Histopathology at autopsy: why bother?

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Aims: The frequency of histopathological sampling at autopsy varies, even though inadequate sampling may limit the value of autopsy reports. This study aims to investigate the contribution of histopathology at autopsy in a major teaching hospital.

Methods and results: A total of 532 coronial autopsy reports from Manchester Royal Infirmary were analysed retrospectively. Gross and microscopic diagnoses were compared and classified as concordant, discordant, histology needed (i.e. indeterminate or unremarkable gross findings) or autolysed. Revisions made to the cause of death following histopathology were categorised as: altered direct cause of death, altered indirect cause of death, concordant with supportive information, irrelevant or inconclusive. The study was limited to brain, heart, kidney, liver, lung and spleen. Histopathology had been requested in 141 cases (27%), which were further analysed. The greatest discordance between gross and microscopic findings was observed in the lung (11.6%). The organs most frequently requiring histopathology to provide a diagnosis were the kidney and lung, at 52.8 and 28.2%, respectively. Alterations were made to the direct cause of death in 45% of cases where histopathology was taken; it provided additional or supportive information in a further 38%. Diagnoses of primary malignancy had a sensitivity of 74% [confidence interval (CI) = 0.59–0.86] and bronchopneumonia had a sensitivity of 45% (CI = 0.29–0.62).

Conclusion: Histopathology has a major impact on the interpretation of organ pathology and determining a cause of death at autopsy.

Keywords: autopsy, cause of death, histology, histopathology, hospitals, microscopy, pathology, teaching

Introduction

The autopsy can provide significant insight into disease progression and treatment efficacy, and establishing an accurate cause of death ensures that reliable mortality statistics are available for public health planning. Despite advances in antemortem diagnostic techniques and postmortem imaging, clinicopathological discrepancies have remained high.¹⁻⁴ Certain pathological features are only visible microscopically and gross examination of organs is fallible: histopathology can improve the quality of autopsy reports and information available to families, clinicians, coroners and public health services.¹⁻⁵⁻⁷ For autopsies where histopathology is taken, diagnostic morphological features at gross examination are described in a provisional autopsy report, which may then be updated or revised following histopathological examination to produce a final autopsy report.

The rate of histopathological sampling at autopsy varies significantly between individual pathologists, different hospitals and even different coronial jurisdictions.⁵ Autopsies in England, Wales and Northern Ireland are almost exclusively performed for the coroner, an independent judicial officer responsible for determining whether a cause of death is natural or
unnatural on the ‘balance of probability’ (i.e. a certainty of greater than 50%) in almost all contexts. Scotland has a separate system.

A coroner must conduct an investigation into a person’s death if the cause of death is unknown, if the person died in custody or otherwise in state detention, or if the coroner has reason to suspect that the cause of death was violent or unnatural (e.g. due to a medical procedure; poisoning; or occupational injury, such as asbestos exposure). Allegedly unnatural deaths require an inquest, which usually means further investigations; these further investigations often, but not always, include autopsy.

The coronial service is divided into 109 jurisdictions. Permission to retain tissue for histopathological sampling is at the discretion of individual coroners, who have very different views from one another. The Coroner’s (Amendment) 2005 Rules state that the coroner must notify the pathologist of the period of time that, in the coroner’s opinion, material should be preserved to determine whether a cause of death is unnatural. The Coroner’s Rules are open to interpretation: if an inquest is not required, as in the majority of autopsies, tissue retention without consent of the next of kin may be regarded as unlawful.

In some jurisdictions, pathologists are permitted to take histopathology to confirm or refine a natural cause of death, whereas coroners in other jurisdictions do not permit any histopathology to be taken when death is thought to be natural. The coroner is not explicitly required to consider the educational benefit of the autopsy, the family’s wishes or relevance to mortality statistics and public health planning, although some coroners will give more consideration to these aspects than others.

Many factors also discourage pathologists from taking histopathology, including workload, remuneration, insufficient training, reduced perception of value and perceived limitations imposed by the 2004 Human Tissue Act (stating that ‘the procedure [autopsy] should not be more extensive than is necessary to achieve its specific aim’, which is also open to interpretation).

