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Developing a pan-cancer research autopsy programme

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ABSTRACT

Aims Rapid procurement of a wide variety of metastatic and primary cancers and normal tissues after death through rapid autopsy opens largely unexplored avenues in cancer research. We describe a high-volume rapid research autopsy programme at a large academic medical centre.

Methods Advanced-stage cancer patients, most commonly inpatients in palliative care facilities, were approached to participate in a cancer research autopsy programme with the goal of acquiring multidimensionally annotated tissue for cancer research. On death of an enrolled patient, a predetermined notification plan was enacted, with the medical oncologist/clinical research coordinator informing a team of pathologists, researchers and allied staff. Quality assurance metrics were measured. Thereafter, tissues were annotated in a tissue bioinformatics database and linked to electronic patient records. All banked tissues were reviewed for tumour integrity, including DNA and RNA quality.

Results Over 100 rapid research autopsies from diverse cancer sites were performed, and specimens were procured and annotated with detailed clinical information, including treatment and response. Tissues were successfully enabling studies of tumour immunology, xenografts, genomics and proteomics.

Conclusions Large-scale rapid procurement and biobanking of cancer tissues from a rapid autopsy programme is feasible. Multidisciplinary integration between health and administrative staff from medical oncology, palliative care, pathology and biospecimen sciences is critical for the success of this challenging endeavour.

INTRODUCTION

Access to high-quality, well-annotated primary and metastatic cancer tissues after treatment with targeted therapeutics and immune checkpoint inhibitors will be key to advancing precision diagnostics and therapeutics ('theranostics').[1 2] Most patient-centred studies of tumour biology have been carried out on surgically resected cancers. While this allows access to large numbers of samples, this approach limits an appreciation of the spectrum of disease development, heterogeneity and mechanisms of therapy resistance in more advanced tumours.[3 4]

Autopsies of end-stage cancer patients have proved to be an increasingly useful mechanism of tissue acquisition to enable cancer research[5 6]. Autopsies (i) accurately determine the nature and extent of metastatic disease, (ii) facilitate the procurement of difficult to obtain invaluable metastatic cancer tissue and (iii) advance our understanding of the molecular mechanisms of treatment-resistant tumours. There have been a few examples of cancer site-limited rapid cancer autopsy programmes worldwide, including breast (Johns Hopkins University), pancreas (University of Nebraska and Johns Hopkins University) and prostate/kidney (University of Michigan, Johns Hopkins University, and University of Washington).[5 7–9] Significant insights have been obtained from these focused rapid autopsy programmes (RAPs).[6 8 9] However, only a few, if any, institutional programmes have taken a pan-cancer approach.

Given its large clinical and research infrastructure, Princess Margaret Cancer Centre within the University Health Network in Toronto, Canada, is in a unique position to establish an institutional pan-cancer research autopsy programme. After initially piloting the programme in melanoma, the programme has thus far performed 105 rapid research autopsies on patients with metastatic cancer spanning all major malignancies. There are several synergies with the existing healthcare infrastructure that facilitate this initiative: (i) a close working relationship of palliative care and the medical oncology staff and facilities; (ii) synergistic research goals of pathology/biospecimen sciences, medical oncology and scientific investigators; (iii) a large and expanding technical base of scientific expertise to take advantage of the samples collected (both tissues and liquids); (iv) expertise, personnel and IT infrastructure to ensure tumour tissues are rapidly procured and annotated and (v) engagement of physician groups involved in the programme.

Herein, we describe the key components of the programme, as well as results of tumour tissue acquisition and quality assessment.

COMPONENTS OF THE PROGRAMME

The design of the autopsy programme recognises the importance of three key interfaces: the patient–physician interface, the autopsy–pathology interface and the biospecimen science/IT/specimen utilisation interface (figure 1). An outline of the procedures covering the consenting and collection process is illustrated in figure 2. A particular feature of our research autopsy protocol is that extensive data abstraction is performed *before* the autopsy is started. This includes a written document that guides optimal harvesting of lesions and normal tissue by the pathologist based on complete medical record review, radiology review, treatment history

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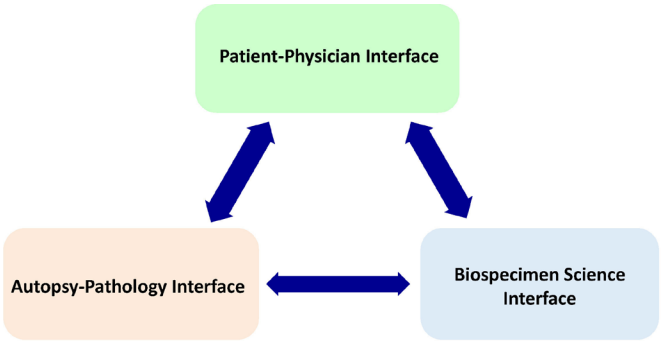

Figure 1 Schematic overview of the three major components of our rapid research autopsy programme.

review and harvest prioritisation of biologically interesting lesions based on the input from the treating oncology team (eg, preselection of harvestable lesions that had shown differential therapy resistance vs therapy response premortem, or temporal sequence of lesion appearance in the patient).

