2. Firstly, most programmes \((n = 12)\) included patients in their last line(s) of treatment and/or in best supportive care setting. The median time between enrolment and death in programmes that allowed only this scenario \((n = 2: \text{Legacy to Life and UPTIDER})\) was 3 and 5 weeks, respectively. Secondly, more than half of the programmes additionally allowed inclusion in early non-curative \((n = 8)\) or even curative treatment settings \((n = 3)\). This answers the documented preference of patients to be active decision makers when the choice is not urgent, as with organ donation \([39]\). Thirdly, six programmes allowed the enrolment of patients after death, via the next-of-kin’s consent. This strategy had the advantages of tailoring inclusion based on timing of death \((e.g.\) avoiding weekend autopsies) and alignment with obtaining consent for clinical autopsies. On the other hand, there was little time for patient-specific autopsy preparation. While many countries allowed after-death next-of-kın consent, this might bring psychological discomfort to the family and researchers. The Michigan Legacy Tissue Program resolved this through after-death consent via the next-of-kin, but only after thorough discussions with the patient during life.

Apart from eligibility criteria and timing, there were other reasons not to approach patients. Seven programmes preferentially did not contact patients who were not coping well with their prognosis, were not well supported by their families, had a strained relationship with their clinicians, or had refused to participate in other research/biobanking studies in the past. Seven programmes reported an estimate on the percentage of patients who are eventually approached out of all eligible patients, with the average being 40% \((range \ 5\%-80\%)\). Of note, some patients were approached carefully but if their initial reaction to the programme was not positive, it was not mentioned thereafter.

With these inclusion strategies, enrolment of patients was highly successful. Of those who received the informed consent documents, 75% \((average \ of \ the \ percentages \ in \ all \ programmes; \ range \ 40\%-100\%)\) signed up. Many reasons for participation were listed by the patients including contributing to scientific advancements, helping future patients, and being offered an alternative for organ donation. The most common reason for not participating was psychosocial distress. Only one programme reported that patients were sometimes not convinced of the project’s scientific value. Almost all programmes \((n = 12)\) allowed opt-out from parts of the study, such as certain anatomical regions \((e.g.\) brain\) being sampled, and collaboration with non-academic partners. Patients seldom \(<10\% \ of \ cases \ in \ all \ but \ one \ programme\) chose these opt-outs.

Importantly, the family played a big role in recruitment and follow-up in most programmes. Family objections because of psychosocial distress or possible impact on funeral services were reported in ten studies as a reason for not participating. In the interval between enrolment and death, programmes maintained contact with caregivers or passively followed up through medical file checks. Table 1 suggests tips for effective interaction and strategies to handle challenges during follow-up.

At death: logistics and tissue donation procedure

Eight programmes performed autopsies 24 h/7 days \((Figure \ 3A)\), with associated challenges discussed in Table 1. Their median postmortem interval \((PMI, \ between \ death \ and \ autopsy \ start)\) was 4 h \((range \ of \ medians \ 2.5\%-14)\) for patients dying outside of the hospital \((vast \ majority)\). In programmes restricting autopsies to \((extended)\) working hours, the median PMI was 9 h \((range \ of \ medians \ 4 \ h \ to \ 4 \ days)\). Transportation of patients who passed away outside of the hospital was performed by a company contracted specifically for the study in seven programmes. Upon arrival, the body was ideally refrigerated until the autopsy commenced. Four programmes performed imaging before the autopsy \((whole \ body \ CT \ and/or \ MRI)\), either as part of the standard forensic procedure or as part of the research protocol.