Ultimately, the level of accuracy required to provide a cause of death in the context of a coronial autopsy is unclear, and the standard expected by the coroner, and advisory bodies such as the Royal College of Pathologists (RCPath), may not align. Where the balance of probability is the standard, it can be difficult to maintain academic integrity.

**Method**

The study was conducted at the Department of Clinical Sciences at Manchester Royal Infirmary. Adult (aged >16 years) autopsy reports from 1 January to 30 June 2017 were analysed retrospectively. Patient data extracted from the autopsy report included age, sex, cause of death and major underlying diseases. Ethical approval was not required for this study, as no identifiable patient information was collected.

First, the gross description of individual organs in the initial macroscopic report were compared with microscopic findings in the final report and differences, if any, were classified using criteria adapted from Bernardi et al. (Table 1). This part of the study

### Table 1. Classification of agreement between the gross and microscopic description of organ pathology; criteria adapted from Bernardi et al.6

| Category       | Class | Definition                                                                 | Examples                                                                                           |
|----------------|-------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|
| Concordant     | 1a    | Absolute agreement between gross and microscopic diagnosis (organs assumed to be unremarkable if omitted from final report) | Confirmation of a gross diagnosis of pulmonary oedema                                               |
|                | 1b    | Microscopic examination refined the gross diagnosis                        | Subclassification of malignancy                                                                   |
| Discordant     | 2     | Disagreement between gross and microscopic diagnosis                        | Gross diagnosis of bronchopneumonia revised to pulmonary oedema                                     |
| Histopathology | 3a    | Indeterminate gross examination: histopathology required for diagnosis     | Myocardial mottling diagnosed as myocardial infarction (with estimate of duration)                |
|                | 3b    | Unremarkable gross examination: histopathology required for diagnosis      | Grossly unremarkable lung subsequently diagnosed with pulmonary oedema                             |
| Autolysed      | 4     | Autolysis prevented meaningful microscopic interpretation                   |                                                                                                    |
was limited to brain, heart, kidney, liver, lung and spleen, as other organs were sampled only very rarely. Differences between gross and microscopic diagnoses were classified as concordant, discordant, histology needed or autolysed. Diseases that are normally visible to the naked eye were categorised as ‘concordant’ or ‘discordant’ according to agreement with microscopic observations, whereas microscopic identification of diseases that are not normally visible to the naked eye were categorised as ‘histology needed’ (with indeterminate gross findings or unremarkable gross findings).

Secondly, revisions made to the cause of death following histopathology were classified according to the manner of alteration (Table 2). In this part of the study, samples from any organ were considered. When the cause of death was unascertained at gross examination, the extent to which histopathology contributed was interpreted in context of the full autopsy report. All autopsies and subsequent histopathological analyses were undertaken or supervised by a consultant pathologist.

**STATISTICAL ANALYSIS**

Autopsy reports were accessed using the MasterLab system and extracted data were recorded on an anonymised Excel spreadsheet. Statistical analysis was undertaken using SPSS statistics software. A comparison was made between the documented cause of death in provisional and final autopsy reports to calculate the sensitivity \[\text{true-positives}/(\text{true-positives} + \text{false-negatives})\] and positive predictive value \[\text{true-positives}/(\text{true positives} + \text{false-positives})\] per condition. Exact binomial 95% confidence intervals were calculated for all sensitivities and PPV. True-negatives and specificity calculations would be arbitrary in this context, as the number of pathological diagnoses absent in any given patient cannot be defined. The 10th revision of the International Classification of Diseases (ICD-10)\(^{14}\) was used to categorise causes of death into relevant system-specific groups.

**Results**

A total of 532 adult autopsies were undertaken between 1 January and 30 June 2017. All autopsies were coronial; no consented autopsies were requested during this period. Histopathology was taken in 141 cases (26.5%), which were included in the study without any other exclusions. The number of samples taken per autopsy ranged from one to 26 (mean = 9; mode = 10); 1315 samples were taken in total. The male to female ratio was 1.75:1, with a mean age of 63 years (range = 16–95). Logistic regression analysis for age and sex associated with each class alteration was not statistically significant.

