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Diagnosis of the cause of death without autopsy: can virtual autopsy with postmortem CT improve clinical diagnosis?

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Key Words

cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

List of abbreviations

95% CI	95% confidence interval
PMCT	postmortem CT

Abstract

Objective: To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

Design: Retrospective observational cohort study. Inclusion criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion criteria: forensic cases, organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as the standard of reference, we compared the correctly identified causes of death, types of pathology and anatomical system involved before and after virtual autopsy using McNemar tests.

Setting: Tertiary referral center.

Participants: 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

Intervention: PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

Primary and secondary outcome measures: The number of correctly identified causes of death, types of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved.

Results: Using PMCT, the number of correctly identified immediate causes of death increased from 53% (95% CI 41 to 64) to 64% (53 to 75) (p=0.05), type of pathology increased from 65% (54 to 76) to 83% (73 to 91) (p=0.001) and the identification of the anatomical system increased from 65% (53 to 75) to 84% (74 to 92) (p=0.001).

Conclusion: While postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy would be desired but is turned down by the deceased's relatives.

Article summary

Strengths and limitations of this study

- In light of decreased autopsy rates, this study investigated whether virtual autopsy with postmortem CT improves clinical diagnosis of the immediate cause of death, with autopsy as the reference standard, rather than only describing the diagnostic accuracy of postmortem CT.

- In addition to scoring the type of pathology and anatomical system involved, the diagnostic accuracy of a detailed immediate cause of death diagnosis was investigated.

- Retrospective observational cohort study, with relative small sample sizes per type of pathology and anatomical system.

- Cause of death was not a categorical variable, so specificity for immediate cause of death diagnosis could not be calculated.

Contributors: LJPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS and WMK interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors revised the manuscript for intellectual content.

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Competing interests: All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

Data sharing: Details on how to obtain additional data from the study (eg, statistical code, datasets) are available from the corresponding author.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Introduction

Autopsies are regarded as the 'gold standard' in quality monitoring of health care. It is therefore remarkable that in a time of heightened interest in patient safety, error prevention and healthcare quality, worldwide autopsy rates continue to decline from roughly 40% in the nineteen sixties, to below 10% nowadays [1-7]. Both religious and emotional objections against the invasiveness of conventional autopsies, both by the relatives and the doctors, are considered as some of the reasons for this decline. At present, determination of the cause of death relies heavily on clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the last decades, major error rates of approximately 25% for the primary cause of death have not substantially decreased [8,9]. Accuracy rates of clinical diagnoses of the immediate cause of death are probably even lower [10,11]. Therefore, there is a need to improve clinical diagnoses using techniques that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have shown that, as yet, PMCT is insufficient to substitute for conventional autopsy [12,13]. This study investigates whether virtual autopsy with PMCT improves clinical diagnosis of the immediate cause of death.

Material and methods

Study design

All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-abdomen autopsy, were excluded. Informed consent was obtained from the relatives for PMCT and autopsy. This retrospective study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

PMCT and conventional autopsy

PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s. PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting, interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single consensus report, all with minimal previous experience in interpreting PMCT images. Conventional autopsy consisted of thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic and microscopic inspection. Radiologists and pathologists were blinded to each other's results, and compiled a report based on their own findings and the clinical information present on the requisition form.

Data collection

For each cadaver the immediate cause of death, type of pathology and anatomical system involved, were collected in retrospect at three moments: before virtual autopsy, after virtual autopsy and

based on autopsy findings. The cause of death before virtual autopsy was based on clinical findings only. The cause of death after virtual autopsy was based on both clinical findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was based on clinical findings only. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of death.

Type of pathology was scored according to the following categories; infection, hemorrhage, perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with hemopericardium were grouped in the hemorrhage category. The type of anatomical system was scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and subcategories used were derived from the classifications of anatomical regions and groups of pathologies as used by Roberts and Wichmann et al. [4,12].

Statistical analysis

The number of correctly identified causes of death, type of pathology and anatomical system were calculated with autopsy as the standard of reference. Sensitivity and specificity were calculated for type of pathology and anatomical system subgroups. Cases where the outcome was not assigned after autopsy were excluded from statistical analysis. McNemar tests (2-sided) were used to test for significant differences before and after virtual autopsy. Logistic regression analysis was performed to evaluate the influence of radiologists' experience. P values of 0.05 or less were considered significant. IBM SPSS Statistics, version 22 was used.

Results

Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on 78 (4%) cadavers. One case was excluded due to organ donation prior to PMCT. A further nine out-of-hospitals deaths on which PMCT and autopsy were performed, but who were not clinically examined in our hospital or by our emergency medical service, were included, leading to a total of 86 cases (51 men, 35 women, with a mean age of 59 years). 54% of the deaths were after a resuscitation attempt. The mean postmortem interval between death and PMCT was 11 hours. In 69% there was no consent for brain autopsy and, in those cases, conventional autopsy consisted of a thorax-abdomen examination only.

An immediate cause of death was not found by autopsy in ten cadavers (12%). In 29 (34%) cadavers the immediate cause of death was not assigned before virtual autopsy, and not in seventeen (20%) cadavers after virtual autopsy. In two of the cases without an immediate autopsy cause of death, an intracerebral hemorrhage and a pulmonary embolism (Figure 1A), there was consensus between the clinicians and the radiologists as for the cause of death. In the first case, there was lack of consent to a brain autopsy and in the second case, the pulmonary embolism was not diagnosed at autopsy. In two other cases with unknown cause of death at autopsy, aspiration and heart failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. Both before and after PMCT, the cause of death was unknown in the remaining six cases.

The additional value of PMCT

The number of correctly identified causes of death before virtual autopsy was 53% (95% CI: 41-64%) and increased to 64% (95% CI 53-75%) after performing a PMCT scan. This improvement was statistically significant (p=0.05). The potential value of PMCT increased further, when PMCT was used to indicate the type of pathology (p=0.001) or anatomical system (p=0.001) involved in the cause of death. The number of cases in which type of pathology was correctly identified increased from 65%

(95% CI: 54-76) to 83% (95% CI: 73-91), and from 65% (95% CI: 53-75) to 84% (95% CI: 74-92) for anatomical system (Table 1).

Evaluation of cause of death, per type of pathology

Table 2 shows all autopsy causes of death, classified by type of pathology and whether they were correctly appointed as cause of death before and after PMCT.

Pneumonia was the most common infectious cause of death. After PMCT, pneumonia was correctly diagnosed and assigned as the cause of death in 73%. In the other 27%, pneumonia was recognized, but not assigned as the cause of death. In two other patients, who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly assigned as the cause of death on PMCT. Using PMCT, two cases of peritonitis (due to a misplaced gastrostomy button and ventriculoperitoneal drain) and one case of pancreatitis, which were clinically missed, were correctly diagnosed as cause of death. In one case, pneumonia was correctly diagnosed as cause of death after PMCT, where clinicians had incorrectly attributed death to interstitial lung disease.

In the group of perfusion disorders, all pulmonary embolisms were diagnosed at PMCT as cause of death. Furthermore, radiologists correctly diagnosed two arrhythmias, one heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac arrhythmia was suspected based on local hyperdensity of myocardial tissue corresponding to fibrosis and, in the other case, heart failure was based upon secondary characteristics, such as dilated atria and pleural effusion, in the absence of other significant findings. Myocardial infarction was correctly diagnosed as cause of death in 44% after PMCT. However, in 71% of these cases, radiologists did not appoint a cause of death, mostly due to absence of significant findings, and myocardial infarction as the cause of death was based on clinical findings only. In the other 29% (n=2), myocardial infarction was also suspected by the radiologists; in one case due to an intravascular hypodensity proximal of a coronary stent and in the other case due to the combination of significant coronary calcifications, enlarged right atrium, clinical history and absence of other significant findings.

Using PMCT, hemorrhagic causes of death were correctly diagnosed in 85%. All five aortic dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed hemothorax and a liver and kidney rupture (Figure 1B). In another traumatic case were death was attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left coronary artery (Figure 1C).

In the category of other pathologies, PMCT showed an esophageal mass which was determined by conventional autopsy as the primary tumor in a case with cerebral metastases where the primary tumor was clinically unidentified. Two other cases of metastasized cancer (esophageal and breast) were both before and after PMCT correctly diagnosed as cause of death. Three other cases with cancer at time of death died from complications (septic cholecystitis, carotid artery bleeding and endocarditis due to immunodeficiency).

Sensitivity and specificity for type of pathology and anatomical system subgroups

Based on type of pathology, the subgroup of perfusion disorders showed a significant improvement (p=0.04) in sensitivity from 56% to 76%, using PMCT (Table 3). When categorized based on anatomical system, the cardiovascular subgroup showed a significant improvement (p=0.02) in sensitivity from 62% to 82%. There were no significant differences in specificity within the subgroups before and after PMCT.

Performance of radiologists

Logistic regression analysis showed no trend in the number of correctly identified causes of death (p=0.41), type of pathology (p=0.81) or anatomical system (p=0.41) as diagnosed by the radiologists, over the four years of initial experience in interpreting PMCT images.

Discussion

The number of correctly identified clinical diagnosis of the immediate cause of death increased from 53% to 64% (p=0.05) after performing PMCT, using conventional autopsy as the reference standard. Our analysis showed that the value of PMCT is variable per subcategory and depends on the cause of death. Where infections played a role, the added value of PMCT is moderate. Normal postmortem changes, such as the occurrence of pulmonary edema, could mask pneumonia (Figure 1D) [14]. In the subgroup of perfusion disorders, pulmonary embolisms, as diagnosed by radiologists, were not confirmed during autopsy in three of the six cases (Figure 1A). This could be due to difficulty to distinguish an ante-mortem thrombus from a post-mortem blood clot with PMCT, or the possibility that the embolus was lost during the autopsy procedure [15-17]. There were no false-negative findings for pulmonary embolisms as cause of death on PMCT. Furthermore, most causes of death in this subgroup were cardiac related. Clinicians are restricted in their ability to differentiate a cause of death, for example, cardiac malfunction, significant internal bleeding, aortic dissection or pneumothorax, due to the acute nature and time constraints of the situations (resuscitation setting) these patients present with. Cardiac causes of death are also difficult to diagnose with PMCT and by autopsy. For example, heart failure and cardiac arrhythmias are clinically diagnosed by means of dynamic examinations, such as echocardiography and electrocardiography. Postmortem angiography, now being developed and validated, can be effective in demonstrating any obstructing thrombi [18]. Autopsy can only detect a myocardial infarction in cases where patients have survived two to three hours post-infarction [19]. However, when secondary characteristics, such as dilated atria, or pulmonary edema are observed in the absence of other significant pathologies, both PMCT and autopsy can indicate a cardiac cause of death.

Table 1 shows increasing value of PMCT in identifying the type of pathology or anatomical system involved, indicating that even when the cause of death is inconclusive after PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential diagnostic possibilities. This particularly applies to cardiac causes of death, as shown by the significant increase in sensitivity

for perfusion disorders as type of pathology and the cardiovascular system as anatomical system involved (Table 3). Clinical evaluation of the cause of death often indicates the failing system (for example, respiratory failure) rather than the underlying illness or structural changes, whereas radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

Amongst non-invasive techniques, Blokker et al. conclude that PMCT and postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing somewhat better when only one of the modalities is used [12,13]. PMCT is less expensive than a conventional autopsy, however, cost-effective analyses have not been formulated. Images can be stored digitally (useful for legal or educational purposes) and results can be audited and promptly reviewed by one or more radiologists. Amongst minimally invasive methods, the highest performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with targeted coronary angiography, showed a sensitivity of 92% for cause of death [17]. Two studies combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for cause of death [20,21].

To our knowledge this is the second study which has investigated the additional value of PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths [22]. This is somewhat higher than we found in our study, one reason could be the fact that less specific causes of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some use broadly defined categorizations and others use well-defined specific causes of death, or some use the immediate cause of death and others the intermediate or underlying cause of death, or do not state their definition of cause of death at all. Furthermore, most previous studies consisted of small sample sizes (n<50) and used different study populations, different outcome parameters (for example, cause of death, major or minor diagnoses) and different parameters of accuracy [4,23-25]. A

large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32% in determining the cause of death with PMCT compared to autopsy [12]. Another study showed a sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in 101 cases [26]. This is in accordance with our results regarding the categorization of cause of death per type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause of death and 5/17=19% for a more specific description of the involved pathogenetic mechanism [23]. Another study by Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both definite and possible findings with PMCT as to cause of death [24]. The study by Puranik et al. supports our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT [25]. A sensitivity of 25% for cause of death was found in a population of seventeen young patients with sudden cardiac death.

Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure 1D), are more confidently diagnosed with PMCT than autopsy [12,27]. Therefore, the presented performance of PMCT will probably be underestimated in cases were pathologies are difficult to confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no longer be considered as the gold standard for all postmortem diagnoses, not only due to the limitations of dissection, but also due to the decline in the number of autopsies performed, leading to a decrease in pathologists' expertise. We would suggest a gold standard involving a multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective studies with larger sample sizes are required to investigate the additional value of PMCT in specific subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques, conventional autopsy will still be required in complex cases where clinical and radiological diagnosis as to cause of death is inconclusive.

Conclusion

While virtual autopsy with postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone. Even in cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.

References

1. Harrington DE, Sayre EA. Managed care and measuring medical outcomes: did the rise of HMOs contribute to the fall in the autopsy rate? *Soc Sci Med.* 2010;70(2):191-198.

2. Blokker BM, Weustink AC, Hunink MGM, Oosterhuis JW. Autopsy rates in the Netherlands: 35 years of decline. *PloS One.* 2017;12(6):e0178200.

3. Kretzschmar H. Brain banking: opportunities, challenges and meaning for the future. *Nat Rev Neurosci.* 2009;10(1):70-78.

4. Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Ann Intern Med.* 2012;156(2):123-130.

5. Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet.* 2007;369(9571):1471-1480.

6. Royal College of Pathologists of Australasia Autopsy Working Party. The decline of the hospital autopsy: a safety and quality issue for healthcare in Australia. *Med J Aust.* 2004;180(6):281-285.

7. Chariot P, Witt K, Pautot V, et al. Declining autopsy rate in a French hospital: physician's attitudes to the autopsy and use of autopsy material in research publications. *Arch Pathol Lab Med.* 2000;124(5):739-745.

8. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *JAMA.* 2003;289(21):2849-2856.

9. Kuijpers CC, Fronczek J, van de Goot FR, Niessen HW, van Diest PJ, Jiwa M. The value of autopsies in the era of high-tech medicine: discrepant findings persist. *J Clin Pathol.* 2014;67(6):512-519.

10. Attems J, Arbes S, Bohm G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wien Med Wochenschr.* 2004;154(7-8):159-162.