The patient–physician interface

As the majority of patients consented were inpatients on the medical oncology or palliative care floors, the patient endorsement of a DNR (Do Not Resuscitate) order was used as a preliminary screen to identify potential patients. Thereafter, the medical oncology staff, nursing staff and a clinical research coordinator closely interacted to ensure potential patients and their families were educated and informed about the key aspects of the research programme, including study-specific consent and general terminal care documentation. We found that patients and their families were both accepting and engaged when discussing the research autopsy programme and its potential benefits to cancer research, with an overall consent rate of approximately 20%–25%. Reasons for refusal most commonly included psychosocial state of the patient/family, inappropriate timing and improvement of the patient's condition (see online supplementary figure 1).

Following consent, a brief clinical summary form was completed by the treating medical oncologist/radiation oncologist detailing the primary, type of treatment given, main metastatic sites of interest based on last imaging scans done and classifying the lesions into sensitive, refractory or stable based on response to chemotherapy/radiotherapy and any targeted therapy.

The autopsy–pathology interface

In most cases, the patient was either hospitalised at the time of death or under hospice care. In cases where the patient died outside of the hospital, the body was transported to the University Health Network morgue following death certificate completion. Simultaneously, the oncologist/clinical research coordinator assembled the autopsy and specimen banking teams. The autopsy team consisted of a pathology fellow, a staff pathologist, a neuropathologist, a pathology assistant, a technical assistant and two members from the biospecimen programme to assist with harvesting and rapid storage. All team members were available to assure availability on weekdays from 08:00 to 22:00. On arrival in the autopsy room, the standard operating procedures were followed, including the confirmation of the patient identity and an external examination of the cadaver. Thereafter, a modified Letulle method followed where heart and lung are dissected out first using the Virchow method[10] with 100 mL of cardiac/venous blood obtained for circulating tumour DNA studies. A neuropathologist removed the brain (where permitted), and sampled any grossly evident metastases in the brain and dura. All