The median number of staff present at each autopsy was 4 \((range \ 2\%-13)\). Essential roles included a pathologist and/or a mortuary technician \((officially \ referred \ to \ as \ an \ anatomical \ pathology \ technologist \ (APT) \ in \ the \ UK \ and \ often \ referred \ to \ as \ a \ morgue \ or \ autopsy \ technician \ in \ many \ other \ countries)\), a coordinator overseeing sample procurement, and research personnel handling sample processing and registration. Autopsies took...
Table 1. Challenges related to rapid autopsy programmes and strategies to overcome them. Combined experience from the 14 programmes.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Strategy/solution</th>
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<tr>
<td><strong>Personnel challenges</strong></td>
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</table>
| Finding skilled team members | - Multidisciplinary team  
- Pathologist and/or mortuary assistant are crucial and should be dedicated [if needed, third-party (private) pathology service to be added on]  
- Psychological skills, high flexibility, and meticulousness are of great value  
- Long-term grants can help to assure job security  
- Having back-ups for every role makes the position more attractive/bearable  
- Set up a structure in which motivated people can temporarily join the team and learn |
| Personnel turnover | - Participation must be voluntary for lab personnel  
- Have a psychological care team (e.g. from hospital) available |
| Emotional impact on team members | - Debrief shortly after an autopsy and allow for emotional difficulties to be discussed |
| Having at least one person on call 24 h/7 days | - Rotate this task within the team |
| Motivating personnel to work outside of business hours | - Prerecord a message on the study phone’s voicemail in case no one can answer  
- Provide financial compensation  
- Allow job flexibility including recovery time  
- Involves personnel in scientific discussions and give co-authorship on publications  
- Show up as a supervisor/principal investigator as often as possible |
| **Budgetary challenges** | | |
| Finding appropriate funding for personnel | - Work with research personnel already covered by other research-related grants |
| Finding appropriate funding for the set-up or downstream research | - Work with existing (clinical) autopsy structures  
- Apply for grants related to infrastructure or biospecimen acquisition  
- Make sure collaborators secure funding and include sample acquisition costs  
- Recover costs where possible (e.g. per-sample fee)  
- Negotiate prices where possible (transport companies, pathology services, …) |
| **Regulatory challenges** | | |
| Discussions with the Ethics Committee (EC) including data sharing, privacy, and informed consent | - Start discussions with the EC early on when designing the programme  
- Introduce the programme when the patient offers cues  
- Provide tips on the use of language and on timing  
- Organise meetings to discuss barriers and exchange inclusion strategies  
- Keep clinicians updated about scientific results  
- Provide all people involved with contact cards and steps to take  
- Make the informed consent allows creation of tumour models, genomic analyses, controlled database posting, and collaboration with non-academic partners, if applicable  
- Encourage organisations to advertise the programme actively to colleagues (presentations, conferences) |
| Signature of the death certificate | - Programme to be advertised actively to colleagues (presentations, conferences)  
-– Rotate authorships for large teams  
- Organise regular and specific communication with those involved about the study conduct as well as on downstream analyses and results  
- Enhance collaborations between different laboratories to integrate sample data on a multi-omics level  
- Find an efficient way of sharing essential patient and sample information |
| **Collaboration challenges** | | |
| Essential collaboration within the institution | - – Programme to be advertised actively to colleagues (presentations, conferences)  
- – Rotate authorships for large teams  
- – Organise regular and specific communication with those involved about the study conduct as well as on downstream analyses and results  
- – Enhance collaborations between different laboratories to integrate sample data on a multi-omics level  
- – Find an efficient way of sharing essential patient and sample information |
| Communication | - Prerecord a message on the study phone’s voicemail in case no one can answer  
- Provide financial compensation  
- Allow job flexibility including recovery time  
- Involves personnel in scientific discussions and give co-authorship on publications  
- Show up as a supervisor/principal investigator as often as possible |
| **Enrolment challenges** | | |
| Motivate physicians to include patients | - Organise meetings to discuss barriers and exchange inclusion strategies  
- Ask permission for the study coordinator to screen and contact patients directly  
- Keep clinicians updated about scientific results  
- Provide tips on the use of language and on timing  
| Patient selection and timing of enrolment | - Select patients with longitudinal samples available, included in clinical trials, or of specific research interest  
- Consider including early in the disease course: patients express they prefer this  
- Introduce the programme when the patient offers cues  
- Educational material in waiting rooms, allowing patients to bring up the topic  
- ‘Tissue donation’ preferred over ‘autopsy’  
- ‘Informed consent’ allows creation of tumour models, genomic analyses, controlled database posting, and collaboration with non-academic partners, if applicable  
- – Programme to be advertised actively to colleagues (presentations, conferences)  
- – Rotate authorships for large teams  
- – Organise regular and specific communication with those involved about the study conduct as well as on downstream analyses and results  
- – Enhance collaborations between different laboratories to integrate sample data on a multi-omics level  
- – Find an efficient way of sharing essential patient and sample information |
| Wording used during enrolment | - Get advice from patient advocates and supportive care staff  
- Minimise taboo and normalise end-of-life discussions and tissue donation  
- Focus on the meaning their donation will have for future generations  
- ‘Tissue donation’ preferred over ‘autopsy’  
- Try to talk to the patient and their family in the same session  
- Be very transparent about the procedures, the timing, impact on the funeral, …  
- Consider asking for feedback from families some time after the tissue donation  
- Consider honouring donating patients with a section on the programme website where families can contribute |
| Involvement of the family | - – Programme to be advertised actively to colleagues (presentations, conferences)  
- – Rotate authorships for large teams  
- – Organise regular and specific communication with those involved about the study conduct as well as on downstream analyses and results  
- – Enhance collaborations between different laboratories to integrate sample data on a multi-omics level  
- – Find an efficient way of sharing essential patient and sample information |
| Follow-up challenges | | |
| Knowing how and how often to follow up | - Passively follow up through patient files  
- Ensure patients/families are updated on procedures when life expectancy shortens – actively follow up with the supportive care team or hospice  
- Provide all people involved with contact cards and steps to take |
around 3 h (median of reported medians) to complete [range of medians 1 h (Semmelweis University) to 6.5 h (UPTIDER)] (Figure 3A). Several factors influenced autopsy times. Research teams performing the autopsies themselves reported longer autopsy durations compared with clinical pathology services. On-site sample processing prolonged the autopsy; many programmes instead transported samples on ice to a research laboratory. Extensive annotation and electronic registration of sample information added to autopsy times (see ‘Sample and data management’ below). Lastly, three programmes implemented body sterilisation and the use of sterile drapes to reduce infection risk in subsequent tumour models, potentially slightly increasing autopsy durations.