11. Ermenc B. Comparison of the clinical and post mortem diagnoses of the causes of death. *Forensic Sci Int.* 2000;114(2):117-119.

12. Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet.* 2012;379(9811):136-142.

13. Blokker BM, Wagensveld IM, Weustink AC, Oosterhuis JW, Hunink MG. Non-invasive or minimally invasive autopsy compared to conventional autopsy of suspected natural deaths in adults: a systematic review. *Eur Radiol.* 2016;26(4):1159-1179.

14. Klein WM. The common pattern of postmortem changes on whole body CT scans. *JOFRI.* 2016;4:47-52.

15. Jackowski C, Thali M, Aghayev E, et al. Postmortem imaging of blood and its characteristics using MSCT and MRI. *Int J Legal Med.* 2006;120(4):233-240.

16. Ross SG, Bolliger SA, Ampanozi G, Oesterhelweg L, Thali MJ, Flach PM. Postmortem CT angiography: capabilities and limitations in traumatic and natural causes of death. *Radiographics.* 2014;34(3):830-846.

17. Rutty GN, Morgan B, Robinson C, et al. Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy for coroner-requested post-mortem investigations: a prospective, masked, comparison study. *Lancet.* 2017;May24. [Epub ahead of print]

18. Grabherr S, Grimm J, Baumann P, Mangin P. Application of contrast media in post-mortem imaging (CT and MRI). *Radiol Med.* 2015;120(9):824-834.

19. Kubat K, Smedts F. The usefulness of the lactate dehydrogenase macroreaction in autopsy practice. *Mod Pathol.* 1993;6(6):743-747.

20. Ross SG, Thali MJ, Bolliger S, Germerott T, Ruder TD, Flach PM. Sudden death after chest pain: feasibility of virtual autopsy with postmortem CT angiography and biopsy. *Radiology.* 2012;264(1):250-259.

21. Bolliger SA, Filograna L, Spendlove D, Thali MJ, Dirnhofer S, Ross S. Postmortem imaging-guided biopsy as an adjuvant to minimally invasive autopsy with CT and postmortem angiography: a feasibility study. *AJR Am J Roentgenol.* 2010;195(5):1051-1056.

22. Inai K, Noriki S, Kinoshita K, et al. Postmortem CT is more accurate than clinical diagnosis for identifying the immediate cause of death in hospitalized patients: a prospective autopsy-based study. *Virchows Arch.* 2016;469(1):101-109.

23. Westphal SE, Apitzsch J, Penzkofer T, Mahnken AH, Knuchel R. Virtual CT autopsy in clinical pathology: feasibility in clinical autopsies. *Virchows Arch.* 2012;461(2):211-219.

24. Takahashi N, Higuchi T, Shiotani M, et al. The effectiveness of postmortem multidetector computed tomography in the detection of fatal findings related to cause of non-traumatic death in the emergency department. *Eur Radiol.* 2012;22(1):152-160.

25. Puranik R, Gray B, Lackey H, et al. Comparison of conventional autopsy and magnetic resonance imaging in determining the cause of sudden death in the young. *J Cardiovasc magn Reson.* 2014;16:44.

26. Ampanozi G, Thali YA, Schweitzer W, et al. Accuracy of non-contrast PMCT for determining cause of death. *Forensic Sci Med Pathol.* 2017;Jun15. [Epub ahead of print].

27. Dirnhofer R, Jackowski C, Vock P, Potter K, Thali MJ. VIRTOPSY: minimally invasive, imaging-guided virtual autopsy. *Radiographics.*2006;26(5):1305-1333.

Figure legends

Figure 1. Examples of discrepant imaging and autopsy findings.

A. A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

B. A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

C. A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

D. A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

Tables

Table 1. Number of correctly identified causes of death, types of pathology and anatomical system involved, before and after virtual autopsy with PMCT.

	Before PMCT (95% CI)	After PMCT (95% CI)	Significance (p-value)
Immediate cause of death Identified at CA (n=76)[a]	53% (41-64%)	64% (53-75%)	0.05
Type of pathology Identified at CA (n=78)[a]	65% (54-76%)	83% (73-91%)	0.001
Anatomical system Identified at CA (n=77)[a]	65% (53-75%)	84% (74-92%)	0.001

[a] Group sizes differ as autopsy was did not assign a cause of death in ten cases, a type of pathology in eight cases and anatomical system in nine cases.

Table 2. Overview of all autopsy causes of death, classified by type pathology and whether they were correctly diagnosed as the immediate cause of death before and after virtual autopsy. ***Incorrect causes of death, as diagnosed after virtual autopsy, are stated in italics.***

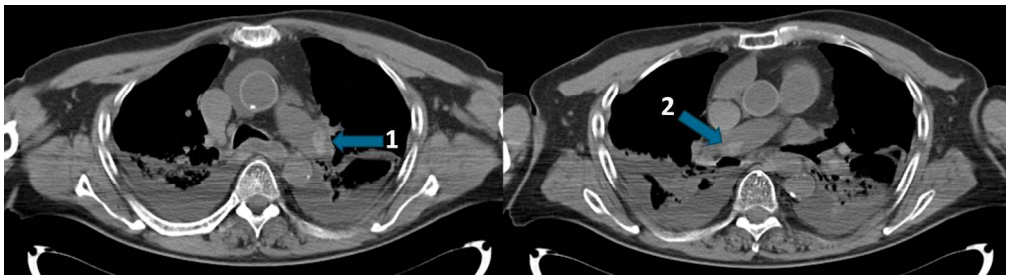
	Correct COD, both before and after PMCT.	**Incorrect COD before PMCT. Correct COD after PMCT.**	**Correct COD before PMCT. Incorrect COD after PMCT.**	**Incorrect COD, both before and after PMCT.**
Infections	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i.[b] 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis[a] 1x diverticulitis and pancreatitis	1x endocarditis *(pericarditis)* 1x HSV hepatitis *(urosepsis)* 1x cerebral aspergillosis *(pneumonia)*	4x pneumonia *(1x COPD, 1x PTLD, 1x fibrotic lung disease, 1x not assigned)* 1x endocarditis / pericarditis *(fistula ureter vs. bowel)*
Perfusion disorders	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure *(pneumonia)*	9x myocardial infarction *(7x not appointed, 1x mediastinitis, 1x pulmonary embolism)* 3x arrhythmia *(1x pulmonary embolism, 1x myocardial infarction, 1x not assigned* 2x heart failure *(1x pulmonary air embolism, 1x not assigned)* 1x pulmonary veno-occlusive disease *(not assigned)* 1x bowel ischemia due to adhesions *(infected aorta graft)*
Hemorrhages	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax *(coronary artery air embolism)* 1x liver and kidney rupture + hemothorax *(spleen rupture + hemothorax)*
Other	1x breast cancer 1x esophageal cancer 1x anaphylaxis 1x (auto-)intoxication	1x esophageal cancer		

[a] Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced ventriculoperitoneal drain in another case. [b] sepsis e causa ignota. COD: cause of death.

Table 3. Sensitivity and specificity per subgroup of type of pathology and anatomical system, diagnosed before and after virtual autopsy with PMCT.

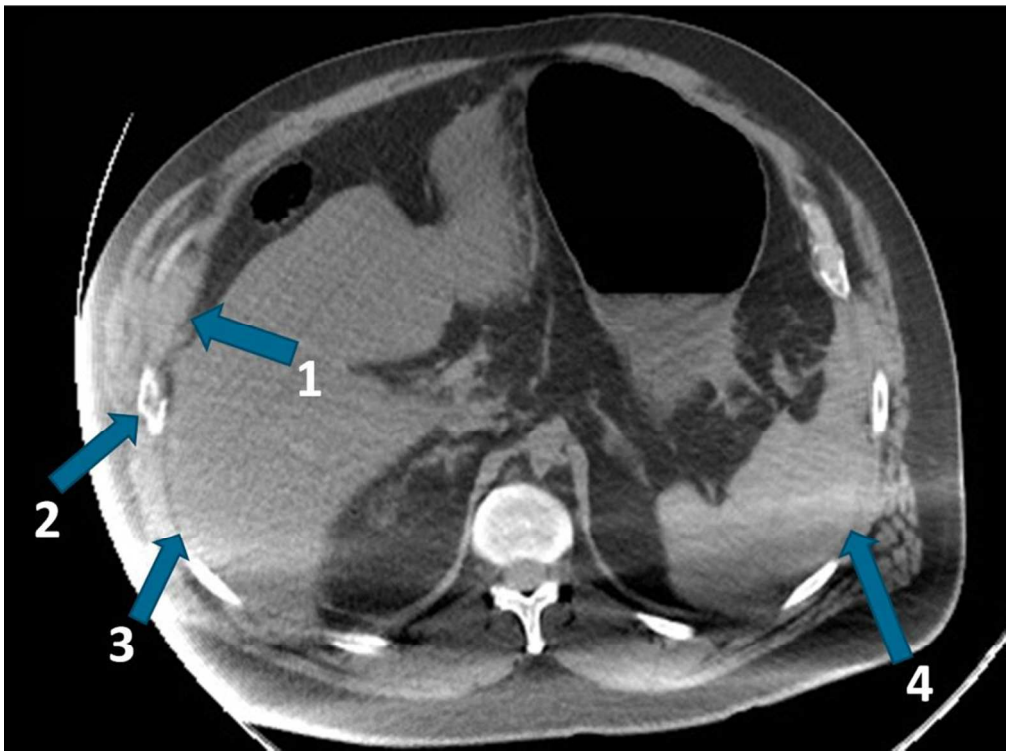
	Sensitivity			Specificity		
	Before PMCT	**After PMCT**	**Sign[a]**	**Before PMCT**	**After PMCT**	**Sign[a]**
A. Type of pathology (n=78)[c]						
1. Infection (n=26)	69%	85%	NS[b]	96%	92%	NS[b]
2. Hemorrhage (n=13)	69%	92%	NS[b]	98%	100%	NS[b]
3. Perfusion disorder (n=34)	56%	76%	0.04	95%	93%	NS[b]
4. Other (n=5)	100%	100%	N/A[d]	99%	99%	NS[b]
B. Anatomical system (n=77)[c]						
1. Pulmonary (n=18)	72%	89%	NS[b]	95%	95%	NS[b]
2. Cardiovascular (n=39)	62%	82%	0.02	100%	95%	NS[b]
3. Gastrointestinal (n=13)	54%	85%	NS[b]	98%	100%	NS[b]
4. Other (n=7)	86%	86%	NS[b]	97%	94%	NS[b]

[a] Significance (p-value). [b] NS: not significant. [c] Autopsy was not able to establish the type of pathology and anatomical system involved in eight and nine deaths respectively. [d] Not applicable.



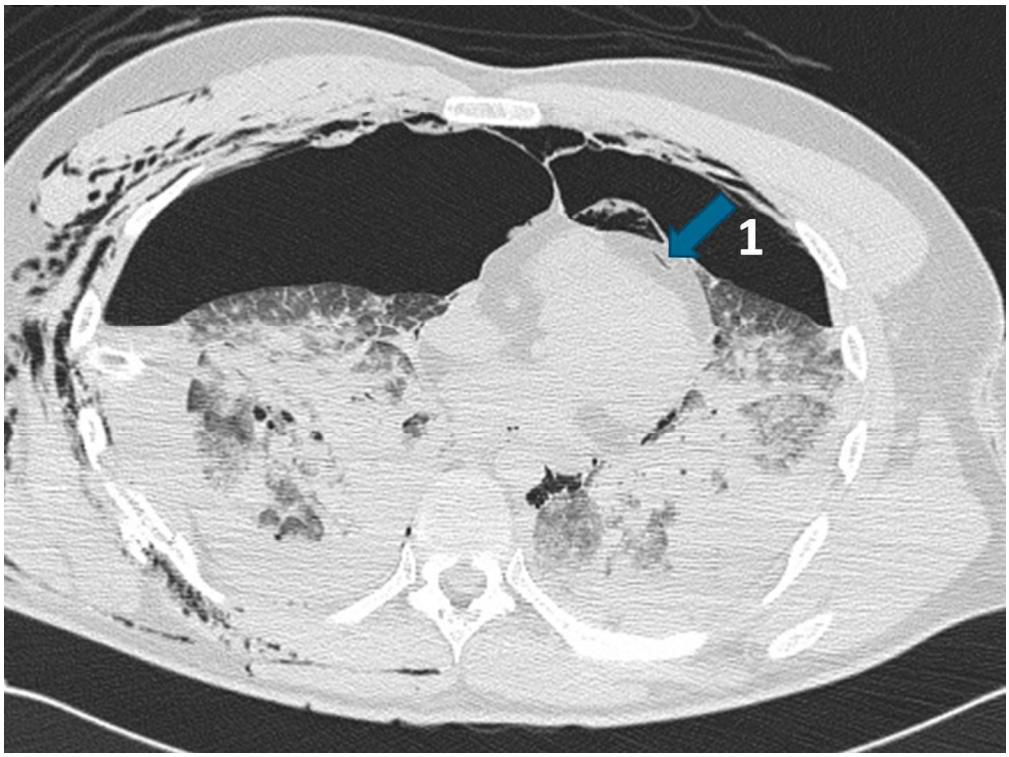
A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

757x203mm (96 x 96 DPI)



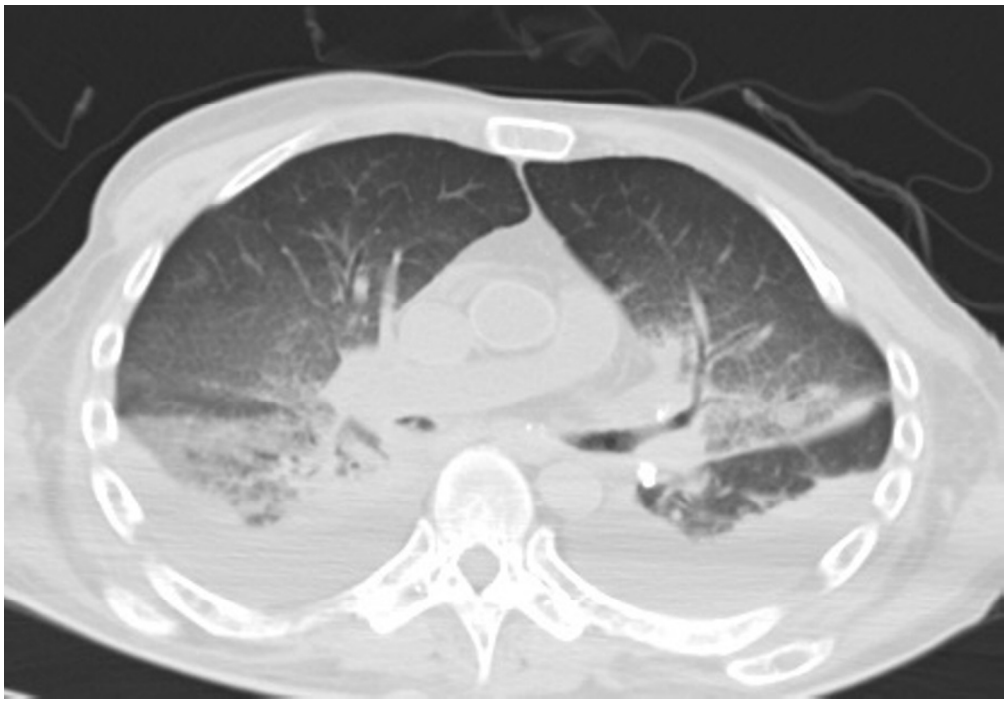
A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

268x200mm (96 x 96 DPI)



A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

380x284mm (96 x 96 DPI)



A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

241x166mm (96 x 96 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
Test methods	**10a**	Index test, in sufficient detail to allow replication	5
	10b	Reference standard, in sufficient detail to allow replication	5
	11	Rationale for choosing the reference standard (if alternatives exist)	5
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	5
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	6
	18	Intended sample size and how it was determined	
RESULTS			
Participants	**19**	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	7
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	7
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	20,22
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	20,22
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11-13
	27	Implications for practice, including the intended use and clinical role of the index test	13
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	15

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Pathology
Keywords:	Computed tomography < RADIOLOGY & IMAGING, cause of death, postmortem, autopsy, sensitivity, specificity

Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Study design: retrospective observational cohort study

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Key Words

cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

List of abbreviations

95% CI	95% confidence interval
COD	immediate cause of death
PMCT	postmortem CT

Abstract

Objective: To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

Design: Retrospective observational cohort study. Inclusion criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as the reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy using McNemar tests.