### Table 2. Classification of alterations made to the cause of death following histopathology

| Class | Definition | Examples |
|-------|------------|----------|
| I     | Histopathology provided or altered the direct (part I) cause of death | Bronchopneumonia revised to pulmonary hypertension |
| II    | Histopathology provided or altered the indirect (part II) cause of death | Identification of underlying cirrhosis that contributed to death |
| III   | Histopathology concordant with the cause of death and provided additional information | Subclassification of malignancy |
| IV    | Histopathology concordant with the cause of death and provided supportive evidence | Confirmation of a gross diagnosis of bronchopneumonia |
| V     | Histopathology was not clearly relevant to the documented cause of death | Incidental findings; sampling of uninvolved organs |
| VI    | Cause of death inconclusive | |

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diagnose lung tissue, 85.8% of diagnoses had been grossly unremarkable, compared to 39.6 and 45.2% for kidney and heart, respectively. The highest rates of overall concordance were demonstrated for brain (80.5%) and spleen (77.1%).

ALTERATIONS MADE TO THE CAUSE OF DEATH FOLLOWING HISTOPATHOLOGY

In the second part of the study we classified alterations made to the cause of death following histopathology (Table 4). In 45.4% of cases, histopathology brought about a revision to the direct cause of death (class I) and a revision to the indirect cause of death (class II) in an additional 7.1%. In 37.9% of cases histopathology provided information concordant with the provisional cause of death: 9.2% of cases yielded additional information about the cause of death (class III) and 27.7% corroborated the gross findings (class IV). In 9.2% of cases histopathology was not relevant to the cause of death (class V).

The most common diseases responsible for altering the cause of death following histopathological examination (classes I and II) were bronchopneumonia and primary malignancy (Table 5). Other causes of pneumonia were aggregated and included in Table 5: two cases each of lobar, interstitial and aspiration pneumonia. False-negative diagnoses at gross examination account for the majority of alterations across all diseases. Considering bronchopneumonia and other causes of pneumonia together, false-negative diagnoses occurred in 29 of 32 of gross autopsy reports. Three false-positive diagnoses were made of bronchopneumonia and two of primary malignancy.

Primary malignancy and bronchopneumonia were the most frequently documented cause of death overall (i.e. across all classes of alteration). Comparing the provisional and final autopsy reports revealed the number of true-positive, false-negative and false-positive findings for each disease, permitting calculation of sensitivity and positive predictive value (Table 6). Primary malignancy had a sensitivity of 74% [confidence interval (CI) = 0.59–0.86] and bronchopneumonia had a sensitivity of 45% (CI = 0.29–0.62). Of the 32 true-positive cases of primary malignancy, histopathology provided the specific tumour subtype in 13 cases.

All diseases documented as a cause of death in the provisional and/or final autopsy report were grouped by ICD-10 classification (Table 7). As some cases had

| Table 3. Frequency of organ diagnoses (% of total) for each classification |
|-----------------------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Organ          | Total diagnoses (n) | 1a. Concordant, n (%) | 1b. Concordant, n (%) | 2. Discordant, n (%) | 3a. Histology needed, n (%) | 3b. Histology needed, n (%) | 4. Autolysed, n (%) |
| Brain          | 41              | 28 (68.3)        | 5 (12.2)          | 0              | 2 (4.9)           | 6 (14.6)         | 0              |
| Heart          | 110             | 46 (41.9)        | 22 (20)           | 9 (8.2)        | 17 (15.5)         | 14 (12.8)        | 2 (1.8)        |
| Kidney         | 72              | 22 (30.6)        | 9 (12.5)          | 1 (1.4)        | 23 (31.9)         | 15 (20.9)        | 2 (2.8)        |
| Liver          | 91              | 28 (30.8)        | 37 (40.7)         | 3 (3.3)        | 9 (9.9)           | 9 (9.9)          | 5 (5.5)        |
| Lung           | 320             | 127 (39.7)       | 64 (20)           | 37 (11.6)      | 13 (4.1)          | 79 (24.7)        | 0              |
| Spleen         | 35              | 12 (34.3)        | 15 (42.9)         | 3 (8.6)        | 3 (8.6)           | 0              | 2 (5.7)        |