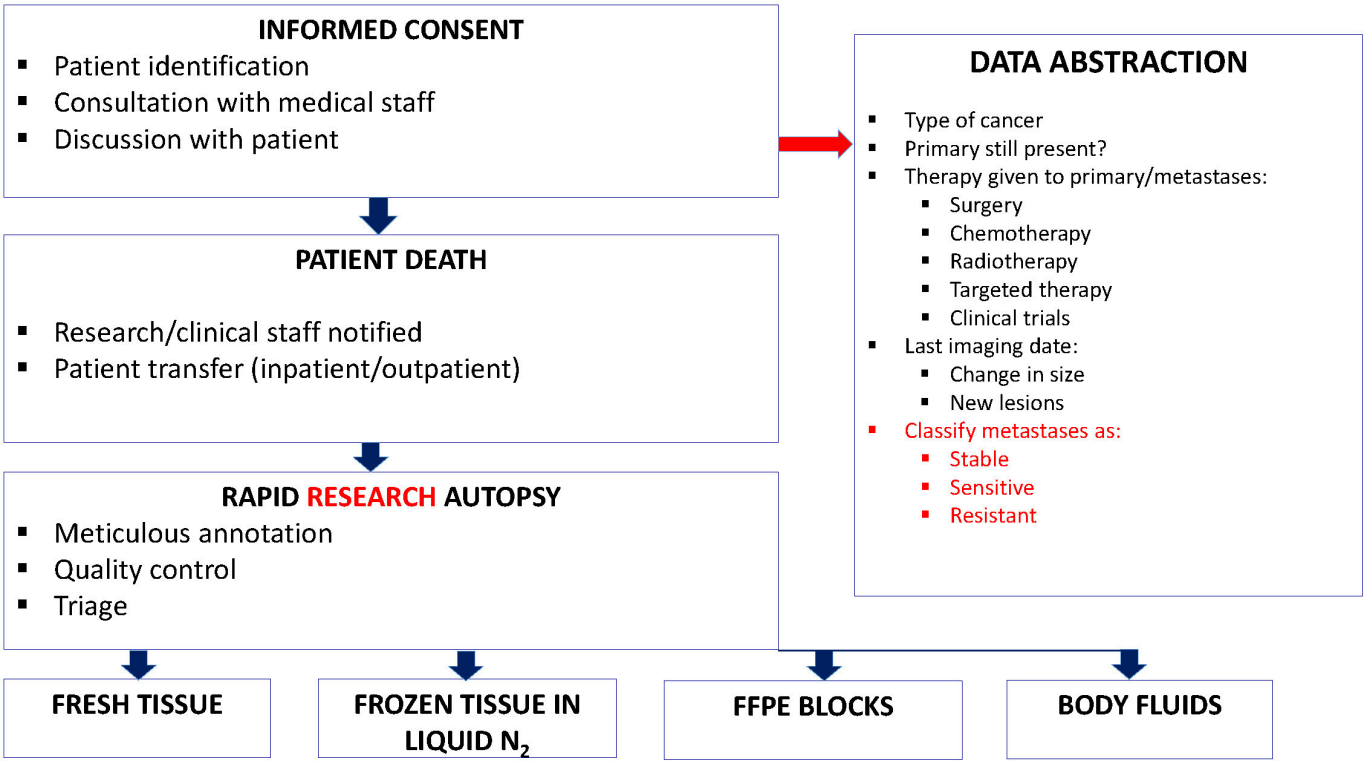

Figure 2 Flowchart of the research autopsy programme process, including consent, logistics of the procedure and comprehensive preprocedure data abstraction to optimally guide sample harvesting. FFPE, formalin-fixed paraffin-embedded; N_2, nitrogen gas.

Table 1 Descriptive summary of the patient cohort in the research autopsy programme (n=105)

	Number	%
Gender		
Female	48	45.7
Male	57	54.3
Age, years		
Median (IQR)	65 (56–72)	
Smoking		
Yes	45	42.9
No	49	46.7
Unknown	11	10.5
Chemotherapy		
Yes	94	89.5
No	11	10.5
Radiotherapy		
Yes	75	71.4
No	30	28.6
Clinical trial participation		
Yes	32	30.5
No	62	59.0
Unknown	11	10.5
Genetic mutations		
Germline	3	2.9
Somatic	24	22.9
No mutations/not tested	78	74.3
Family history of cancer		
Yes	32	30.5
No	10	9.5
Unknown	63	60.0

metastatic sites and additional findings were photographed in situ as well as individual organs with external tumour and gross appearance of cut surface of involved organs.

Once the tissue harvest was complete, the autopsy proceeded in accordance with the standard protocol in conjunction with the patient's wishes. A standard protocol was created for tissue acquisition such that all metastatic lesions and lesions of interest (that had either responded or progressed while on therapy/clinical trials), as well as adjacent normal tissue, were sampled. This information was available through a preautopsy programme patient summary guide filled by the treating physician and guided rapid and comprehensive tissue acquisition. This guide detailed type, locations and treatment history of the cancer as well as the most up-to-date known sites of metastases based on most recent imaging.

Biospecimen science/IT/specimen utilisation interface

On the basis of the information provided by the treating clinician, the primary site of cancer and sites of metastatic spread were identified, and all lesions were classified as 'responsive', 'progressive' or 'stable' disease to chemotherapy, radiotherapy, targeted therapy and immunotherapy.[11] All normal and malignant tissues were collected as both snap-frozen tissue using liquid nitrogen and as formalin-fixed tissue. All samples were anonymised and electronically accessioned using an electronic caTissue Suite biobank database,[12] mapped to specific storage locations and annotated with detailed information about tissue site, time and type of processing, number of aliquots and relative sample hierarchy (see online supplementary figure 2). All tissues were also linked to detailed clinical and pathological (including genomic sequencing) data through integration with hospital clinical care databases.

RESULTS

Descriptive summary characteristics of the 105 patients who consented to research autopsies over the first 1.5 years of the programme are outlined in table 1. Patient age ranged from 24 to 86 years (median, 65 years), and gender distribution was 57 males and 48 females. Cancer types (figures 3 and 4) were 21 gastrointestinal cancers (oesophageal, gastric, colorectal, pancreatic, liver and biliary), 19 respiratory tract cancers (non-small cell carcinoma, small cell carcinoma and others), 18 genitourinary tract-related cancers, 17 melanomas, 9 gynaecological cancers, 8 breast cancers, 5 haematological malignancies (multiple myeloma, CLL with blastoid transformation and biphenotypic acute leukaemia), 2 sarcomas, 3 central nervous system cancers and 3 head and neck cancers (eg, see case vignettes 1 and 2 in online supplementary figures). Importantly, 30.5% of the patients had been enrolled in one or more clinical trials during their treatment.