Setting: Tertiary referral centre.

Participants: 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

Intervention: PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

Primary and secondary outcome measures: Sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

Results: Using PMCT, the sensitivity for immediate cause of death increased from 53% (95% CI: 41 to 64) to 64% (53 to 75) (p=0.049), for type of pathology from 65% (54 to 76) to 83% (73 to 91) (p=0.001) and for anatomical system from 65% (53 to 75) to 84% (74 to 92) (p=0.001).

Conclusion: While postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

Article summary

Strengths and limitations of this study

- This study investigated the diagnostic performance for clinical cause of death determination by use of postmortem CT and takes into account the added value over clinical diagnosis alone.
- The immediate cause of death (i.e. direct cause of death) was the main outcome rather than the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical point of view, diagnosis and treatment of the immediate cause of death is the most urgent.
- The sensitivity for clinical cause of death determination, with and without postmortem CT, is investigated on multiple levels of precision; both the determination of the immediate cause of death as well as the involved type of pathology and anatomical location were investigated.
- The retrospective design in a tertiary care centre has probably introduced a selection-bias towards patients with diagnostic difficulties or unresolved issues, resulting in an underestimation of the diagnostic performance compared to more general causes of death.
- Subgroups for type of pathology and anatomical system were relatively small due to the unexpected low consent rate for postmortem CT in general, as well as in cases with consent for conventional autopsy.

Contributors: LJPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS, WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors revised the manuscript for intellectual content.

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Competing interests: All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

Data sharing: Details on how to obtain additional data from the study (eg, statistical code, datasets) are available from the corresponding author.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Introduction

Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is therefore remarkable that in a time of heightened interest in improving patient safety, healthcare quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the nineteen sixties, to below 10% nowadays.[1-7] Religious and emotional objections to the invasiveness of conventional autopsies, both by the relatives and the doctors, are considered as some of the reasons given for this decline. At present, determination of the cause of death relies heavily on clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the last decades, major error rates of approximately 25% have not substantially decreased.[8-10] According to the Goldman classification system, major errors are defined as clinically missed diagnoses related to the cause of death. In half of these cases this might have led to a change in therapy and prolonged survival, if known before death.[8] National mortality statistics are generally based on the primary cause of death (i.e. underlying cause or basic illness), which could be a longstanding, chronic disease.[11] However from an individual and clinical point of view, diagnosis and treatment of the immediate cause of death (i.e. direct cause of death) is the most urgent. Accuracy rates for immediate causes of death are probably lower than for underlying causes of death[12,13], due to time constraints of the often acute situations these diagnoses present with. The high error rates emphasize the need to improve clinical diagnoses using techniques that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have shown that as yet, PMCT is an insufficient substitute but can be used in adjunct to a conventional autopsy.[14,15] In order to provide answers and quality control also in cases without consent for conventional autopsy, we investigated whether virtual autopsy with PMCT improves clinical diagnosis of the immediate cause of death.

Material and methods

Study design

All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and conventional autopsy in all cases of death. This retrospective study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

PMCT and conventional autopsy

PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s. PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting, interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single consensus report. All radiologists had minimal previous experience in interpreting postmortem PMCT images, as postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted of thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic and microscopic inspection. Radiologists and pathologists were blinded to each other's results, but had otherwise full access to the electronic patient files. Radiologists and pathologists compiled a report based on their own findings and clinical findings.

Data collection

For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and anatomical system involved, were collected in retrospect at three moments: before virtual autopsy, after virtual autopsy and based on autopsy findings. The cause of death before virtual autopsy was based on clinical findings only. The cause of death after virtual autopsy was based on both clinical findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was based on clinical findings only. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of death.

Type of pathology was scored according to the following categories; infection, hemorrhage, perfusion disorder, other or uncertain (i.e. not assigned). Perfusion disorders comprised all cardiac and vascular perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with hemopericardium were grouped in the hemorrhage category. The type of anatomical system was scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and subcategories used were derived from the classifications of anatomical regions and groups of pathologies as used by Roberts and Wichmann et al.[4,14]

Statistical analysis

Sensitivity and specificity were calculated with conventional autopsy as reference standard. Cases where the outcome (cause of death, type of pathology or anatomical system) was uncertain after autopsy were excluded from statistical analysis. McNemar tests (2-sided) were used to test for significant differences in sensitivity or specificity before and after virtual autopsy. Logistic regression analysis was performed to evaluate radiologists' improvement in reporting PMCT-scans over the four years of initial experience. Odds ratios were calculated for each year of experience in reporting

PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS Statistics, version 22 was used.

Results

Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases, conventional autopsy consisted of a thorax-abdomen examination only.

Conventional autopsy, as standard of reference, was not able to assign an immediate cause of death in ten cadavers (12%)(Figure 1). Therefore, these cases were excluded of sensitivity and specificity analyses for cause of death.

The additional value of PMCT

The number of correctly identified causes of death before virtual autopsy was 53% (95% CI: 41-64%) and increased to 64% (95% CI 53-75%) after performing a PMCT scan. This improvement was statistically significant (p=0.049). The additional value of PMCT increased further, when PMCT was used to indicate the type of pathology (p=0.001) or anatomical system (p=0.001) involved in the immediate cause of death. The number of cases in which type of pathology was correctly identified increased from 65% (95% CI: 54-76) to 83% (95% CI: 73-91), and from 65% (95% CI: 53-75) to 84% (95% CI: 74-92) for anatomical system (Table 2). 2-by-2 tables of the number of correctly diagnosed immediate causes of death, type of pathology and anatomical system before and after PMCT are presented in Table 3.

Evaluation of cause of death, per type of pathology

Table 4 shows all autopsy causes of death classified by type of pathology and whether or not they were correctly appointed as cause of death before and after PMCT.

Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4), pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.

In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant findings. In the other case, heart failure was also based upon secondary characteristics, such as dilated atria and pleural effusion, in the absence of other significant findings. Myocardial infarction was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these cases, myocardial infarction was not visible on PMCT and diagnosis of myocardial infarction was based on the combination of clinical findings and absence of significant pathologies at PMCT. In the two other cases, myocardial infarction was also suspected at imaging; once due to an intravascular hypodensity proximal of a coronary stent, which might indicate a (fat) embolism, and once due to the combination of significant coronary calcifications, enlarged right atrium, clinical history and absence of other significant findings.

Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case were death was attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left coronary artery (Figure 4).

In the category of other pathologies, there were three patients who died from malignant disease. The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to (unidentified) brain metastases. There were three other cases with cancer at time of death died, but those patients died from complications (septic cholecystitis, carotid artery bleeding and endocarditis due to immunodeficiency).

Sensitivity and specificity for type of pathology and anatomical system subgroups

Based on the type of pathology, the subgroup of perfusion disorders showed a significant improvement (p=0.04) in sensitivity from 19/34=56% to 26/34=76%, using PMCT (Table 5). When categorized based on anatomical system, the cardiovascular subgroup showed a significant improvement (p=0.02) in sensitivity from 24/39=62% to 32/3982%. There were no significant differences in specificity within the subgroups before and after PMCT.

Performance of radiologists

Logistic regression analysis showed no significant improvement in radiologists' performance over the four years of initial experience in reporting PMCT-scans. Odds ratios for each year of experience were 0.85 (95% CI: 0.56 to 1.27, (p=0.41) for correct assignment of the immediate cause of death, 0.95 (95% CI: 0.61 to 1.48, p=0.81) for type of pathology and 0.82 (95% CI: 0.51 to 1.32, p=0.41) for anatomical system involved.

Discussion

The number of correctly identified clinical diagnoses of the immediate cause of death increased from 53% to 64% (p=0.049) after performing PMCT. Analyses showed that the value of PMCT is variable per subcategory and depends on the cause of death. Unfortunately, subgroups were a lot smaller than expected. The main reason for this was the unexpected low consent rate for PMCT in cases with consent for conventional autopsy. We did not investigate the reason for this low consent rate as motives for performing or not performing a PMCT-scan were not extensively documented. In case of death, clinicians had to ask consent for both PMCT and autopsy. Though some clinicians mentioned that they only requested for PMCT in case of refusal of conventional autopsy.

Pneumonia was the most common missed infectious cause of death, both before and after PMCT. Normal postmortem changes, such as the occurrence of pulmonary edema, could mask pneumonia (Figure 5).[16] In the subgroup of perfusion disorders, diagnosis of pulmonary embolism at unenhanced PMCT is challenging as it is notoriously difficult to distinguish an ante-mortem thrombus from a post-mortem blood clot.[17-19] This, or the possibility that the embolus was lost during the autopsy procedure, may explain why in three cases the pulmonary embolism was not confirmed during autopsy. Postmortem angiography, now being developed and validated, can be effective in demonstrating any obstructing thrombi.[20] Most causes of death in the subgroup of perfusion disorders were cardiac related. Clinicians are often restricted in their ability to differentiate a cause of death due to the acute nature and time constraints of the situations (resuscitation setting) these patients present with. On the contrary, cardiac arrhythmia and heart failure are impossible to diagnose by postmortem examinations only. Furthermore, an autopsy can only detect a myocardial infarction in cases where patients have survived two to three hours post-infarction.[21] ATherefore, radiologists and pathologists had access to clinical information in order to assign the most probable cause of death based on postmortem findings and clinical finings as well. Accordingly, both PMCT and autopsy could indicate a cardiac cause of death, based on clinical findings and secondary characteristics in the absence of other significant pathologies.

Table 1 and 5 show an increased additional value of PMCT when PMCT is used to identify the type of pathology or anatomical system involved. This indicates that even when the cause of death is uncertain after PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential diagnostic possibilities. By using PMCT, the sensitivity for type of pathology and anatomical system increased by approximately 20% for all three main subgroups with the use of PMCT (Table 5). Clinical evaluation of the cause of death often indicates the failing system (for example, respiratory failure) rather than the underlying illness or structural changes, whereas radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing somewhat better when only one of the modalities is used.[14,15] PMCT is less expensive than a conventional autopsy, however, cost-effective analyses have not been formulated.[22] Images can be stored digitally (useful for legal or educational purposes) and results can be audited and promptly reviewed by one or more radiologists. Amongst minimally invasive methods, the highest performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with targeted coronary angiography, showed a sensitivity of 92% for cause of death.[19] Two studies combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for cause of death.[23,24]

To our knowledge this is the second study which has investigated the additional value of unenhanced PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.[25] This is somewhat higher than we found in our study, one reason could be the fact that less specific causes of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some

use broadly defined categorizations and others use well-defined specific causes of death, or some use the immediate cause of death and others the intermediate or underlying cause of death, or do not state their definition of cause of death at all. Furthermore, most previous studies consisted of small sample sizes (n<50) and used different study populations, different outcome parameters (for example, cause of death, major or minor diagnoses) and different parameters of accuracy.[4,26-28] A large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32% in determining the cause of death with PMCT compared to autopsy.[14] Another study showed a sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in 101 cases.[29] This is in accordance with our results regarding the categorization of cause of death per type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause of death and a sensitivity of 5/17=19% for a more specific description of the involved pathogenetic mechanism.[26] Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both definite and possible findings with PMCT as to cause of death.[27] The study by Puranik et al. supports our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.[28] A sensitivity of 25% for cause of death was found in a population of seventeen young patients with sudden cardiac death.

Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure 4), are more confidently diagnosed with PMCT than autopsy.[14,30] Therefore, the presented performance of PMCT will probably be underestimated in cases were pathologies are difficult to confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no longer be considered as the gold standard for all postmortem diagnoses, not only due to the limitations of dissection, but also due to the decline in the number of autopsies performed, leading to a decrease in pathologists' expertise. We would suggest a gold standard involving a multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective studies with larger sample sizes are required to investigate the additional value of PMCT in specific subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques,

conventional autopsy will still be required in complex cases where clinical and radiological diagnosis as to cause of death is inconclusive.

Conclusion

While virtual autopsy with postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone. Even in cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.