Table 4. Documented alterations made to the cause of death following histopathology

| Class | Frequency | Percentage |
|-------|-----------|------------|
| I     | 64        | 45.4       |
| II    | 10        | 7.1        |
| III   | 13        | 9.2        |
| IV    | 39        | 27.7       |
| V     | 13        | 9.2        |
| VI    | 2         | 1.4        |

Table 5. The most common diseases responsible for altering the cause of death following histopathology

| Disease              | n (AF) | FN | FP |
|----------------------|--------|----|----|
| Bronchopneumonia     | 26     | 22 | 4  |
| Primary malignancy   | 13     | 11 | 2  |
| Other pneumonia*     | 6      | 6  | 0  |

AF, Autopsy findings; FN, False negative diagnoses; FP, False positive diagnoses.
*Two cases each of lobar, interstitial and aspiration pneumonia.
more than one ICD cause of death, the summed frequencies exceed the total number of autopsies. ICD chapters where there were no deaths are omitted: these include mental and behavioural disorders, diseases of the eye and ear and conditions related to pregnancy and the perinatal period.

Respiratory and circulatory diseases were each included in more than 50% of all cases, followed by neoplasms in 31.9% of cases. This reflects UK mortality data recorded by the Office for National Statistics.\textsuperscript{15}

Diseases of the digestive system were implicated in 17.7% of all deaths, and all other ICD chapters accounted for less than 13% each. Figure 1 displays the number of cases occurring in each ICD-10 category for all classes of alteration, and for classes I and II together.

In 71 cases the cause of death was unascertained following gross examination. The final causes of death in such cases were predominantly cardiac ($n=34$) and respiratory ($n=36$) disease. The direct cause of death was determined by histopathological examination in 56.3% of cases when a provisional cause of death was unascertained ($n=40$). Toxicology had been taken in 20 of these cases. When an interim cause of death was provided, histopathology altered the direct cause of death in 33.8% of cases ($n=24$).

Table 6. Sensitivity and PPV of the most common diseases found at autopsy across all classes of alteration

| Disease                  | $n$ (AF) | TP | FN | FP | Sensitivity | 95% CI     | PPV | 95% CI     |
|--------------------------|----------|----|----|----|-------------|------------|-----|------------|
| Primary malignancy       | 45       | 32 | 11 | 2  | 0.74        | 0.59 - 0.86| 0.94| 0.93 - 0.95|
| Bronchopneumonia         | 44       | 18 | 22 | 4  | 0.45        | 0.29 - 0.62| 0.82| 0.76 - 0.86|

AF, Autopsy findings; TP, True positive diagnoses; FN, False negative diagnoses; FP, False positive diagnoses; CI, Confidence interval; PPV, Positive predictive value.

Table 7. All causes of death grouped by ICD-10 chapter

| ICD-10 chapter | Number of reports (% total, $n=141$) |
|----------------|--------------------------------------|
| I. A00–B99: Certain infectious and parasitic diseases | 11 (7.8) |
| II. C00–D48: Neoplasms | 45 (31.9) |
| III. D50–D89: Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism | 1 (0.7) |
| IV. E00–E90: Endocrine, nutritional and metabolic diseases | 14 (9.9) |
| VI. G00–G99: Diseases of the nervous system | 4 (2.8) |
| IX. I00–199: Diseases of the circulatory system | 73 (51.8) |
| X. J00–J99: Diseases of the respiratory system | 84 (59.6) |
| XI. K00–K93: Diseases of the digestive system | 25 (17.7) |
| XII. L00–L99: Diseases of the skin and subcutaneous tissue | 1 (0.7) |
| XIII. M00–M99: Diseases of the musculoskeletal system and connective tissue | 1 (0.7) |
| XIV. N00–N99: Diseases of the genitourinary system | 8 (5.7) |
| XVII. Q00–Q99: Congenital malformations, deformations and chromosomal abnormalities | 1 (0.7) |
| XIX. S00–T98: Injury, poisoning and certain other consequences of external causes | 18 (12.8) |

As some causes of death include more than one ICD-10 category, the sum of frequencies does not add up to 100%. Chapters where there were no deaths are omitted from the table. ICD-10, International Classification of Diseases 10th Revision.