Table 1. Continued

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Strategy/solution</th>
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| Challenges related to the tissue donation procedure and sample processing | – Attribute specific roles
| – Standardise operating procedures (SOPs) and collection methods
| – If needed, minimise the amount of information collected per sample and reduce the number of samples per organ
| Availability of the morgue and equipment in the morgue | – Back-up strategies such as university autopsy rooms
| – Bring any missing equipment in
| – Decide whether to explore the brain based on previous or postmortem imaging (or CSF)
| – Subject the skin to careful inspection
| – Subject all other organs to gross dissection and macroscopical evaluation
| Collecting all metastases | – Pay specific attention to dissect lymph nodes
| Collection of non-tumour tissues | – Think well in advance of research questions making the collection worthwhile
| – Talk to colleagues; there can be huge research potential
| Different sample processing protocols for different collaborators | – Facilitate discussions among collaborators to simplify and homogenise the protocols
| Sample processing is time-consuming | – Make sure collaborators put effort into training the autopsy team for specific protocols
| – Divide the work as much as possible
| – Have multiple people trained for processing
| – Encourage the pick-up and processing of fresh samples by collaborators themselves
| – Freeze at autopsy; process later
| Challenges related to the set-up of a data management system | – Comply with biobank requirements from the start
| – Personnel dedicated to this task should have a scientific and IT background
| Logistical challenges related to sample registering/annotation | – Have specific SOPs per sub-study/cancer type that clearly state labelling instructions
| Uniform labelling in multicenter studies | – Pre-label samples
| – Have templates during the tissue donation
| – Adopt a quick, uniform coding system
| – Photographic documentation during the autopsy can help to rectify mistakes
| Labelling is time-consuming | – Time of collection/freezing is the most crucial timepoint
| – If feasible, set up a system where barcode scanning is linked to timestamping
| Registering sample-specific timepoints | – Start the autopsy as soon as possible
| – Cool the body as soon as possible after death
| – For long-duration autopsies, organ cooling can be preferred over body cooling
| – Give feedback to tissue processing members when quality data become available
| – Implement a waterfall strategy to make sure no resources are wasted (e.g. first confirmation of tumour content before any downstream analyses)
| – Insist on getting feedback from collaborators on sample quality
| – Take repeated samples from the same site to assess declines in quality with time
| – Mimic autopsy procedure on mice harbouring PDXs to assess sample quality with increasing postmortem interval
| – Document any changes in sample collection/processing strategy very well
| Challenges related to sample quality | – Identify clinical/research studies that may store patient samples and collaborate from the start
| – Actively consult the pathology department
| – Centralise standard histological characterisation of samples
| Other scientific challenges | – Make sure this information is accessible to all team members and collaborators
| Getting access to historical samples | – In case access to clinical data is lost after death, make sure all relevant information is captured beforehand
| Integrating different analyses performed on the samples | – Document any changes in sample collection/processing strategy very well
| Getting access to clinical data after death | – Communicate well with the mortuary (often referred to as morgue in countries other than the UK), transport companies, and funeral homes
| Challenges related to the impact of the procedure on the funeral | – Be transparent about whether any incisions will be visible
| – Advise providing clothes that cover collarbones and sternum for open cof
durance
| – Advise providing a wig or scarf for open coffin viewing
| – Minimise incisions in the neck region by dissecting subcutaneous layers neatly upwards
| – Communicate well with the mortuary (often referred to as morgue in countries other than the UK), transport companies, and funeral homes