References

1. Harrington DE, Sayre EA. Managed care and measuring medical outcomes: did the rise of HMOs contribute to the fall in the autopsy rate? *Social science & medicine (1982).* 2010;70(2):191-198.
2. Blokker BM, Weustink AC, Hunink MGM, Oosterhuis JW. Autopsy rates in the Netherlands: 35 years of decline. *PloS one.* 2017;12(6):e0178200.
3. Kretzschmar H. Brain banking: opportunities, challenges and meaning for the future. *Nature reviews Neuroscience.* 2009;10(1):70-78.
4. Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Annals of internal medicine.* 2012;156(2):123-130.
5. Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet (London, England).* 2007;369(9571):1471-1480.
6. The decline of the hospital autopsy: a safety and quality issue for healthcare in Australia. *The Medical journal of Australia.* 2004;180(6):281-285.
7. Chariot P, Witt K, Pautot V, et al. Declining autopsy rate in a French hospital: physician's attitudes to the autopsy and use of autopsy material in research publications. *Archives of pathology & laboratory medicine.* 2000;124(5):739-745.
8. Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. *The New England journal of medicine.* 1983;308(17):1000-1005.
9. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *Jama.* 2003;289(21):2849-2856.
10. Kuijpers CC, Fronczek J, van de Goot FR, Niessen HW, van Diest PJ, Jiwa M. The value of autopsies in the era of high-tech medicine: discrepant findings persist. *Journal of clinical pathology.* 2014;67(6):512-519.
11. Group OfNSDCA. Guidance for doctors completing medical certificates of cause of death in England and Wales. . 2010. Accessed 3 June, 2016.
12. Attems J, Arbes S, Bohm G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wiener medizinische Wochenschrift (1946).* 2004;154(7-8):159-162.
13. Ermenc B. Comparison of the clinical and post mortem diagnoses of the causes of death. *Forensic science international.* 2000;114(2):117-119.
14. Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet (London, England).* 2012;379(9811):136-142.
15. Blokker BM, Wagensveld IM, Weustink AC, Oosterhuis JW, Hunink MG. Non-invasive or minimally invasive autopsy compared to conventional autopsy of suspected natural deaths in adults: a systematic review. *European radiology.* 2016;26(4):1159-1179.
16. Klein WM. The common pattern of postmortem changes on whole body CT scans. *Journal of Forensic Radiology and Imaging.* 2016;4:47-52.
17. Jackowski C, Thali M, Aghayev E, et al. Postmortem imaging of blood and its characteristics using MSCT and MRI. *International journal of legal medicine.* 2006;120(4):233-240.
18. Ross SG, Bolliger SA, Ampanozi G, Oesterhelweg L, Thali MJ, Flach PM. Postmortem CT angiography: capabilities and limitations in traumatic and natural causes of death. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2014;34(3):830-846.
19. Rutty GN, Morgan B, Robinson C, et al. Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy for coroner-requested post-mortem investigations: a prospective, masked, comparison study. *Lancet (London, England).* 2017.

20. Grabherr S, Grimm J, Baumann P, Mangin P. Application of contrast media in post-mortem imaging (CT and MRI). *La Radiologia medica.* 2015;120(9):824-834.
21. Kubat K, Smedts F. The usefulness of the lactate dehydrogenase macroreaction in autopsy practice. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 1993;6(6):743-747.
22. Weustink AC, Hunink MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW. Minimally invasive autopsy: an alternative to conventional autopsy? *Radiology.* 2009;250(3):897-904.
23. Ross SG, Thali MJ, Bolliger S, Germerott T, Ruder TD, Flach PM. Sudden death after chest pain: feasibility of virtual autopsy with postmortem CT angiography and biopsy. *Radiology.* 2012;264(1):250-259.
24. Bolliger SA, Filograna L, Spendlove D, Thali MJ, Dirnhofer S, Ross S. Postmortem imaging-guided biopsy as an adjuvant to minimally invasive autopsy with CT and postmortem angiography: a feasibility study. *AJR American journal of roentgenology.* 2010;195(5):1051-1056.
25. Inai K, Noriki S, Kinoshita K, et al. Postmortem CT is more accurate than clinical diagnosis for identifying the immediate cause of death in hospitalized patients: a prospective autopsy-based study. *Virchows Archiv : an international journal of pathology.* 2016;469(1):101-109.
26. Westphal SE, Apitzsch J, Penzkofer T, Mahnken AH, Knuchel R. Virtual CT autopsy in clinical pathology: feasibility in clinical autopsies. *Virchows Archiv : an international journal of pathology.* 2012;461(2):211-219.
27. Takahashi N, Higuchi T, Shiotani M, et al. The effectiveness of postmortem multidetector computed tomography in the detection of fatal findings related to cause of non-traumatic death in the emergency department. *European radiology.* 2012;22(1):152-160.
28. Puranik R, Gray B, Lackey H, et al. Comparison of conventional autopsy and magnetic resonance imaging in determining the cause of sudden death in the young. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance.* 2014;16:44.
29. Ampanozi G, Thali YA, Schweitzer W, et al. Accuracy of non-contrast PMCT for determining cause of death. *Forensic science, medicine, and pathology.* 2017.
30. Dirnhofer R, Jackowski C, Vock P, Potter K, Thali MJ. VIRTOPSY: minimally invasive, imaging-guided virtual autopsy. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2006;26(5):1305-1333.

Figure legends

Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

[a] No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. [b] In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy.

A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.

A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.

A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

Figure 5. Normal postmortem changes could mask underlying pathology

A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

Tables

Table 1. Patient characteristics

	Study population (n=86), n (%)
Sex	
Male	51 (59%)
Female	35 (41%)
Age, median (IQR)	62 (47-74)
Place of death	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
CPR performed	
Yes	46 (53%)
No	40 (47%)
Brain autopsy performed	
Yes	27 (31%)
No	59 (69%)
Immediate cause of death	
Infectious	26 (30%)
Perfusive disorder	32 (37%
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

IQR: interquartile range. CPR: cardiopulmonary resuscitation.

Table 2. Sensitivity for immediate cause of death, type of pathology and anatomical system involved, before and after virtual autopsy with PMCT.

	Sensitivity before PMCT (95% CI)	Sensitivity after PMCT (95% CI)	Significance (p-value[b])
Immediate cause of death Identified at CA (n=76)[a]	40/76=53% (41-64%)	49/76=64% (53-75%)	0.049
Type of pathology Identified at CA (n=78)[a]	51/78=65% (54-76%)	65/78=83% (73-91%)	0.001
Anatomical system Identified at CA (n=77)[a]	50/77=65% (53-75%)	47/65=84% (74-92%)	0.001

[a] Group sizes differ as conventional autopsy (CA) was not able to assign a cause of death in ten cases (Figure 1), a type of pathology in eight cases and anatomical system in nine cases. [b] p-values were calculated by use of McNemar tests.

Table 3. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology (B) and anatomical system (C), before and after PMCT

A.		**COD after PMCT**		
		Correct	**Incorrect**	
COD before PMCT	**Correct**	36	4	40
	Incorrect	13	23	36
		49	27	76

B.	**Type of pathology after PMCT**		
	Correct	**Incorrect**	

Type of pathology before PMCT	**Correct**	50	1	51
	Incorrect	15	12	27
		65	13	78

C.		**Type of anatomical system after PMCT**		
		Correct	**Incorrect**	
Type of anatomical system before PMCT	**Correct**	47	3	50
	Incorrect	18		27
		65	12	77

COD: immediate cause of death.

Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they were correctly diagnosed as the immediate cause of death before and after virtual autopsy.

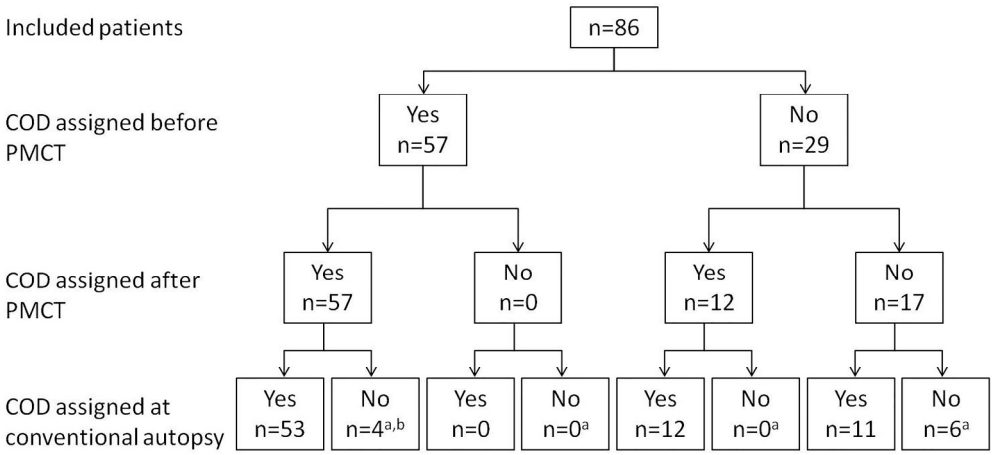
	Correct COD, both before and after PMCT.	**Incorrect COD before PMCT. Correct COD after PMCT.**	**Correct COD before PMCT. Incorrect COD after PMCT.**	**Incorrect COD, both before and after PMCT.**
Infections	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i.[b] 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis[a] 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
Perfusion disorders	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno-occlusive disease 1x bowel ischemia due to adhesions
Hemorrhages	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
Other	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

[a] Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced ventriculoperitoneal drain in another case. [b] sepsis e causa ignota. COD: immediate cause of death.

Table 5. Sensitivity and specificity for type of pathology and anatomical system per subgroup diagnosed before and after virtual autopsy with PMCT.

	Sensitivity			Specificity		
	Before PMCT (95% CI)	**After PMCT (95% CI)**	**p-value[a]**	**Before PMCT (95% CI)**	**After PMCT (95% CI)**	**p-value[a]**
A. Type of pathology (n=78)[c]						
1. Infection (n=26)	69% (48-86)	85% (65-96)	0.130.25	96% (87-100)	92% (81-98)	0.501.00
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)		98% (92-100)	100% (94-100)	
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	0.04	95% (85-99)	93% (81-99)	1.00
4. Other (n=5)	100% (48-100)	100% (48-100)	N/A[c]	99% (93-100%)	99% (93-100%)	1.00
B. Anatomical system (n=77)[c]						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	0.25	95% (86-99)	95% (86-99)	1.00
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	0.02	100% (91-100)	95% (82-99)	0.50
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	0.22	98% (92-100)	100% (94-100)	1.00
4. Other (n=7)	86% (42-100)	86% (42-100)	1.00	97% (90-100)	94% (86-98)	0.50

[a] p-values were calculated by use of McNemar tests. [b] NS: not significant. [c] Autopsy was not able to establish the type of pathology and anatomical system involved in eight and nine deaths respectively. [d] Not applicable.



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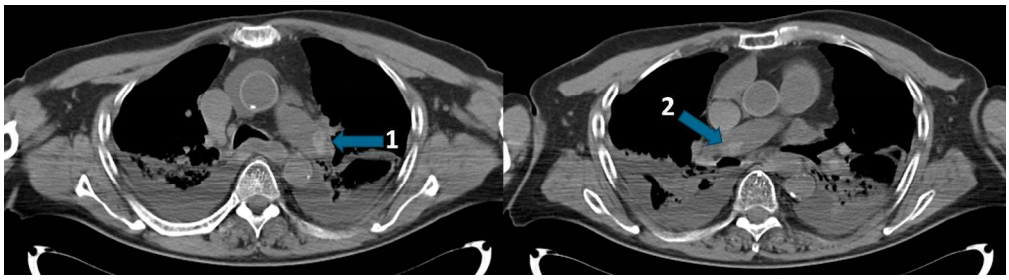

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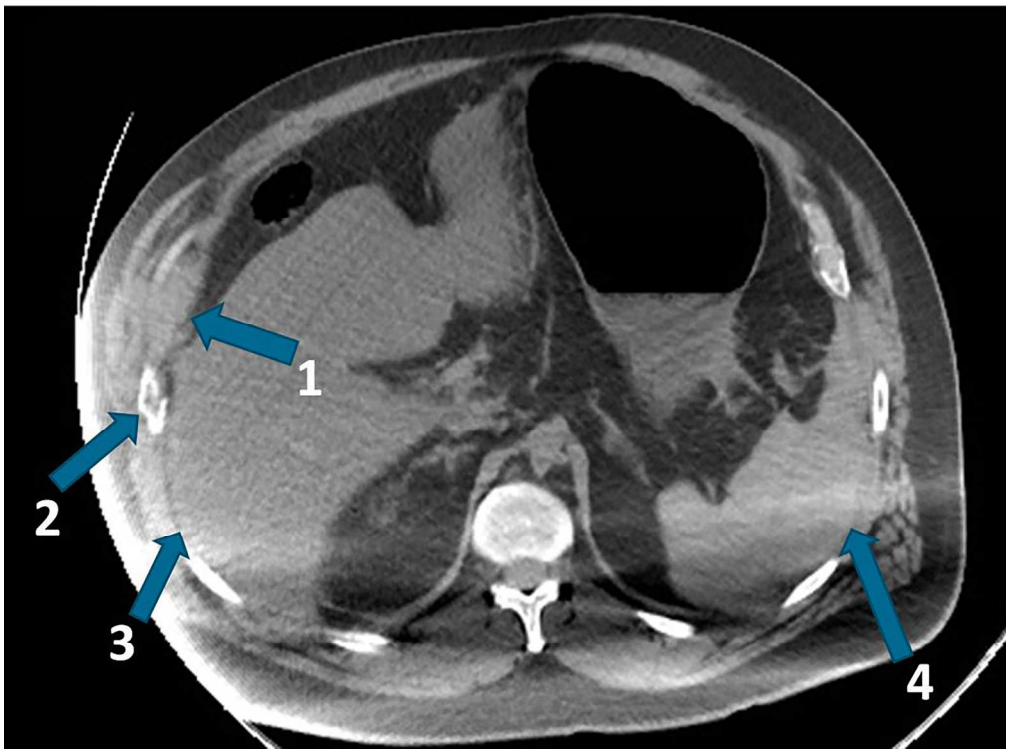

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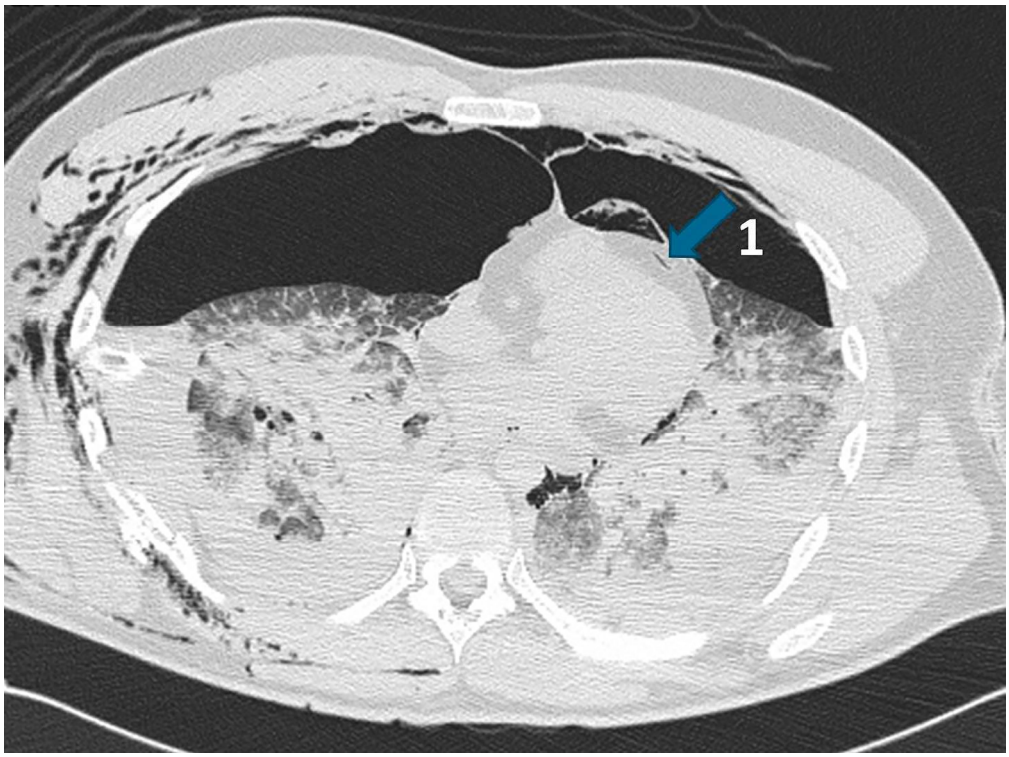