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Discussion

Rates of histopathological examination at autopsy are highly variable, and the low rates in many jurisdictions may limit the quality of autopsy reports and educational opportunities. In this study, microscopic examination revealed pathology in organs with no gross evidence of disease, predominantly demonstrated in the lung (24.1%), kidney (20.9%) and heart (12.8%). The greatest proportion of positive gross diagnoses changed by microscopy were in the lung (11.6%), which is consistent with other studies showing high rates of discrepancy between gross and microscopic lung pathology.

We included tissue samples from organs that were grossly unremarkable to reduce bias towards obviously diseased tissue. The highest rate of concordance was observed in the brain, and conveys an agreement between unremarkable gross and microscopic findings in 73% of cases. Confirmation of negative findings can be as valuable in determining the cause of death as confirmation or clarification of positive diagnoses.

The brain is not always examined if a definite cause of death is identified in the other organs, especially an acute cause such as massive pulmonary thromboembolism – but again, practice is very variable. A specialist neuropathologist is rarely involved in the gross or microscopic examination of brain tissue as the coroner does not require a specific pathological diagnosis of a natural cause of death, such as a known neurodegenerative disease following its natural course. Although evidence of specific inheritable neurological diseases (e.g. familial Alzheimer’s disease) may be particularly valuable to families, such diagnoses are usually made clinically and might not be investigated by the coroner unless an unnatural cause of death was suspected.

Two potentially notifiable diseases were first identified by microscopy: one each of tuberculosis (TB) and necrotising fasciitis. In the first example, silicosis was reported as the direct cause of death following gross examination, which was revised to tuberculosis and silicosis following histopathology. In the case of necrotising fasciitis, the cause of death was unascertained at gross examination and the autopsy report described an ‘erythematous surgical incision’. A skeletal muscle sample was taken from the surgical site at autopsy and described microscopically as showing ‘extensive necrosis and polymorphic neutrophilic aggregates’. This was considered alongside samples of lung tissue showing ‘thrombotic inflammatory emboli and intra-alveolar haemorrhage’. It is unclear whether a systemic infection was recognised in life, but the microscopic findings provide evidence of an acute infectious cause of death.

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Figure 1. ICD-10 classification of autopsy reports. The total number of autopsy reports per ICD-10 disease classification are shown with the proportion of reports documented as classes I and II alterations. The total number of reports exceeds the total number of classes I and II alterations (n = 74), as multiple disease classifications were included in the cause of death. ICD-10, International Classification of Diseases 10th Revision.
In the second part of the study we found that histopathology brought about a revision to the direct cause of death in 45.4% of cases. Other studies have produced similar results: Humex et al.\(^7\) demonstrated a 50% discordance between gross and microscopic cause of death, and Langlois\(^1,6\) found that histopathology provided, altered or confirmed a cause of death in 53% of cases.

Lung disease and malignancy (in any organ) were frequently responsible for altering the direct cause of death. Ascertaining a cause of death of bronchopneumonia by gross examination demonstrated the lowest sensitivity at 45% (95% CI = 0.29–0.62), reflecting the findings of Langlois\(^1,6\) and Kuipers et al.\(^1\) Accurately elucidating lung pathology from gross examination alone is notoriously difficult, and has a similarly poor clinicopathological correlation.\(^2,17,18\)

Microscopic classification of malignancy is necessary to assess efficacy of clinical diagnostic techniques and may provide information about cancers with familial inheritance patterns or related to industrial exposures.

Another interesting example of lung pathology was documented in this study, whereby acute pneumonitis was corrected to acute pneumonitis with amiodarone reaction. This correction must have been interpreted in context of the patient’s medical history, and highlights the importance of utilising histopathology alongside clinical information.

Toxicological samples had been taken in 46 autopsies in total. A toxicological cause of death was identified in 10 of these cases, although negative toxicology results may have also informed the diagnosis of cause of death. The extent to which toxicology may have contributed to the documented cause of death has not been fully explored in this study, and it should be noted that toxicology is sometimes taken at the request of the coroner to assess whether the individual was intoxicated prior to committing the act leading to death, rather than to explore the possibility of deliberate or accidental poisoning. The exploration of certain conditions, such as diabetes mellitus, for instance, may benefit from a combination of toxicology and histopathology, allowing clinicopathological correlation of glycaemic control and evidence of organ damage.