CSF, cerebrospinal fluid.
A **PEACE programme** - inclusion in any treatment line, autopsy only during WH

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Start autopsy</th>
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<tbody>
<tr>
<td>Pan-cancer, any treatment line</td>
<td>Liquid biopsies, all types (n=7)</td>
</tr>
<tr>
<td>Patient consent (or family after death)</td>
<td>Tumour lesions, n=28 (1–81)</td>
</tr>
<tr>
<td>No communicable disease</td>
<td>Non-invaded tissue, n=21 (1–126)</td>
</tr>
<tr>
<td>Death at home is allowed</td>
<td></td>
</tr>
<tr>
<td>Inclusion sampling (blood)</td>
<td></td>
</tr>
</tbody>
</table>

**Follow-up**
- 15 weeks (1–205)

**PMI**
- 4 days (1–15)

**Autopsy**
- 2 hours (1–3)

**Closure**
- Transport to funeral home
- Thank you letter to family

Death

End autopsy

B **UPTIDER programme** - inclusion in last treatment line(s) only, 24 h/7 d autopsy

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Start autopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer, last treatment line(s)</td>
<td>Liquid biopsies, all types (n=7)</td>
</tr>
<tr>
<td>Patient consent</td>
<td>Tumour lesions, n=31 (5–90)</td>
</tr>
<tr>
<td>No communicable disease</td>
<td>Non-invaded tissue, n=9.5 (5–22)</td>
</tr>
<tr>
<td>Death at home is allowed</td>
<td></td>
</tr>
<tr>
<td>Inclusion sampling (blood, saliva, urine)</td>
<td></td>
</tr>
</tbody>
</table>

**Follow-up**
- 5 weeks (1–20)

**PMI**
- 3 hours (2–6)

**Autopsy**
- 6 hours (4–9)

**Closure**
- Transport to funeral home
- Thank you letter to family

Death

End autopsy

C **Akita Rapid Autopsy program** - in-hospital after-death inclusion only, autopsy only during WH

<table>
<thead>
<tr>
<th>Start autopsy</th>
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</thead>
<tbody>
<tr>
<td>Liquid biopsies, blood, ascites</td>
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</tr>
<tr>
<td>Tumour lesions, n=3 (1–15)</td>
<td></td>
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<tr>
<td>Non-invaded tissue, n=1 (1–2)</td>
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</tbody>
</table>