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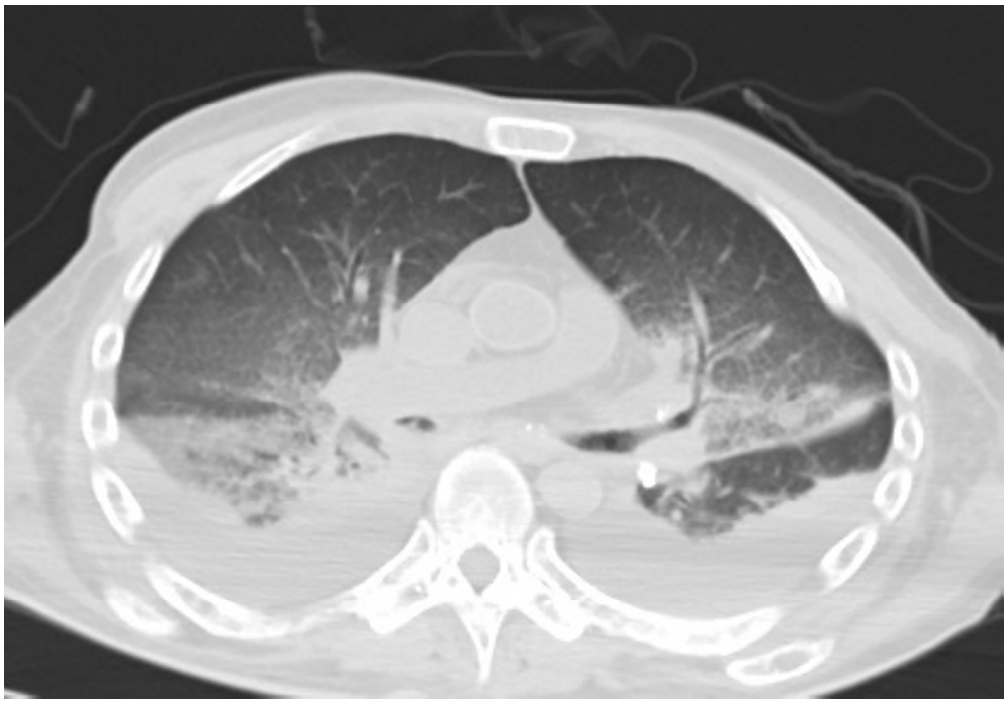

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333x231mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	**6**	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	See supplementary file: 'response to editorial request'
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	10
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3, page 22-23
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 2 + 5
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	13-15
	27	Implications for practice, including the intended use and clinical role of the index test	13-15
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5
	30	Sources of funding and other support; role of funders	5

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

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Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Key Words

cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

List of abbreviations

COD	immediate cause of death
PMCT	postmortem CT

Abstract

Objective: To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

Design: Retrospective observational cohort study. Inclusion-criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion-criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy.

Setting: Tertiary referral centre.

Participants: 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

Intervention: PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

Primary and secondary outcome measures: Increase in sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

Results: Using PMCT, the sensitivity for immediate cause of death increased with 12% (95% CI: -4 to 28) from 53% (41 to 64) to 64% (53 to 75), with 18% (4 to 32)from 65% (54 to 76) to 83% (73 to 91) for type of pathology and with 19% (6 to 33) from 65% (54 to 76) to 85% (75 to 92) for anatomical system.

Conclusion: While unenhanced postmortem CT is an insufficient substitute for conventional autopsy, it canimprove diagnosis of cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

Article summary

Strengths and limitations of this study

- This study investigated the diagnostic performance for clinical cause of death determination by use of postmortem CT and takes into account the added value over clinical diagnosis alone.
- The immediate cause of death (i.e. direct cause of death) was the main outcome rather than the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical point of view, diagnosis and treatment of the immediate cause of death is the most urgent.
- The sensitivity for clinical cause of death determination, with and without postmortem CT, is investigated on multiple levels of precision; the immediate cause of death as well as the involved type of pathology and anatomical location were investigated.
- The retrospective design in a tertiary care centre has probably introduced a selection-bias towards patients with diagnostic difficulties or unresolved issues, resulting in an underestimation of the diagnostic performance compared to more general causes of death.
- An unexpected low consent rate for postmortem CT in cases with consent for conventional autopsy resulted in a reduction of the statistical power of this study.

Contributors: LJPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS, WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors revised the manuscript for intellectual content.

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Ethical approval: This study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

Data sharing: Details on how to obtain additional data from the study (eg, statistical code, datasets) are available from the corresponding author.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Introduction

Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is therefore remarkable that in a time of heightened interest in improving patient safety, healthcare quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the nineteen sixties, to below 10% nowadays.[1-7] Religious and emotional objections to the invasiveness of conventional autopsies, both by the relatives and the doctors, are considered as some of the reasons given for this decline. At present, determination of the cause of death relies heavily on clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the last decades, major error rates of approximately 25% have not substantially decreased.[8-10] According to the Goldman classification system, major errors are defined as clinically missed diagnoses related to the cause of death. In half of these cases this might have led to a change in therapy and prolonged survival, if known before death.[8]

National mortality statistics are generally based on the primary cause of death (i.e. underlying cause or basic illness), which could be a longstanding, chronic disease.[11] However from an individual and clinical point of view, diagnosis and treatment of the immediate cause of death (i.e. direct cause of death) is the most urgent. Accuracy rates for immediate causes of death are probably lower than for underlying causes of death[12,13], due to time constraints of the often acute situations these diagnoses present with. The high error rates emphasize the need to improve clinical diagnoses using techniques that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have shown that as yet, PMCT is an insufficient substitute but can be used in adjunct to conventional autopsy.[14,15] In order to provide answers and quality control also in cases without consent for conventional autopsy, we investigated whether virtual autopsy with PMCT improves clinical diagnosis of the immediate cause of death.

Material and methods

Study design

All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and conventional autopsy in all cases of death. This retrospective study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

PMCT and conventional autopsy

PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s. PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting, interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single consensus report. All radiologists had minimal previous experience in interpreting PMCT images, as postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted of thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic and microscopic inspection. Radiologists and pathologists were blinded to each other's results, but had otherwise full access to electronic patient files. Radiologists and pathologists compiled a report based on their own findings and clinical findings.

Data collection

For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and anatomical system involved, were collected in retrospect at three moments: before PMCT, after PMCT and based on conventional autopsy findings. The cause of death before virtual autopsy was based on clinical findings only. The cause of death after virtual autopsy was based on both clinical findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was primarily based on clinical findings. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of death.

Type of pathology was scored according to the following categories; infection, hemorrhage, perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with hemopericardium were grouped in the hemorrhage category. The type of anatomical system was scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and subcategories used were derived from the classification of anatomical regions and groups of pathologies as used by Roberts and Wichmann et al.[4,14]

Statistical analysis

Sensitivity and specificity were calculated with conventional autopsy as reference standard. 95% confidence intervals (CI) of the differences in sensitivity or specificity before and after PMCT were calculated. Cases where the cause of death, type of pathology or anatomical system could not be established after conventional autopsy were excluded from statistical analysis. A sample size of n=113 was required to demonstrate a difference of 15% in sensitivity with α=0.05 and β=0.10. Logistic regression analysis was performed to evaluate radiologists' improvement in reporting PMCT-

scans during the four year study period. Odds ratios were calculated for each additional year of experience in reporting PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS Statistics, version 22 was used.

Results

Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases, conventional autopsy consisted of a thorax-abdomen examination only. Conventional autopsy, as standard of reference, was not able to assign the immediate cause of death in ten cadavers (12%) (Figure 1). The type of pathology and anatomical system involved were both not assigned in eight cadavers. Therefore, analyses were based on the remaining 76 or 78 cadavers. Table 2 shows 2-by-2-tables of the number of correct diagnoses before and after PMCT.

Sensitivity for immediate cause of death

The overall sensitivity for immediate cause of death increased with 12% (-4 to 28) from 53% (41 to 64) to 64% (53 to 75) after performing a PMCT-scan. Sensitivities specified per type of pathology or anatomical system are shown in Table 3. All autopsy causes of death, and whether or not they were correctly appointed before and after PMCT, are shown in Table 4.

Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4), pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.

In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant findings. In the other case, heart failure was also based upon presence of secondary characteristics (dilated atria and pleural effusion) in the absence of other significant findings. Myocardial infarction was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these cases, the myocardial infarction was not directly visible on PMCT and was based on the combination of clinical findings and absence of significant pathologies at PMCT. In the two other cases, imaging was suspect for myocardial infarction; once due to an intravascular hypodensity proximal of a coronary stent, which might indicate a (fat) embolism, and once due to the combination of significant coronary calcifications, enlarged right atrium, clinical history and absence of other significant findings.

Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case were death was attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left coronary artery (Figure 4).

In the category of other pathologies, there were three patients who died from malignant disease. The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in

metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to (unidentified) brain metastases. There were three other cases with cancer at time of death died, but those patients died from complications (septic cholecystitis, carotid artery bleeding and endocarditis due to immunodeficiency).

Sensitivity and specificity for type of pathology and anatomical system involved in the immediate cause of death

The overall sensitivity for type of pathology increased with 18% (4 to 32) from 65% (54 to 76) to 83% (73 to 91) and with 19% (6 to 33) from 65% (54 to 76) to 85% (75 to 92) for the anatomical system (Table 5). These improvements were statistically significant. In the subgroups of cardiovascular causes and perfusion disorders as cause of death, where the sensitivity for immediate cause of death was rather low, we observed (nearly) significant improvements of 21% (1 to 41) and 21% (-2 to 43) for the identification of the involved anatomical system and type of pathology respectively. This illustrates that PMCT can indicate a cardiovascular or perfusive cause of death, even in cases when the exact cause of death within that subgroup cannot be differentiated. There were no significant differences in specificity within the subgroups before and after PMCT.

Performance of radiologists

Logistic regression analysis showed no significant improvement in the performance of radiologists in assigning the correct cause of death over the four-year study period. Odds ratios for each year of additional experience in reporting PMCT-scans were 0.85 (95% CI: 0.56 to 1.27, p=0.41) for correct assignment of the immediate cause of death, 0.95 (95% CI: 0.61 to 1.48, p=0.81) for type of pathology and 0.82 (95% CI: 0.51 to 1.32, p=0.41) for anatomical system involved.

Discussion

The sensitivity for immediate cause of death increased from 53% to 64% after performing PMCT. Analyses showed that the value of PMCT is variable per subcategory and depends on the cause of death. Unfortunately, subgroups were a lot smaller than expected, resulting in a lower statistical power and large confidence intervals. We had predicted to include 272 cases (4 years of inclusion * average 80 thoraco-abdominal autopsies each year * 0.85 PMCT consent rate). The main reason for the limited number of included patients was the unexpected low consent rate (78/304=26%) for PMCT in cases with consent for conventional autopsy. We did not investigate the reason for this low consent rate as motives for performing or not performing a PMCT-scan were not extensively documented. In case of death, clinicians had to ask consent for both PMCT and autopsy. Though some clinicians mentioned that they only requested for PMCT in case of refusal of conventional autopsy.

Pneumonia was the most common missed infectious cause of death, both before and after PMCT. Resuscitation induced changes and normal postmortem changes, such as the occurrence of pulmonary edema, could mask pneumonia (Figure 5).[16] In the subgroup of perfusion disorders, diagnosis of pulmonary embolism at unenhanced PMCT is challenging as it is notoriously difficult to distinguish an ante-mortem thrombus from a post-mortem blood clot.[17-19] This, or the possibility that the embolus was lost during the autopsy procedure, may explain why in three cases the pulmonary embolism was not confirmed during autopsy. Postmortem angiography, now being developed and validated, can be effective in demonstrating any obstructing thrombi.[20] Most causes of death in the subgroup of perfusion disorders were cardiac related. Clinicians are often restricted in their ability to differentiate a cause of death due to the acute nature and time constraints of the situations (resuscitation setting) these patients present with. On the contrary, cardiac arrhythmia and heart failure are impossible to diagnose by postmortem examinations only. Furthermore, an autopsy can only detect a myocardial infarction in cases where patients have survived two to three hours post-infarction.[21] Therefore, radiologists and pathologists had access to clinical information in order to

assign the most probable cause of death based on postmortem findings and clinical findings as well. Accordingly, both PMCT and autopsy could indicate a cardiac cause of death, based on clinical findings and secondary characteristics observed during postmortem examination in the absence of other significant pathologies.

Table 3 and 5 show an increase in overall sensitivity from 64% to 83-85% when PMCT is used for identification of the type of pathology or anatomical system involved rather than for assigning the exact immediate cause of death. This indicates that even when the cause of death is uncertain after PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential diagnostic possibilities. Clinical evaluation of the cause of death often indicates the failing system (for example, respiratory failure) rather than the underlying illness or structural changes, whereas radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing somewhat better when only one of the modalities is used.[14,15] PMCT is less expensive than a conventional autopsy, however, cost-effective analyses have not been formulated.[22] Images can be stored digitally (useful for legal or educational purposes) and results can be audited and promptly reviewed by one or more radiologists. Amongst minimally invasive methods, the highest performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with targeted coronary angiography, showed a sensitivity of 92% for cause of death.[19] Two studies combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for cause of death.[23,24]

To our knowledge this is the second study which has investigated the additional value of unenhanced PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.[25] This is

somewhat higher than we found in our study, one reason could be the fact that less specific causes of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some use broadly defined categorizations and others use well-defined specific causes of death, or some use the immediate cause of death and others the intermediate or underlying cause of death, or do not state their definition of cause of death at all. Furthermore, most previous studies consisted of small sample sizes (n<50) and used different study populations, different outcome parameters (for example, cause of death, major or minor diagnoses) and different parameters of accuracy.[4,26-28] A large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32% in determining the cause of death with PMCT compared to autopsy.[14] Another study showed a sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in 101 cases.[29] This is in accordance with our results regarding the categorization of cause of death per type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause of death and a sensitivity of 5/17=19% for a more specific description of the involved pathogenetic mechanism.[26] Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both definite and possible findings with PMCT as to cause of death.[27] The study by Puranik et al. supports our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.[28] A sensitivity of 25% for cause of death was found in a population of seventeen young patients with sudden cardiac death.

Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure 4), are more confidently diagnosed with PMCT than autopsy.[14,30] Therefore, the presented performance of PMCT will probably be underestimated in cases were pathologies are difficult to confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no longer be considered as the gold standard for all postmortem diagnoses, not only due to the limitations of dissection, but also due to the decline in the number of autopsies performed, leading to a decrease in pathologists' expertise. We would suggest a gold standard involving a

multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective studies with larger sample sizes are required to investigate the additional value of PMCT in specific subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques, conventional autopsy will still be required in complex cases where clinical and radiological diagnosis as to cause of death is inconclusive.

Conclusion

While virtual autopsy with postmortem CT is an insufficient substitute for conventional autopsy, it can improve diagnosis of the cause of death over clinical diagnosis alone. Even in cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.

References

1. Harrington DE, Sayre EA. Managed care and measuring medical outcomes: did the rise of HMOs contribute to the fall in the autopsy rate? *Social science & medicine (1982).* 2010;70(2):191-198.
2. Blokker BM, Weustink AC, Hunink MGM, Oosterhuis JW. Autopsy rates in the Netherlands: 35 years of decline. *PloS one.* 2017;12(6):e0178200.
3. Kretzschmar H. Brain banking: opportunities, challenges and meaning for the future. *Nature reviews Neuroscience.* 2009;10(1):70-78.
4. Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Annals of internal medicine.* 2012;156(2):123-130.
5. Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet (London, England).* 2007;369(9571):1471-1480.
6. The decline of the hospital autopsy: a safety and quality issue for healthcare in Australia. *The Medical journal of Australia.* 2004;180(6):281-285.
7. Chariot P, Witt K, Pautot V, et al. Declining autopsy rate in a French hospital: physician's attitudes to the autopsy and use of autopsy material in research publications. *Archives of pathology & laboratory medicine.* 2000;124(5):739-745.
8. Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. *The New England journal of medicine.* 1983;308(17):1000-1005.
9. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *Jama.* 2003;289(21):2849-2856.
10. Kuijpers CC, Fronczek J, van de Goot FR, Niessen HW, van Diest PJ, Jiwa M. The value of autopsies in the era of high-tech medicine: discrepant findings persist. *Journal of clinical pathology.* 2014;67(6):512-519.
11. Group OfNSDCA. Guidance for doctors completing medical certificates of cause of death in England and Wales. . 2010. Accessed 3 June, 2016.
12. Attems J, Arbes S, Bohm G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wiener medizinische Wochenschrift (1946).* 2004;154(7-8):159-162.
13. Ermenc B. Comparison of the clinical and post mortem diagnoses of the causes of death. *Forensic science international.* 2000;114(2):117-119.
14. Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet (London, England).* 2012;379(9811):136-142.
15. Blokker BM, Wagensveld IM, Weustink AC, Oosterhuis JW, Hunink MG. Non-invasive or minimally invasive autopsy compared to conventional autopsy of suspected natural deaths in adults: a systematic review. *European radiology.* 2016;26(4):1159-1179.
16. Klein WM. The common pattern of postmortem changes on whole body CT scans. *Journal of Forensic Radiology and Imaging.* 2016;4:47-52.
17. Jackowski C, Thali M, Aghayev E, et al. Postmortem imaging of blood and its characteristics using MSCT and MRI. *International journal of legal medicine.* 2006;120(4):233-240.
18. Ross SG, Bolliger SA, Ampanozi G, Oesterhelweg L, Thali MJ, Flach PM. Postmortem CT angiography: capabilities and limitations in traumatic and natural causes of death. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2014;34(3):830-846.
19. Rutty GN, Morgan B, Robinson C, et al. Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy for coroner-requested post-mortem investigations: a prospective, masked, comparison study. *Lancet (London, England).* 2017.

20. Grabherr S, Grimm J, Baumann P, Mangin P. Application of contrast media in post-mortem imaging (CT and MRI). *La Radiologia medica.* 2015;120(9):824-834.
21. Kubat K, Smedts F. The usefulness of the lactate dehydrogenase macroreaction in autopsy practice. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 1993;6(6):743-747.
22. Weustink AC, Hunink MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW. Minimally invasive autopsy: an alternative to conventional autopsy? *Radiology.* 2009;250(3):897-904.
23. Ross SG, Thali MJ, Bolliger S, Germerott T, Ruder TD, Flach PM. Sudden death after chest pain: feasibility of virtual autopsy with postmortem CT angiography and biopsy. *Radiology.* 2012;264(1):250-259.
24. Bolliger SA, Filograna L, Spendlove D, Thali MJ, Dirnhofer S, Ross S. Postmortem imaging-guided biopsy as an adjuvant to minimally invasive autopsy with CT and postmortem angiography: a feasibility study. *AJR American journal of roentgenology.* 2010;195(5):1051-1056.
25. Inai K, Noriki S, Kinoshita K, et al. Postmortem CT is more accurate than clinical diagnosis for identifying the immediate cause of death in hospitalized patients: a prospective autopsy-based study. *Virchows Archiv : an international journal of pathology.* 2016;469(1):101-109.
26. Westphal SE, Apitzsch J, Penzkofer T, Mahnken AH, Knuchel R. Virtual CT autopsy in clinical pathology: feasibility in clinical autopsies. *Virchows Archiv : an international journal of pathology.* 2012;461(2):211-219.
27. Takahashi N, Higuchi T, Shiotani M, et al. The effectiveness of postmortem multidetector computed tomography in the detection of fatal findings related to cause of non-traumatic death in the emergency department. *European radiology.* 2012;22(1):152-160.
28. Puranik R, Gray B, Lackey H, et al. Comparison of conventional autopsy and magnetic resonance imaging in determining the cause of sudden death in the young. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance.* 2014;16:44.
29. Ampanozi G, Thali YA, Schweitzer W, et al. Accuracy of non-contrast PMCT for determining cause of death. *Forensic science, medicine, and pathology.* 2017.
30. Dirnhofer R, Jackowski C, Vock P, Potter K, Thali MJ. VIRTOPSY: minimally invasive, imaging-guided virtual autopsy. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2006;26(5):1305-1333.

Figure legends

Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

[a] No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. [b] In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy.

This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.

This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.

This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

Figure 5. Normal postmortem changes could mask underlying pathology

This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

Tables

Table 1. Patient characteristics

	Study population (n=86), n (%)
Sex	
Male	51 (59%)
Female	35 (41%)
Age, median (IQR)	62 (47-74)
Place of death	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
CPR performed	
Yes	46 (53%)
No	40 (47%)
Brain autopsy performed	
Yes	27 (31%)
No	59 (69%)
Immediate cause of death	
Infectious	26 (30%)
Perfusive disorder	32 (37%
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

IQR: interquartile range. CPR: cardiopulmonary resuscitation.

Table 2. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology (B) and anatomical system (C), before and after PMCT

A.		**COD after PMCT**		
		Correct	**Incorrect**	
COD before PMCT	**Correct**	36	4	40
	Incorrect	13	23	36
		49	27	76

B.		**Type of pathology after PMCT**		
		Correct	**Incorrect**	
Type of pathology before PMCT	**Correct**	50	1	51
	Incorrect	15	12	27
		65	13	78

C.		**Type of anatomical system after PMCT**		
		Correct	**Incorrect**	
Type of anatomical system before PMCT	**Correct**	48	3	51
	Incorrect	18	9	27
		66	12	78

COD: immediate cause of death.

Table 3. Sensitivity for immediate cause of death before and after virtual autopsy with PMCT.

	Sensitivity		
	Before PMCT (95% CI)	**After PMCT (95% CI)**	**Difference (95% CI)**
Immediate cause of death (n=76)[a]	**53% (41-64)**	**64% (53-75)**	**12% (-4-28)**
Per subgroup of type of pathology:			
1. Infection (n=26)	65% (44-83)	69% (48-86)	4% (-22-29)
2. Hemorrhage (n=13)	69% (39-91)	85% (55-98)	15% (-17-48)
3. Perfusion disorder (n=32)	31% (16-50)	47% (29-65)	16% (-8-40)
4. Other (n=5)	80% (28-99)	100% (48-100)	20% (-17-57)
Per subgroup of anatomical system:			
1. Pulmonary (n=18)	56% (31-78)	67% (41-87)	11% (-21-43)
2. Cardiovascular (n=37)	43% (27-61)	54% (37-71)	11% (-12-34)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-5-66)
4. Other (n=8)	88% (47-100)	75% (35-97)	-13% (-50-25)

[a] Conventional autopsy was not able to establish a cause of death in ten cases.

Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they were correctly diagnosed as the immediate cause of death before and after virtual autopsy.

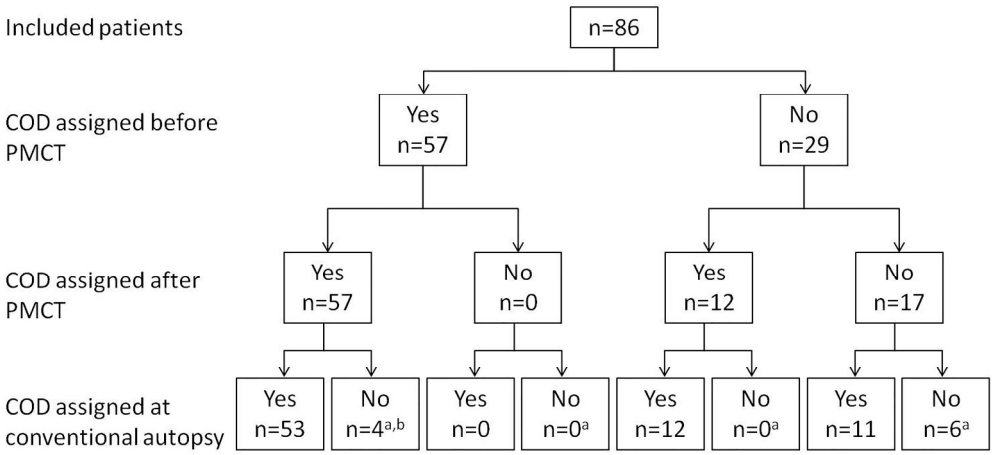
	Correct COD, both before and after PMCT.	Incorrect COD before PMCT. Correct COD after PMCT.	Correct COD before PMCT. Incorrect COD after PMCT.	Incorrect COD, both before and after PMCT.
Infections	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i.[b] 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis[a] 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
Perfusion disorders	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno-occlusive disease 1x bowel ischemia due to adhesions
Hemorrhages	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
Other	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

[a] Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced ventriculoperitoneal drain in another case. [b] sepsis e causa ignota. COD: immediate cause of death.

Table 5. Sensitivity and specificity for type of pathology and anatomical system diagnosed before and after virtual autopsy with PMCT.

	Sensitivity			Specificity		
	Before PMCT (95% CI)	**After PMCT (95% CI)**	**Difference (95% CI)**	**Before PMCT (95% CI)**	**After PMCT (95% CI)**	**Difference (95% CI)**
A. Type of pathology (n=78)[a]	**65% (54-76)**	**83% (73-91)**	**18% (4-32)**	**N/A[b]**	**N/A[b]**	
Per subgroup:						
1. Infection (n=26)	69% (48-86)	85% (65-96)	15% (-8-38)	96% (87-100)	92% (81-98)	-4% (-13-5)
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)	23% (-7-53)	98% (92-100)	100% (94-100)	2% (-2-5)
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	21% (-2-43)	95% (85-99)	93% (81-99)	-2% (-12-7)
4. Other (n=5)	100% (48-100)	100% (48-100)	0% (0-0)	99% (93-100%)	99% (93-100%)	0% (-4-4)
B. Anatomical system (n=78)[a]	**65% (54-76)**	**85% (75-92)**	**19% (6-33)**	**N/A[b]**	**N/A[b]**	
Per subgroup:						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	17% (-9-43)	95% (86-99)	95% (86-99)	0% (-8-8)
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	21% (1-41)	100% (91-100)	95% (82-99)	-5% (-12-2)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (5-66)	98% (92-100)	100% (94-100)	2% (-2-5)
4. Other (n=8)	88% (48-100)	88% (48-100)	0% (-32-32)	97% (90-100)	94% (86-98)	-3% (-10-4)

[a] Autopsy was not able to establish the involved type of pathology and anatomical system in eight cases. [b] Not applicable.