The declining use of histopathology at autopsy can impact the education of pathology trainees and influence the sampling habits of consultant pathologists. Inadequate exposure may lead to undervaluing of histopathology or diminished confidence in interpreting cadaveric tissue. Multidisciplinary mortality meetings present an opportunity to discuss clinicopathological correlation with students and clinicians but, anecdotally, pathologists are often not invited to attend. Although the attendance of a pathologist is now mandatory at cancer multidisciplinary team meetings, the primary aim of the meeting is to determine the treatment and prognosis of living patients, with an emphasis on reviewing radiological findings and other clinical investigations. They rarely, if ever, allow sufficient time for discussion of deaths. These meetings are an underutilised resource where information gained at autopsy, and especially discrepancies between clinical and autopsy diagnoses, could inform future clinical decision making, and so improve diagnostic accuracy.\(^19,22\)

Indeed, a relationship between autopsy rate and diagnostic accuracy was identified by Shojania et al.\(^,\) finding that major clinical errors decreased at a rate of 12.4% (95% CI = 7.0–17.6) for every 10% increase in autopsy rate.\(^22\)

The autopsy is essential in many contexts, permitting early identification of adverse events in novel therapeutic treatment\(^23\) and informing clinical management of infectious disease outbreaks.\(^24,25\)

Although the vast majority of autopsies undertaken in England, Wales and Northern Ireland are at the request of the coroner, the responsibility of the coroner to inform academic and public health interests is contentious.\(^26,27\) The quality that pathologists should aim to achieve in context of coroner’s autopsy is unclear, and there is a longstanding need to reconcile expectations of the coroner and RCPPath guidelines.\(^5,10,12\)

Pathologists report multiple administrative and self-imposed barriers preventing compliance with RCPPath histopathology guidelines, including time pressures, poor renumeration and concerns surrounding the Human Tissue Act.\(^5,12\) Moreover, the coroner may not grant permission to take histopathology even when deemed necessary by the pathologist.\(^27\)

Realistic guidelines are needed to support pathologists and give due consideration to the value of histopathological sampling. Given that autopsies are predominately coronial, there needs to be a frank assessment of whether they can meet public health requirements and support the needs of the medical profession and patient relatives. If we cannot improve medical practice from within the coronial system, medical professionals will need to look elsewhere to fulfil these needs.

**Limitations**

There are several limitations to this study. The cases studied were performed more than 3 years ago, mainly because of the low priority accorded to the completion of toxicology results may have also informed the diagnosis of cause of death, and there is a longstanding need to reconcile expectations of the coroner and RCPPath guidelines.\(^5,10,12\)
of autopsy histology due to the pressures of work with living patients. We think our conclusions remain valid, because there have been no changes of practice in the intervening period (aside from those associated with the coronavirus pandemic). We only collected data from autopsies where histopathology was taken, introducing an obvious selection bias. The decision to take histopathology was not systematic, being at the discretion of individual pathologists with different levels of experience and educational backgrounds. Although sampling was not conducted systematically, it is representative of the routine practices in our department and in many other hospitals. Reassuringly, there was no bias of age or gender within our sample, and the distribution of ICD-10 causes of death reflect UK mortality statistics.\textsuperscript{15}

When a provisional cause of death was unascertained, the full autopsy report was considered to determine whether microscopy was able to provide a final cause of death. The varying quality of autopsy reports and possible omission of pertinent findings presented challenges in data collection. In such cases, histopathology may have influenced a pathologist’s decision-making more than is evident in the report, or the contribution of histopathology may have been overestimated if gross findings in the provisional report were sparse. Of note, toxicology was taken in 58% of cases where a cause of death was unascertained, although toxicology is usually taken at request of coroner, and not according to the pathologist’s judgement.

A prospective study may be valuable and could include documentation of a pathologist’s decision-making about the potential of histopathology in each case. This would also clarify the extent to which clinical and autopsy diagnosis and the value of post mortem histology: a meta-analysis and review. Histopathology 2005; 47: 551–559.

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