High-volume biobanking

Over 10 838 samples were banked from the 105 rapid autopsies (figure 4). The number of samples banked ranged from 14 to 178 per autopsy (median, 71). The number of harvested sample units breaks down into frozen tissues (3822), formalin-fixed paraffin-embedded (FFPE) (3311), whole blood (689), plasma (2223), serum (188) and frozen buffy coat cell pellets (605) (figure 4A). Tissue samples were classified as 'cancer' (3702), 'normal' (2678) and 'abnormal' (753; preneoplastic/dysplastic lesions and non-neoplastic or inflammatory lesions) (figure 4B). Importantly, the samples cover all anatomic sites (figure 4C).

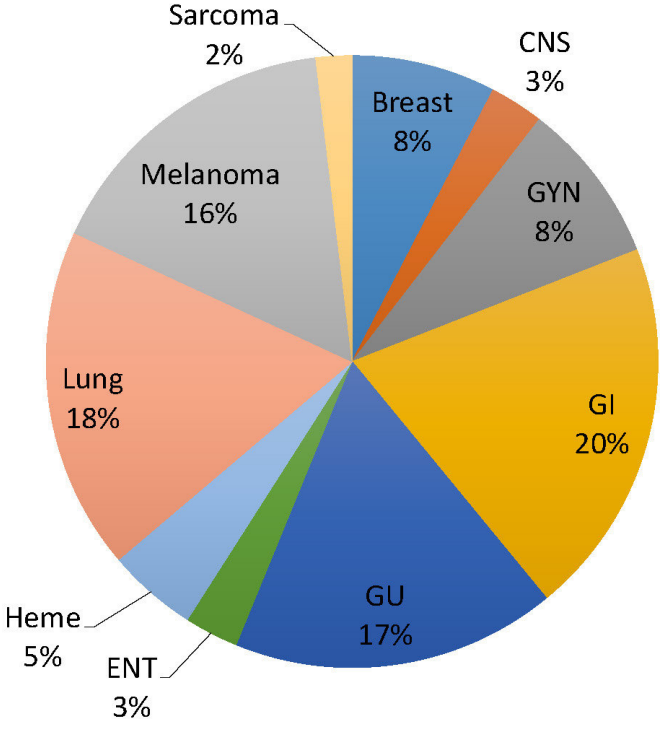

Figure 3 Pie chart illustrating the relative distribution of primary sites/tumour types from 105 patients. CNS, central nervous system; ENT, ear/nose/throat; GI, gastrointestinal; GU, genitourinary; GYN, gynaecological; Heme, haematological.