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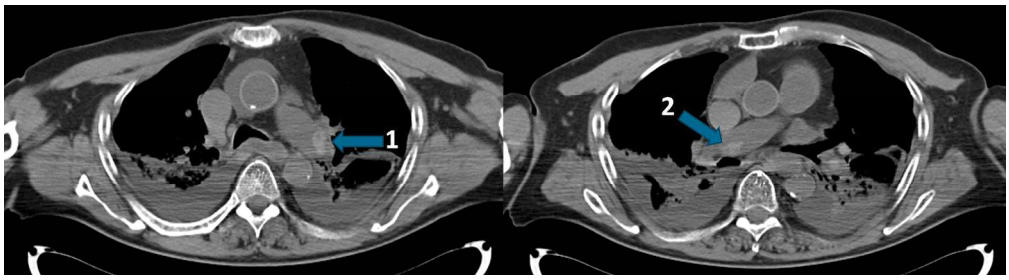

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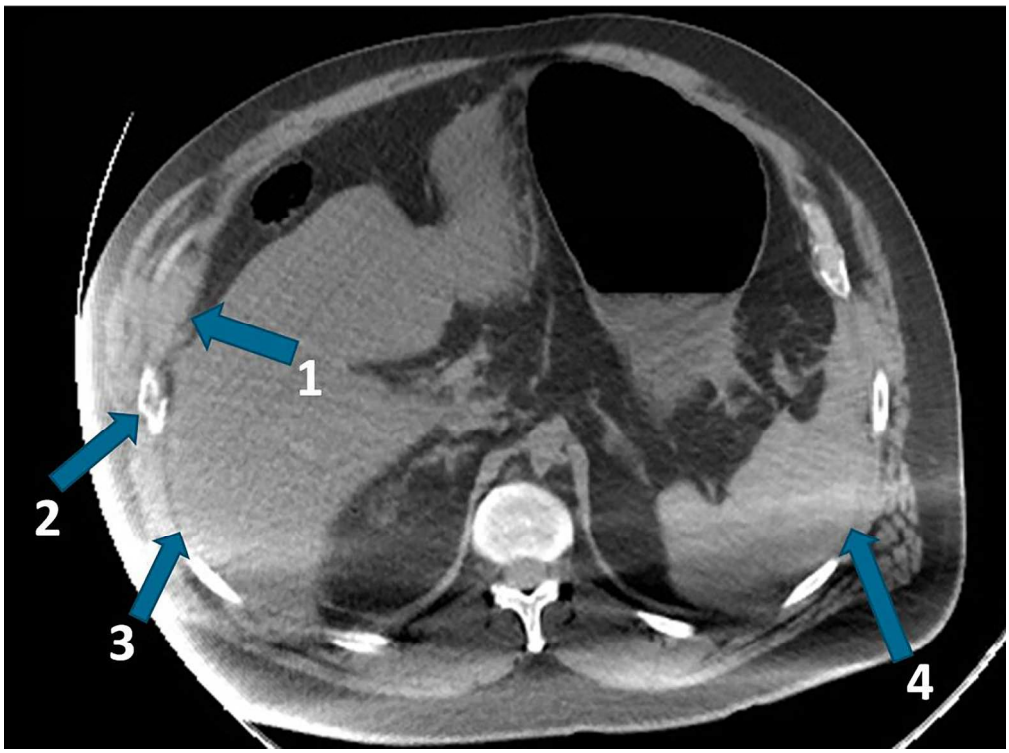

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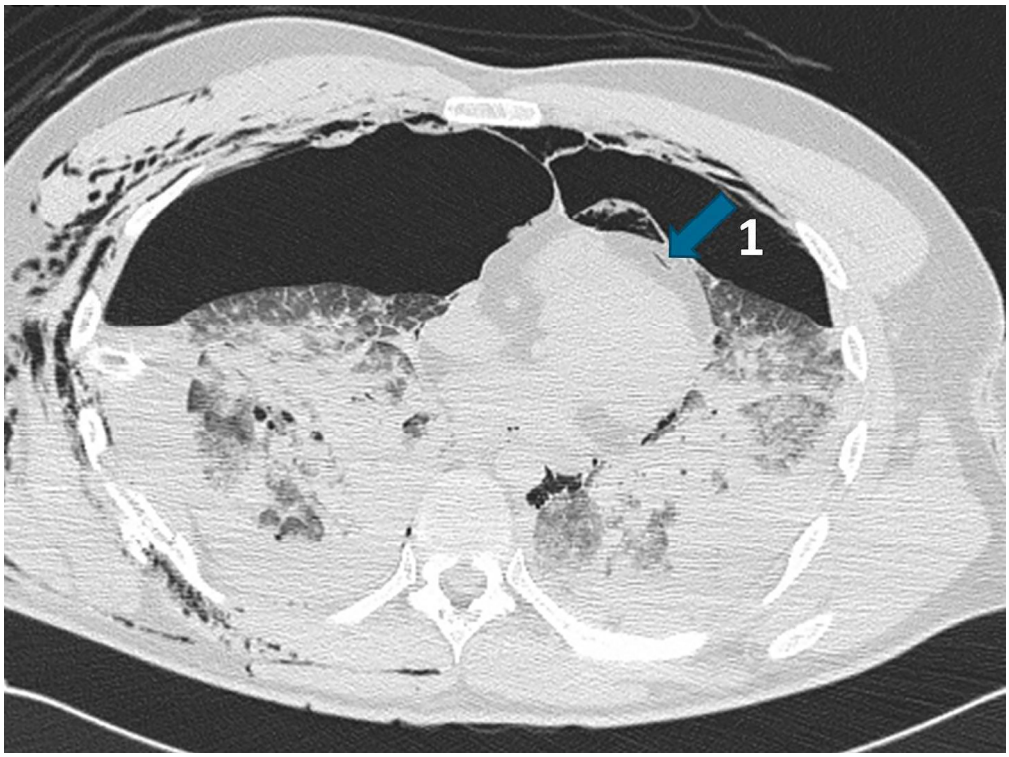

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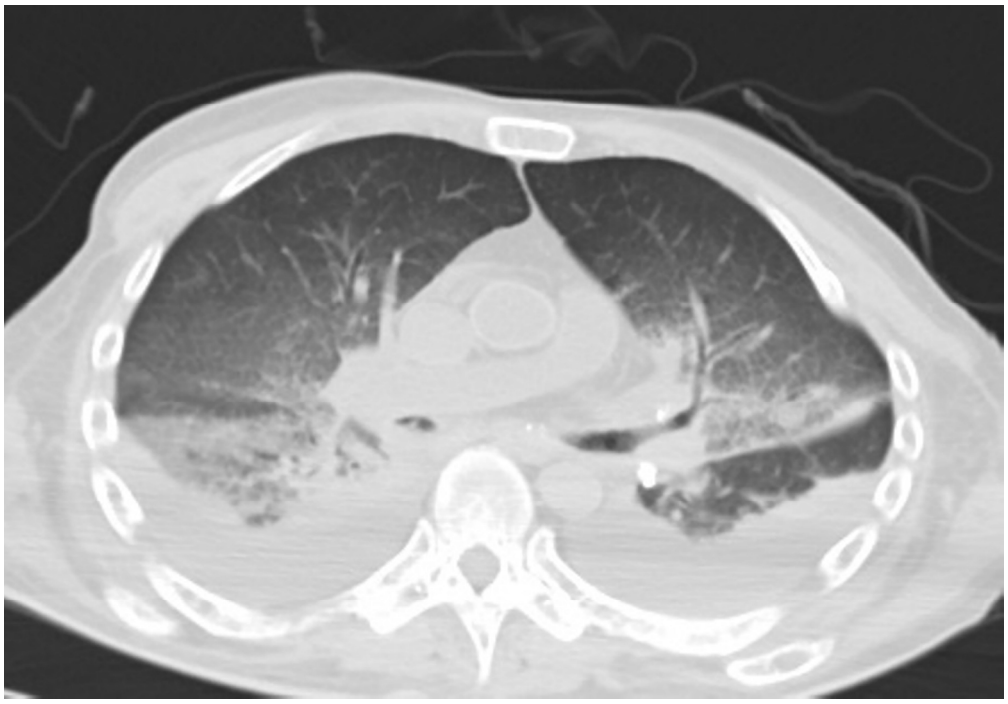

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333x231mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	**6**	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	(6)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	8 ~~See supplementary file: 'response to editorial request'~~
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	10
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table ~~2~~3, page 22-~~23~~
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table ~~2~~3 + 5
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	4, 13-1~~6~~5
	27	Implications for practice, including the intended use and clinical role of the index test	13-1~~6~~5
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5

	30	Sources of funding and other support; role of funders	5

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Manuscript ID	bmjopen-2017-018834.R3
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Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Pathology
Keywords:	Computed tomography < RADIOLOGY & IMAGING, cause of death, postmortem, autopsy, sensitivity, specificity

Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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Study design: retrospective observational cohort study

Word count: 3225

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Field Code Changed

Key Words

cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

List of abbreviations

COD	immediate cause of death
PMCT	postmortem CT

Abstract

Objective: To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

Design: Retrospective observational cohort study. Inclusion-criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion-criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy.

Setting: Tertiary referral centre.

Participants: 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

Intervention: PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with/without brain autopsy.

Primary and secondary outcome measures: Increase in sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

Results: Using PMCT, the sensitivity for immediate cause of death increased with 12% (95% CI: 2 to 22) from 53% (41 to 64) to 64% (53 to 75), with 18% (9 to 27)from 65% (54 to 76) to 83% (73 to 91) for type of pathology and with 19% (9 to 30) from 65% (54 to 76) to 85% (75 to 92) for anatomical system.

Conclusion: While unenhanced postmortem CT is an insufficient substitute for conventional autopsy, it can improve diagnosis of cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

Article summary

Strengths and limitations of this study

- This study investigated the diagnostic performance for clinical cause of death determination by use of postmortem CT and takes into account the added value over clinical diagnosis alone.
- The immediate cause of death (i.e. direct cause of death) was the main outcome rather than the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical point of view, diagnosis and treatment of the immediate cause of death is the most urgent.
- The sensitivity for clinical cause of death determination, with and without postmortem CT, is investigated on multiple levels of precision; the immediate cause of death as well as the involved type of pathology and anatomical location were investigated.
- The retrospective design in a tertiary care centre has probably introduced a selection-bias towards patients with diagnostic difficulties or unresolved issues, resulting in an underestimation of the diagnostic performance compared to more general causes of death.
- An unexpected low consent rate for postmortem CT in cases with consent for conventional autopsy resulted in a reduction of the statistical power of this study.

Contributors: LJPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS, WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors revised the manuscript for intellectual content.

Funding: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests: All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: This study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

Data sharing: Details on how to obtain additional data from the study (eg, statistical code, datasets) are available from the corresponding author.

Transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Introduction

Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is therefore remarkable that in a time of heightened interest in improving patient safety, healthcare quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the nineteen sixties, to below 10% nowadays.[1-7] Religious and emotional objections to the invasiveness of conventional autopsies, both by the relatives and the doctors, are considered as some of the reasons given for this decline. At present, determination of the cause of death relies heavily on clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the last decades, major error rates of approximately 25% have not substantially decreased.[8-10] According to the Goldman classification system, major errors are defined as clinically missed diagnoses related to the cause of death. In half of these cases this might have led to a change in therapy and prolonged survival, if known before death.[8]

National mortality statistics are generally based on the primary cause of death (i.e. underlying cause or basic illness), which could be a longstanding, chronic disease.[11] However from an individual and clinical point of view, diagnosis and treatment of the immediate cause of death (i.e. direct cause of death) is the most urgent. Accuracy rates for immediate causes of death are probably lower than for underlying causes of death[12,13], due to time constraints of the often acute situations these diagnoses present with. The high error rates emphasize the need to improve clinical diagnoses using techniques that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have shown that as yet, PMCT is an insufficient substitute but can be used in adjunct to conventional autopsy.[14,15] In order to provide answers and quality control also in cases without consent for conventional autopsy, we investigated whether virtual autopsy with PMCT improves clinical diagnosis of the immediate cause of death.

Material and methods

Study design

All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and conventional autopsy in all cases of death. This retrospective study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

PMCT and conventional autopsy

PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s. PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting, interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single consensus report. All radiologists had minimal previous experience in interpreting PMCT images, as postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted of thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic and microscopic inspection. Radiologists and pathologists were blinded to each other's results, but had otherwise full access to electronic patient files. Radiologists and pathologists compiled a report based on their own findings and clinical findings.

Data collection

For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and anatomical system involved, were collected in retrospect at three moments: before PMCT, after PMCT and based on conventional autopsy findings. The cause of death before virtual autopsy was based on clinical findings only. The cause of death after virtual autopsy was based on both clinical findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was primarily based on clinical findings. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of death.

Type of pathology was scored according to the following categories; infection, hemorrhage, perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with hemopericardium were grouped in the hemorrhage category. The type of anatomical system was scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and subcategories used were derived from the classification of anatomical regions and groups of pathologies as used by Roberts and Wichmann et al.[4,14]

Statistical analysis

Sensitivity and specificity were calculated with conventional autopsy as reference standard. 95% confidence intervals (CI) of the differences in sensitivity or specificity before and after PMCT were calculated. Cases where the cause of death, type of pathology or anatomical system could not be established after conventional autopsy were excluded from statistical analysis. A sample size of n=113 was required to demonstrate a difference of 15% in sensitivity with α=0.05 and β=0.10. Logistic regression analysis was performed to evaluate radiologists' improvement in reporting PMCT-

scans during the four year study period. Odds ratios were calculated for each additional year of experience in reporting PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS Statistics, version 22 was used.

Results

Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases, conventional autopsy consisted of a thorax-abdomen examination only. Conventional autopsy, as standard of reference, was not able to assign the immediate cause of death in ten cadavers (12%) (Figure 1). The type of pathology and anatomical system involved were both not assigned in eight cadavers. Therefore, analyses were based on the remaining 76 or 78 cadavers. Table 2 shows 2-by-2-tables of the number of correct diagnoses before and after PMCT.

Sensitivity for immediate cause of death

The overall sensitivity for immediate cause of death increased with 12% (2 to 22) from 53% (41 to 64) to 64% (53 to 75) after performing a PMCT-scan. Sensitivities specified per type of pathology or anatomical system are shown in Table 3. All autopsy causes of death, and whether or not they were correctly appointed before and after PMCT, are shown in Table 4.

Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4), pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.

In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant findings. In the other case, heart failure was also based upon presence of secondary characteristics (dilated atria and pleural effusion) in the absence of other significant findings. Myocardial infarction was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these cases, the myocardial infarction was not directly visible on PMCT and was based on the combination of clinical findings and absence of significant pathologies at PMCT. In the two other cases, imaging was suspect for myocardial infarction; once due to an intravascular hypodensity proximal of a coronary stent, which might indicate a (fat) embolism, and once due to the combination of significant coronary calcifications, enlarged right atrium, clinical history and absence of other significant findings.

Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case were death was attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left coronary artery (Figure 4).

In the category of other pathologies, there were three patients who died from malignant disease. The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in

metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to (unidentified) brain metastases. There were three other cases with cancer at time of death died, but those patients died from complications (septic cholecystitis, carotid artery bleeding and endocarditis due to immunodeficiency).

Sensitivity and specificity for type of pathology and anatomical system involved in the immediate cause of death

The overall sensitivity for type of pathology increased with 18% (9 to 27) from 65% (54 to 76) to 83% (73 to 91) and with 19% (9 to 30) from 65% (54 to 76) to 85% (75 to 92) for the anatomical system (Table 5). These improvements were statistically significant. In the subgroups of cardiovascular causes and perfusion disorders as cause of death, where the sensitivity for immediate cause of death was rather low, we observed significant improvements of 21% (6 to 35) and 21% (5 to 36) for the identification of the involved anatomical system and type of pathology respectively. This illustrates that PMCT can indicate a cardiovascular or perfusive cause of death, even in cases when the exact cause of death within that subgroup cannot be differentiated. There were no significant differences in specificity within the subgroups before and after PMCT.

Performance of radiologists

Logistic regression analysis showed no significant improvement in the performance of radiologists in assigning the correct cause of death over the four-year study period. Odds ratios for each year of additional experience in reporting PMCT-scans were 0.85 (95% CI: 0.56 to 1.27, p=0.41) for correct assignment of the immediate cause of death, 0.95 (95% CI: 0.61 to 1.48, p=0.81) for type of pathology and 0.82 (95% CI: 0.51 to 1.32, p=0.41) for anatomical system involved.