**PMI**
- 3.5 hours (1–13)

**Autopsy**
- 2.5 hours (2–3)

Death

End autopsy

Clinical autopsy rooms were usually used and additional equipment was brought in for the procedure. Supplementary material, Figure S2 depicts the room’s set-up in two different programmes. Almost all programmes (n = 11) collected blood first and all programmes (n = 14) collected other types of body fluids, such as ascites, bone marrow, pleural fluid, pericardial fluid, cerebrospinal fluid, urine, vitreous fluid, or aqueous humour (Figure 3D). Next, a patient-specific order of organ inspection was followed in eight programmes, while others stuck to the order in standard clinical autopsies. Photographical documentation of lesions was implemented in 12 programmes. The number of malignant lesions sampled per patient depended on disease burden, tissue viability assessment, and extent of exploration of bone and lymph node metastases. The median number of lesions sampled per patient was 15.5 (median of all medians) and even ≥20 in six...
Figure 3

Legend on next page.
programs (Figure 3B). Many programmes implemented multiregional sampling for large lesions [up to 38 regions for one tumour site (PEACE)]. All but one programme collected both snap-frozen and formalin-fixed samples, sometimes alongside other processing methods (fresh, viably frozen, ...). One programme froze any remaining tumour material in vacuum bags. Normal tissue from the same organ with metastases was collected in almost all programmes (n = 13). Other non-invaded organ samples were additionally collected in 12 programmes, either as part of the autopsy routine or to answer specific research questions (Figure 3E). The median number of samples collected during each autopsy per patient ranged from 4 (Akita Rapid Autopsy Program) to 250 (UPTIDER), with the median of all medians being 58 (Figure 3C).

Sample and data management

The high number of samples retrieved within a short timeframe demanded an efficient sample registration strategy. Half of the programmes (n = 7) created sample labels before autopsy start. Barcoding helped seven programmes to track samples, though only one programme used it at autopsy for registration of sample-specific timepoints and storage locations. Information ultimately recorded for each sample often included the organ (based on anatomical nomenclature or using organ codes [40]) and the exact location of sampling (for correlation with imaging or treatment response [41–43]), alongside the processing method and sample-specific timepoints. While most programmes try to access the tumour samples that were collected during the patient’s life, this can be challenging, especially with regard to the primary tumour, which has often been surgically removed in another hospital many years before the autopsy (Table 1).

Capturing comprehensive clinical patient information was equally challenging due to the complex and diverse disease trajectory of metastatic disease. Eight programmes had set up electronic databases, most commonly in RedCap (n = 5). Usually, access to the patient’s medical file remained available after death for information extraction as research questions evolved.

Other logistical considerations

Most programmes (n = 11) purchased equipment specifically for the study including processing equipment, bone drills, logistic equipment, sterilisation equipment, and consumables. Estimating the total price per patient was challenging for five programmes. The Akita Rapid Autopsy Program reported a cost of only USD 20 per patient due to enrolling in-hospital patients only and covering the pathologist’s salary through their clinical position. For seven programmes, the price ranged between USD 1,000 and 5,000 per patient; one programme even reported a price range of USD 3,000–10,000. The price was often highly influenced by personnel costs, with some researcher time covered through grants and other personnel requiring full funding. Two programmes reported an autopsy fee of USD 1,500 being charged per patient. Transport of the body either was done in-kind or range between USD 185 and 1,500 in median price. Postmortem imaging costs ranged between USD 250 and 750 per patient, or was included in the autopsy fee.

The biggest financial contributors were research foundations [mentioned in nine programmes, median contribution out of total budget 45% (range 5–100%)]. This was followed by funding through the host university [seven programmes, median contribution 50% (range 10–95%)] and the affiliated hospitals [four programmes, median contribution 70% (range 6–100%)]. Three programmes additionally received support through private donors, accounting for 20%, 50%, and 50% of their total budget. Of interest, two programmes implemented cost recovery structures where end users were charged for the samples received (contribution to total budget: 25% and 30%), incentivising them to include cost recovery in grants. Prices varied based on collaboration type (close academic partners versus non-affiliated institutes or industry/commercial partners). No programmes reported structural funding from industry or pharmaceutical companies.