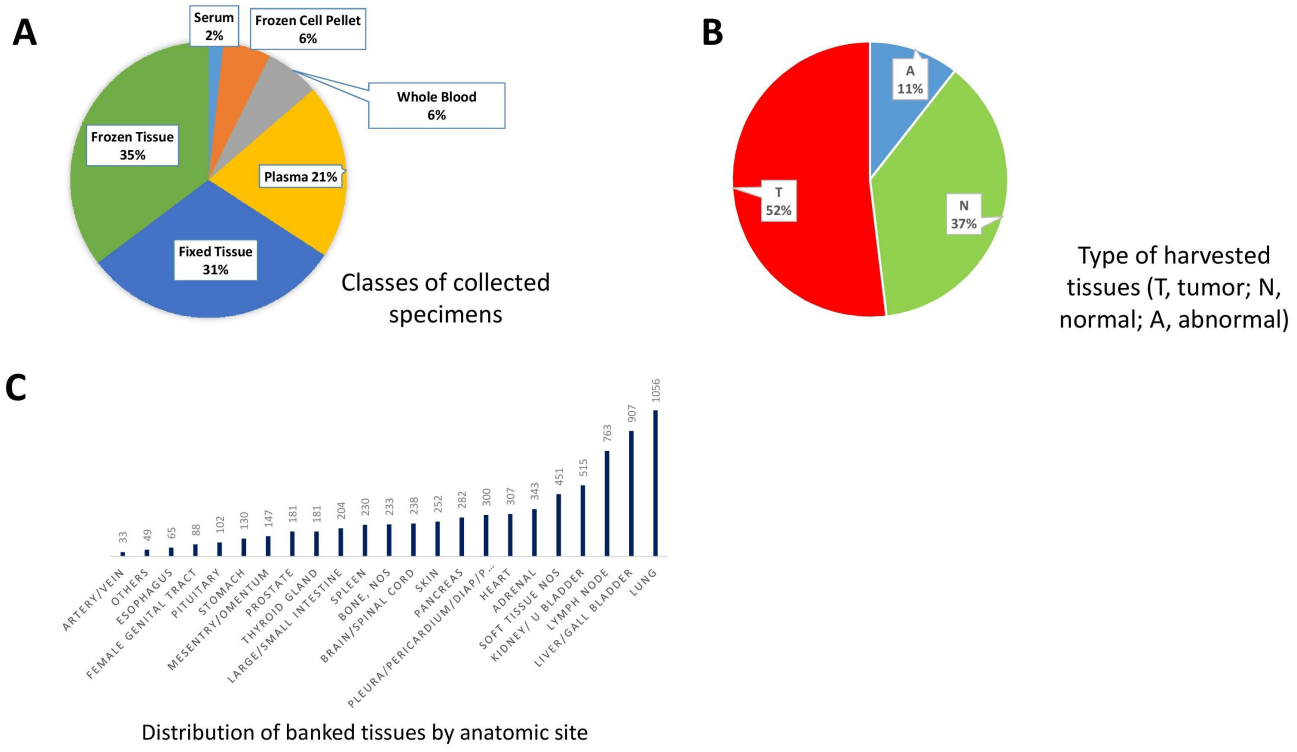

Figure 4 (A) Pie chart illustrating the relative distribution of classes of samples collected. (B) Pie chart illustrating the relative distribution of gross annotation of collected tissue samples as tumour (T), normal (N) or abnormal (A). The latter includes, for example, areas of fibrosis, inflammation or other non-malignant gross abnormality. (C) Bar chart illustrating the absolute distribution of banked tissues by anatomic site of procurement. NOS, not otherwise specified, DIAP/P, diaphragm/peritoneum.

Time points

Detailed time point metrics of the autopsy series with analysis were available for 76 patients (figure 5). The median number of days from consent to autopsy was 9 with an upper limit of greater than 140 days. The median interval from first to the last sample banked per autopsy was 1.75 hours (25%–75% IQR, 0.12–2.50 hours). After excluding patients who died during holidays and weekends, the median of time of death to start of autopsy was 9.54 hours (25%–75% IQR, 4.75–16.01 hours). Median time from death to first sample banked was 9.58 hours (25%–75% IQR, 4.94–16.01 hours), highlighting the speed of harvest after the start of the procedure by using a prepared lesion targeting document as described above (figure 2). While the time between death and refrigeration of the body was not captured routinely in our current study, inclusion of this parameter would be a valuable future addition.

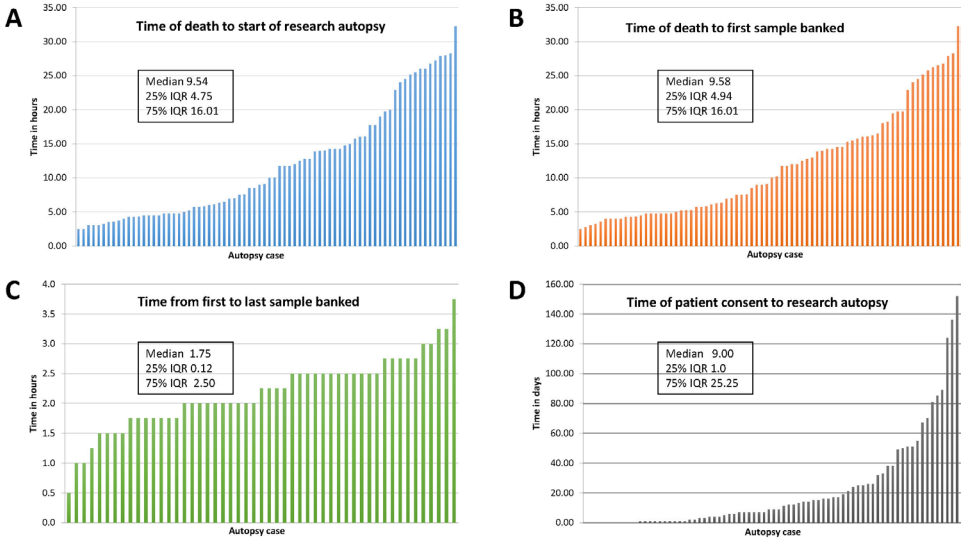

Figure 5 (A) Bar chart showing the ordered time intervals (in hours) between death and start of the research autopsy (n=105). (B) Bar chart showing the ordered time intervals (in hours) between death and first sample banked (n=105). (C) Bar chart showing the ordered time intervals (in hours) between first and last sample banked (n=105). (D) Bar chart showing the ordered time intervals (in days) between first and last sample banked (n=105).

Figure 6 (A) Ordered bar chart showing % tumour cellularity in each tumour sample as assessed by histological review of H&E slides from FFPE blocks. (B) Ordered bar chart showing % tumour cellularity in each tumour sample procured from the liver as assessed by histological review of H&E slides from FFPE blocks. (C) Ordered bar chart showing % tumour cellularity in each tumour sample procured from lung as assessed by histological review of H&E slides from FFPE blocks. (D) Ordered bar chart showing % tumour cellularity in each tumour sample procured from lymph nodes as assessed by histological review of H&E slides from FFPE blocks. FFPE, formalin-fixed paraffin-embedded.

Systematic assessment of tumour purity by histological review

H&E slides from all banked FFPE tumour blocks were reviewed by a trained pathologist (PB) to ascertain tumour cellularity by documenting the percentage of viable tumour, necrosis, and presence of normal tissue and stroma for every case. Median tumour cellularity across all banked tumours was 83.2% (25%–75% IQR, 45.2%–100%), and the median tumour cellularities for liver, lung and lymph node metastasis were 80.3%, 100% and 100%, respectively (figure 6).

RNA integrity number assessment of samples

Although quality of genomic DNA obtained from rapid autopsy specimens has been shown to be fairly robust and of good quality for sequencing studies using either Sanger or Next Generation Sequencing techniques, RNA integrity has not been studied systematically.[13] Therefore, we decided to determine the effect of time between patient death and tissue processing on RNA integrity.

RIN scores were determined for primary tumours, metastatic lesions and normal uninvolved tissues from the harvested tissue samples. The time between patient death and tissue processing was recorded. RNA integrity number (RIN) scores were determined from snap-frozen tissue using a Bioanalyzer (Agilent) and reported on a scale of 1–10, with 10 indicating fully intact RNA, 5 indicating partially degraded RNA and 3 or lower indicating fully degraded RNA. As an illustrative example, two autopsies performed within 5 and 18 hours after death were selected to assess RNA integrity. RIN scores of the primary tumour, liver metastasis and normal kidney from a patient with lung cancer sampled 5 hours postmortem were 5.6, 7.6 and 4.8, respectively. Tumour tissues collected from a second patient with lung cancer sampled 18 hours postmortem had RIN scores of 6.6 (primary) and 6.9 (liver metastasis), while normal kidney tissue showed only degraded RNA (<3). We next examined RIN scores for 71 tumour samples as a function of time between death and freezing of each sample (figure 7) and found that tumour samples retain high-quality RNA for up to 9 hours postmortem.

CONCLUSIONS AND FUTURE DIRECTIONS

We have developed a comprehensive pan-cancer research RAP at a major academic cancer institute to obtain large-scale spatially indexed biospecimens for cancer research. Focused acquisition of tumour samples from primary and metastatic sites, with specific attention to ‘responsive’ and ‘resistant’ deposits within a given patient, has provided us with a valuable resource to study the heterogeneity of tumour biology, including mechanisms of treatment resistance and response. To date, samples acquired through this programme have been used to characterise subclonal relationships in metastases of BRAF mutant melanoma,[14] to define glucagon physiology in the heart,[15] and to discover a chromothripsis model of carcinogenesis in pancreatic cancer.[16]

We describe a large-scale research autopsy programme in oncology in the setting of an integrated single institution academic health system in North America. Developing similar programmes in other geographies, such as the UK and mainland Europe, may face different challenges based on national, regional and local biospecimen ethics rules and regulations, autopsy procedures, patient and next of kin interactions and values, and overall setup of the healthcare system. All research autopsies in our programme were performed as ‘hospital autopsies’ and not coronial or medicolegal autopsies (which are performed for cause of death investigations). A similar distinction exists in the UK and most European countries, where medical autopsies require next of kin consent similar to our situation. In the UK, for example, the Human Tissue Acts of 2004 and 2006 created the Human Tissue Authority that regulates the removal, storage, use and disposal of human bodies, organs and tissue for research, transplantation, and education and training. Data protection is another important consideration to which varying regulations may apply, such as the Health Insurance Portability and Accountability Act in the USA (narrower and limited to Protected Health