Research opportunities and achievements

Postmortem programmes allow high-volume sample collection of tumour tissue, non-tumour tissue, and liquid biopsies, sometimes in combination with longitudinal sampling (the original primary tumour and/or metastases during life) (Figure 4A). This has already enabled high-impact research, as highlighted in Figure 4B and Table 2 with examples from the 14 programmes. Genomics, particularly sequencing multiple metastases per patient, has revealed insights into metastatic seeding, driver events, ...
Figure 4. Opportunities of tissue donation programmes. (A) Opportunities for sample collection in the context of rapid autopsy programmes. Tissue samples requested from clinical and study archives and liquid biopsies collected specifically for the programme can form a biorepository of premortem (longitudinal) samples. At autopsy, the sample collection opportunities are virtually unlimited, and include extensive tumour and liquid biopsy sampling as well as the collection of non-tumour tissues for specific research questions. (B) Opportunities for understanding metastatic cancer through research autopsies. Created with Biorender.com.
### Intra-patient inter-lesion heterogeneity in genomic and phenotypic characteristics

<table>
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<tr>
<th>Mechanisms of metastasis evolution and spread, including phylogenetic reconstruction</th>
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| Almost all targetable drivers in metastases in patients with breast cancer are already present in the primary tumour. Multiclonal spreading is often observed as two possible scenarios of dissemination patterns of breast cancer (monoclonal and multiclonal) are observed, as well as cross-seeding between metastases. While some patients may have metastatic breast cancer presented with predominantly monoclonal seeding patterns, others showed predominantly multiclonal seeding. Clonal dynamics as assessed on multiple metastases at autopsy confirmed different modes of metastatic dissemination in clear-cell renal cell carcinoma. Phylogenetic trees in metastatic pancreatic cancer show organ-specific branches. Copy number and cell ploidy changes drive evolution to end-stage disease in melanoma. Most genetic changes conferring treatment resistance were shared between metastases in the same patient with melanoma. No correlation between ERG and expression of PSA or androgen receptor in individual metastases in prostate cancer. Prognostic and predictive biomarker expression differs between primary breast cancer and matched metastases and might depend on the organ of metastasis. Immune profiles were heterogeneous too. Characterisation and comparison of non-osseous bone metastases to non-osseous metastases from the same prostate cancer patients. Immune activation varies by organ site of involvement in metastatic breast cancer. Multi-omic analyses on primary breast tumours versus during-life (mostly liver) and after-death (many other soft tissues) metastases reveal events that may explain metastatic tumour behaviours.

### Patterns of metastatic spread

| The pattern of metastasis observed at autopsy showed visceral involvement to be more common than generally thought in metastatic prostate cancer. Patterns of metastatic disease differ between patients with breast and ovarian cancer who are BRCA1/2 carriers and those who are non-carriers, suggesting different mechanisms of dissemination.

### Evaluation of mechanisms of treatment resistance/response

| Association between certain genomic alterations and treatment response in metastatic prostate cancer, such as longer responses to carboplatin in patients with defects in DNA-repair proteins. ESR1 fusion enrichment may represent secondary resistance to more aggressive endocrine therapies in breast cancer. New genomic mechanisms of disruption of androgen receptor signalling identified in metastatic prostate cancer. Convergent loss of PTEN is a mechanism of resistance to PI3K inhibition in breast cancer. Mechanisms of resistance to immunotherapy in melanoma. Different types of reversion mutations found in the BRCA2 gene in patients with ovarian cancer, representing a mechanism of resistance to PARP inhibition. |

(Continues)
Evaluation of non-tumour tissue samples

**EGFR driver** mutations were found in non-cancerous lung samples retrieved at autopsy, highlighting the presence of pre-existing mutant cells possibly susceptible to pollution-associated tumour promotion [76].

Potential of liquid biopsies and blood–based analyses

Circulating tumour DNA could be detected in blood collected postmortem in patients with prostate cancer and allowed identification of mutations present in different metastases [67].