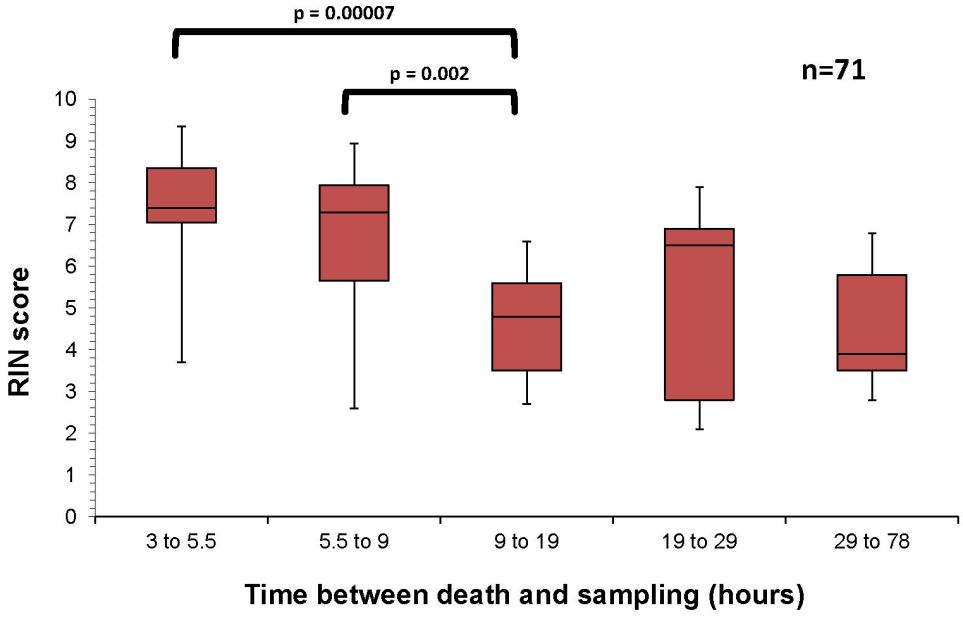

Figure 7 RNA integrity number (RIN) score comparison of 71 fresh-frozen tumour samples binned by time between death and sampling. Note that there is a time dependence between loss of RIN and time, especially after 9 hours postmortem. Pairwise comparisons used Student's t testing.

Information), the General Data Protection Regulation in the EU (broader and applicable beyond health data) or the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada. Finally, data and sample sharing between research organisations in North America requires fully executed Data Sharing Agreements and Material Transfer Agreements to be in place at both the sending institution (ie, site of the RAP) and the receiving institution. Both sender and recipient also have to have active ethics approvals of an active research protocol at each of their institutions. Analogous rules exist in other countries. We acknowledge that developing a research autopsy programme in a regional or multi-institutional decentralised structure would likely be more difficult than at a single high-volume academic reference centre because issues of standard operating procedure harmonisation, data exchange, biospecimen collection and transport, patient selection and tracking, and overall quality assurance and ethics monitoring would be logistically demanding and more resource-intensive.

Especially for an autopsy-based programme, assurance of molecular sample integrity is key for the scientific utility of samples. We observed adequate RNA integrity in metastatic tumour samples obtained up to 18 hours after patient death, which is reassuring for the use of this bioresource in other profiling studies across cancer sites. Normal tissue RNA appears

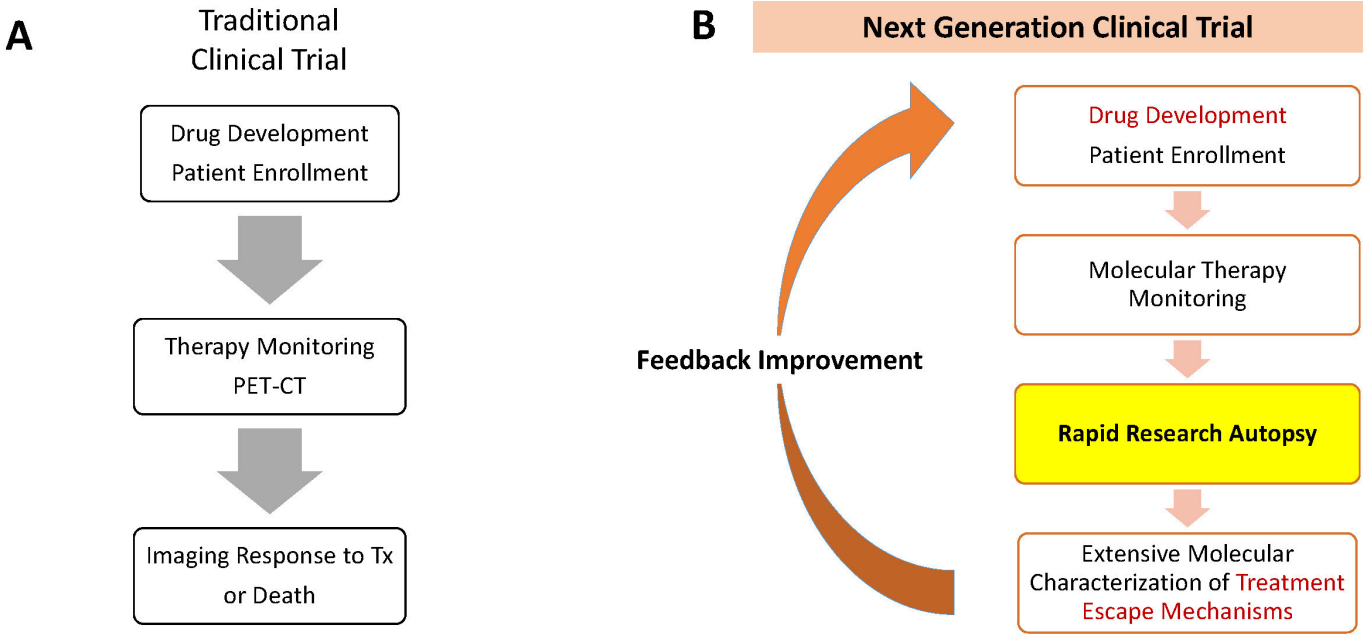

Figure 8 (A) Traditional unidirectional clinical trial flow without ability to further characterise mechanisms of therapy resistance during treatment. (B) Next Generation Clinical Trial design that routinely incorporates molecular assessment of lesions during/post-treatment and at resistance, allowing for rapid feedback into drug development to counter mechanisms of treatment escape. PET–CT, positron emission tomography–CT; Tx, therapy.

to be more sensitive to degradation postmortem, in agreement with prior findings.[17] A RIN analysis has since become routine QC for all patients in our RAP.

Mechanisms of treatment escape of cancers remain a fundamentally unaddressed issue in cancer research. Our programme permits comprehensive deep molecular analyses of events that contribute to cancer metastasis, spatiotemporal heterogeneity, differential treatment response and ultimate treatment escape of most lesions under treatment. In addition, our autopsy programme features high tissue yields for facilitating the development of preclinical models of disease through establishment of xenografts, organoids and cryobanking of samples for immunotherapy-based studies. Given these advantages, we feel that research autopsies should be more routinely integrated into academic oncological practice and clinical trial design (figure 8). Our programme has been primarily designed to collect valuable samples, but has also demonstrated both benefits and challenges of carrying out a pan-cancer autopsy programme in an integrated cancer setting. While the medical infrastructure at the Princess Margaret Cancer Centre is fully integrated and relatively unique with the co-location of palliative care and hospice services, the limitations of retrieving deceased patients from outside locations, such as nursing homes, when required, proved challenging and, on occasion, limited the ability of the patients to continue in the programme. We applaud the work of others in the field who have designed disease-specific questions that have been successfully answered through the use of autopsy tissue.[18] It is worth noting that more than 30% of the patients in our programme participated in at least one clinical trial, perhaps suggesting that certain patients are more willing to contribute to science and that programmes like ours offer significant potential to augment the understanding of resistance mechanisms to novel drugs. In sum, we have created a powerful resource for pan-cancer tissue analyses that will uniquely advance oncological research.

Take home messages

- We describe a comprehensive pan-cancer research rapid autopsy programme at a major academic cancer institute to obtain large-scale spatially indexed biospecimens for cancer research.
- Our programme enables comprehensive deep molecular analyses of events that contribute to cancer metastasis, spatiotemporal heterogeneity, differential treatment response and ultimate treatment escape of most lesions under therapy.
- Pan-cancer research autopsies facilitate the development of preclinical models of disease through establishment of xenografts, organoids and cryobanking of samples for immunotherapy-based studies.
- Research autopsies should be routinely integrated into academic oncological practice and clinical trial design.

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Contributors PB performed autopsies, pathological analyses and clinicopathological correlations, and prepared the figures. MS coordinated patient consenting and clinical database maintenance, and provided organisational support for the programme. TA-S performed RIN analyses and assisted with specimen collection. DC oversaw specimen collection and banking. ND provided support for patient consenting and medical oncology input. JB oversaw the autopsy procedures as medical director. AMJ and MHR obtained funding, and designed, implemented and directed the programme. PB, AMJ and MHR wrote the paper with input from all the authors. All the authors reviewed the manuscript.

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Patient consent for publication Obtained.

Ethics approval The study was approved by the Institutional Research Ethics Board (REB) of the University Health Network (UHN), Toronto, Ontario, Canada. All parts of the study were carried out in accordance with this REB approval.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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