Analysis of T-cell repertoires across multiple tumour lesions as well as in circulation in a patient with renal cell carcinoma highlights pitfalls in interpreting T-cell cross-reactivity between tumours and immune checkpoint inhibitor immune-related adverse events based on profiles in peripheral blood or one sample only [62].

Tumour model development

Patient-derived xenografts established from two postmortem metastases allowed the evaluation of the role of androgen receptor splice variant-7 in treatment resistance and tumour evolution in prostate cancer [74].

Successfully established patient-derived xenografts from postmortem samples allowed the investigation of candidate therapies in castration-resistant prostate cancer to prioritise treatments for clinical translation [75].

**Discussion**

We present here the shared experience and accomplishments of 14 research autopsy programmes that were created to advance metastatic cancer research around the world. At the geographical level, most programmes are in the United States and we could not identify any programme in South America or Africa. This means that, currently, these programmes might not be capturing the full spectrum of the disease.

The programmes ranged from slight modification of clinical autopsy procedures to extensive postmortem tissue sampling performed by research personnel. Autopsies performed 24 h/7 days had a median PMI of only 4 h, enabling the qualitative collection of fragile molecules and viable cells. This structure, however, came at a psychological and logistical cost. All programmes have successfully collected highly valuable liquid and tissue samples, with a median of 58 samples stored per patient across all programmes, including from organs otherwise unethical/impossible to sample. The rapid nature of the procedures (often completed within 12 h after death) and implementation of cooling mitigated postmortem effects on molecules/RNA degradation. Genomic analyses were possible in every programme, leading to major discoveries in metastatic tumour progression and biology. Sample prioritisation, sterile procurement, and reduced transport times have facilitated the creation of unique tumour models shaping future drug discoveries and testing.

In the era of precision medicine, autopsy programmes can be an invaluable link in the research chain towards better patient outcomes. Through this work, we hope to foster collaborations (contact details are provided in supplementary material, Table S2 for all programmes) and to encourage the creation of new programmes. A society of research autopsy programmes will help to achieve this goal and is currently being created, including non-oncological and paediatric programmes. Importantly, we also plan on further exploring how the role of patients in the design and support of the programmes can be increased in the future, as they are the cornerstone of and the sole reason for the research we do.

**Acknowledgements**

We would like to emphasise that none of the work presented would have been possible without the willingness and courage of patients to contribute. We also acknowledge and thank all patients’ families for their support. Tissue donation programmes are highly multidisciplinary, and we acknowledge and thank all team members and collaborators involved in the set-up of the different programmes, the inclusion of patients, the performance of the autopsies, sample and data management, and downstream analyses. The Hope for OTHERS programme also acknowledges the critical
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**Author contributions statement**

TG was responsible for conceptualisation, methodology, validation, formal analysis, investigation, resources, data curation, writing the original draft, review and editing of the manuscript, visualisation and project administration. MM was responsible for conceptualisation, methodology, review and editing of the manuscript and project administration. JEH was responsible for resources, review and editing of the manuscript and supervision. SO, AVL, WVD and GF were responsible for methodology, resources, and review and editing of the manuscript. LM, JMA, MR, SP, HT, LD, DB, ERB, KI, MS, LR, ALW, LG, RMu, PC, AK, CN-L, HB, CS, MJ-H, LK, CM, MC, AMC, AW, RMe, ZR, LAC, EK, DM, AG, JK, MS, BS and A-MT helped with resources and writing the manuscript (review and editing). CD was involved in conceptualisation, methodology, review and editing of the manuscript and supervision.

**Data availability statement**

To avoid misinterpretation, the filled-out fact sheets of individual programmes will not be shared. However, programmes agreeing to be contacted for further information have their details listed in supplementary material, Table S2.

**References**

Shared experience from 14 research autopsy programmes in oncology worldwide

SUPPLEMENTARY MATERIAL ONLINE

Figure S1. Flow diagram of the number of rapid autopsy programmes identified, contacted, and finally included in the survey

Figure S2. Examples of the set-up of the autopsy room in two different programmes

Table S1. Blank version of the five fact sheets containing all questions in the survey

Table S2. Main characteristics of the respective programmes