Discussion

The sensitivity for immediate cause of death increased from 53% to 64% after performing PMCT. Analyses showed that the value of PMCT is variable per subcategory and depends on the cause of death. Unfortunately, subgroups were a lot smaller than expected, resulting in a lower statistical power and large confidence intervals. We had predicted to include 272 cases (4 years of inclusion * average 80 thoraco-abdominal autopsies each year * 0.85 PMCT consent rate). The main reason for the limited number of included patients was the unexpected low consent rate (78/304=26%) for PMCT in cases with consent for conventional autopsy. We did not investigate the reason for this low consent rate as motives for performing or not performing a PMCT-scan were not extensively documented. In case of death, clinicians had to ask consent for both PMCT and autopsy. Though some clinicians mentioned that they only requested for PMCT in case of refusal of conventional autopsy.

Pneumonia was the most common missed infectious cause of death, both before and after PMCT. Resuscitation induced changes and normal postmortem changes, such as the occurrence of pulmonary edema, could mask pneumonia (Figure 5).[16] In the subgroup of perfusion disorders, diagnosis of pulmonary embolism at unenhanced PMCT is challenging as it is notoriously difficult to distinguish an ante-mortem thrombus from a post-mortem blood clot.[17-19] This, or the possibility that the embolus was lost during the autopsy procedure, may explain why in three cases the pulmonary embolism was not confirmed during autopsy. Postmortem angiography, now being developed and validated, can be effective in demonstrating any obstructing thrombi.[20] Most causes of death in the subgroup of perfusion disorders were cardiac related. Clinicians are often restricted in their ability to differentiate a cause of death due to the acute nature and time constraints of the situations (resuscitation setting) these patients present with. On the contrary, cardiac arrhythmia and heart failure are impossible to diagnose by postmortem examinations only. Furthermore, an autopsy can only detect a myocardial infarction in cases where patients have survived two to three hours post-infarction.[21] Therefore, radiologists and pathologists had access to clinical information in order to

assign the most probable cause of death based on postmortem findings and clinical findings as well. Accordingly, both PMCT and autopsy could indicate a cardiac cause of death, based on clinical findings and secondary characteristics observed during postmortem examination in the absence of other significant pathologies.

Table 3 and 5 show an increase in overall sensitivity from 64% to 83 or 85% when PMCT is used for identification of the type of pathology or anatomical system involved rather than for assigning the exact immediate cause of death. This indicates that even when the cause of death is uncertain after PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential diagnostic possibilities. Clinical evaluation of the cause of death often indicates the failing system (for example, respiratory failure) rather than the underlying illness or structural changes, whereas radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing somewhat better when only one of the modalities is used.[14,15] PMCT is less expensive than a conventional autopsy, however, cost-effective analyses have not been formulated.[22] Images can be stored digitally (useful for legal or educational purposes) and results can be audited and promptly reviewed by one or more radiologists. Amongst minimally invasive methods, the highest performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with targeted coronary angiography, showed a sensitivity of 92% for cause of death.[19] Two studies combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for cause of death.[23,24]

To our knowledge this is the second study which has investigated the additional value of unenhanced PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.[25] This is

somewhat higher than we found in our study, one reason could be the fact that less specific causes of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some use broadly defined categorizations and others use well-defined specific causes of death, or some use the immediate cause of death and others the intermediate or underlying cause of death, or do not state their definition of cause of death at all. Furthermore, most previous studies consisted of small sample sizes (n<50) and used different study populations, different outcome parameters (for example, cause of death, major or minor diagnoses) and different parameters of accuracy.[4,26-28] A large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32% in determining the cause of death with PMCT compared to autopsy.[14] Another study showed a sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in 101 cases.[29] This is in accordance with our results regarding the categorization of cause of death per type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause of death and a sensitivity of 5/17=19% for a more specific description of the involved pathogenetic mechanism.[26] Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both definite and possible findings with PMCT as to cause of death.[27] The study by Puranik et al. supports our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.[28] A sensitivity of 25% for cause of death was found in a population of seventeen young patients with sudden cardiac death.

Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure 4), are more confidently diagnosed with PMCT than autopsy.[14,30] Therefore, the presented performance of PMCT will probably be underestimated in cases were pathologies are difficult to confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no longer be considered as the gold standard for all postmortem diagnoses, not only due to the limitations of dissection, but also due to the decline in the number of autopsies performed, leading to a decrease in pathologists' expertise. We would suggest a gold standard involving a

multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective studies with larger sample sizes are required to investigate the additional value of PMCT in specific subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques, conventional autopsy will still be required in complex cases where clinical and radiological diagnosis as to cause of death is inconclusive.

Conclusion

While virtual autopsy with postmortem CT is an insufficient substitute for conventional autopsy, it can improve diagnosis of the cause of death over clinical diagnosis alone. Even in cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.

References

1. Harrington DE, Sayre EA. Managed care and measuring medical outcomes: did the rise of HMOs contribute to the fall in the autopsy rate? *Social science & medicine (1982).* 2010;70(2):191-198.
2. Blokker BM, Weustink AC, Hunink MGM, Oosterhuis JW. Autopsy rates in the Netherlands: 35 years of decline. *PloS one.* 2017;12(6):e0178200.
3. Kretzschmar H. Brain banking: opportunities, challenges and meaning for the future. *Nature reviews Neuroscience.* 2009;10(1):70-78.
4. Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Annals of internal medicine.* 2012;156(2):123-130.
5. Burton JL, Underwood J. Clinical, educational, and epidemiological value of autopsy. *Lancet (London, England).* 2007;369(9571):1471-1480.
6. The decline of the hospital autopsy: a safety and quality issue for healthcare in Australia. *The Medical journal of Australia.* 2004;180(6):281-285.
7. Chariot P, Witt K, Pautot V, et al. Declining autopsy rate in a French hospital: physician's attitudes to the autopsy and use of autopsy material in research publications. *Archives of pathology & laboratory medicine.* 2000;124(5):739-745.
8. Goldman L, Sayson R, Robbins S, Cohn LH, Bettmann M, Weisberg M. The value of the autopsy in three medical eras. *The New England journal of medicine.* 1983;308(17):1000-1005.
9. Shojania KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *Jama.* 2003;289(21):2849-2856.
10. Kuijpers CC, Fronczek J, van de Goot FR, Niessen HW, van Diest PJ, Jiwa M. The value of autopsies in the era of high-tech medicine: discrepant findings persist. *Journal of clinical pathology.* 2014;67(6):512-519.
11. Group OfNSDCA. Guidance for doctors completing medical certificates of cause of death in England and Wales. . 2010. Accessed 3 June, 2016.
12. Attems J, Arbes S, Bohm G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wiener medizinische Wochenschrift (1946).* 2004;154(7-8):159-162.
13. Ermenc B. Comparison of the clinical and post mortem diagnoses of the causes of death. *Forensic science international.* 2000;114(2):117-119.
14. Roberts IS, Benamore RE, Benbow EW, et al. Post-mortem imaging as an alternative to autopsy in the diagnosis of adult deaths: a validation study. *Lancet (London, England).* 2012;379(9811):136-142.
15. Blokker BM, Wagensveld IM, Weustink AC, Oosterhuis JW, Hunink MG. Non-invasive or minimally invasive autopsy compared to conventional autopsy of suspected natural deaths in adults: a systematic review. *European radiology.* 2016;26(4):1159-1179.
16. Klein WM. The common pattern of postmortem changes on whole body CT scans. *Journal of Forensic Radiology and Imaging.* 2016;4:47-52.
17. Jackowski C, Thali M, Aghayev E, et al. Postmortem imaging of blood and its characteristics using MSCT and MRI. *International journal of legal medicine.* 2006;120(4):233-240.
18. Ross SG, Bolliger SA, Ampanozi G, Oesterhelweg L, Thali MJ, Flach PM. Postmortem CT angiography: capabilities and limitations in traumatic and natural causes of death. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2014;34(3):830-846.
19. Rutty GN, Morgan B, Robinson C, et al. Diagnostic accuracy of post-mortem CT with targeted coronary angiography versus autopsy for coroner-requested post-mortem investigations: a prospective, masked, comparison study. *Lancet (London, England).* 2017.

20. Grabherr S, Grimm J, Baumann P, Mangin P. Application of contrast media in post-mortem imaging (CT and MRI). *La Radiologia medica.* 2015;120(9):824-834.
21. Kubat K, Smedts F. The usefulness of the lactate dehydrogenase macroreaction in autopsy practice. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc.* 1993;6(6):743-747.
22. Weustink AC, Hunink MG, van Dijke CF, Renken NS, Krestin GP, Oosterhuis JW. Minimally invasive autopsy: an alternative to conventional autopsy? *Radiology.* 2009;250(3):897-904.
23. Ross SG, Thali MJ, Bolliger S, Germerott T, Ruder TD, Flach PM. Sudden death after chest pain: feasibility of virtual autopsy with postmortem CT angiography and biopsy. *Radiology.* 2012;264(1):250-259.
24. Bolliger SA, Filograna L, Spendlove D, Thali MJ, Dirnhofer S, Ross S. Postmortem imaging-guided biopsy as an adjuvant to minimally invasive autopsy with CT and postmortem angiography: a feasibility study. *AJR American journal of roentgenology.* 2010;195(5):1051-1056.
25. Inai K, Noriki S, Kinoshita K, et al. Postmortem CT is more accurate than clinical diagnosis for identifying the immediate cause of death in hospitalized patients: a prospective autopsy-based study. *Virchows Archiv : an international journal of pathology.* 2016;469(1):101-109.
26. Westphal SE, Apitzsch J, Penzkofer T, Mahnken AH, Knuchel R. Virtual CT autopsy in clinical pathology: feasibility in clinical autopsies. *Virchows Archiv : an international journal of pathology.* 2012;461(2):211-219.
27. Takahashi N, Higuchi T, Shiotani M, et al. The effectiveness of postmortem multidetector computed tomography in the detection of fatal findings related to cause of non-traumatic death in the emergency department. *European radiology.* 2012;22(1):152-160.
28. Puranik R, Gray B, Lackey H, et al. Comparison of conventional autopsy and magnetic resonance imaging in determining the cause of sudden death in the young. *Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance.* 2014;16:44.
29. Ampanozi G, Thali YA, Schweitzer W, et al. Accuracy of non-contrast PMCT for determining cause of death. *Forensic science, medicine, and pathology.* 2017.
30. Dirnhofer R, Jackowski C, Vock P, Potter K, Thali MJ. VIRTOPSY: minimally invasive, imaging-guided virtual autopsy. *Radiographics : a review publication of the Radiological Society of North America, Inc.* 2006;26(5):1305-1333.

Figure legends

Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

[a] No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. [b] In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy.

This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.

This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.

This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

Figure 5. Normal postmortem changes could mask underlying pathology

This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

Tables

Table 1. Patient characteristics

	Study population (n=86), n (%)
Sex	
Male	51 (59%)
Female	35 (41%)
Age, median (IQR)	62 (47-74)
Place of death	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
CPR performed	
Yes	46 (53%)
No	40 (47%)
Brain autopsy performed	
Yes	27 (31%)
No	59 (69%)
Immediate cause of death	
Infectious	26 (30%)
Perfusive disorder	32 (37%
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

IQR: interquartile range. CPR: cardiopulmonary resuscitation.

Table 2. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology (B) and anatomical system (C), before and after PMCT

A.		**COD after PMCT**		
		Correct	**Incorrect**	
COD before PMCT	**Correct**	36	4	40
	Incorrect	13	23	36
		49	27	76

B.		**Type of pathology after PMCT**		
		Correct	**Incorrect**	
Type of pathology before PMCT	**Correct**	50	1	51
	Incorrect	15	12	27
		65	13	78

C.		**Type of anatomical system after PMCT**		
		Correct	**Incorrect**	
Type of anatomical system before PMCT	**Correct**	48	3	51
	Incorrect	18	9	27
		66	12	78

COD: immediate cause of death.

Table 3. Sensitivity for immediate cause of death before and after virtual autopsy with PMCT.

	Sensitivity		
	Before PMCT (95% CI)	**After PMCT (95% CI)**	**Difference (95% CI)**
Immediate cause of death (n=76)[a]	**53% (41-64)**	**64% (53-75)**	**12% (2-22)**
Per subgroup of type of pathology:			
1. Infection (n=26)	65% (44-83)	69% (48-86)	4% (-16-24)
2. Hemorrhage (n=13)	69% (39-91)	85% (55-98)	15% (-4-35)
3. Perfusion disorder (n=32)	31% (16-50)	47% (29-65)	16% (0-31)
4. Other (n=5)	80% (28-99)	100% (48-100)	20% (-15-55)
Per subgroup of anatomical system:			
1. Pulmonary (n=18)	56% (31-78)	67% (41-87)	11% (-3-26)
2. Cardiovascular (n=37)	43% (27-61)	54% (37-71)	11% (-4-25)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-2-64)
4. Other (n=8)	88% (47-100)	75% (35-97)	-13% (-35-10)

[a] Conventional autopsy was not able to establish a cause of death in ten cases.

Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they were correctly diagnosed as the immediate cause of death before and after virtual autopsy.

	Correct COD, both before and after PMCT.	Incorrect COD before PMCT. Correct COD after PMCT.	Correct COD before PMCT. Incorrect COD after PMCT.	Incorrect COD, both before and after PMCT.
Infections	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i.[b] 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis[a] 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
Perfusion disorders	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno-occlusive disease 1x bowel ischemia due to adhesions
Hemorrhages	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
Other	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

[a] Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced ventriculoperitoneal drain in another case. [b] sepsis e causa ignota. COD: immediate cause of death.

Table 5. Sensitivity and specificity for type of pathology and anatomical system diagnosed before and after virtual autopsy with PMCT.

	Sensitivity			Specificity		
	Before PMCT (95% CI)	**After PMCT (95% CI)**	**Difference (95% CI)**	**Before PMCT (95% CI)**	**After PMCT (95% CI)**	**Difference (95% CI)**
A. Type of pathology (n=78)[a]	**65% (54-76)**	**83% (73-91)**	**18% (9-27)**	**N/A[b]**	**N/A[b]**	
Per subgroup:						
1. Infection (n=26)	69% (48-86)	85% (65-96)	15% (2-29)	96% (87-100)	92% (81-98)	-4% (-9-1)
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)	23% (0-46)	98% (92-100)	100% (94-100)	2% (-1-5)
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	21% (5-36)	95% (85-99)	93% (81-99)	-2% (-12-87)
4. Other (n=5)	100% (48-100)	100% (48-100)	0% (0-0)	99% (93-100%)	99% (93-100%)	0% (0-0)
B. Anatomical system (n=78)[a]	**65% (54-76)**	**85% (75-92)**	**19% (9-30)**	**N/A[b]**	**N/A[b]**	
Per subgroup:						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	17% (-1-34)	95% (86-99)	95% (86-99)	0% (-8-8)
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	21% (6-35)	100% (91-100)	95% (82-99)	-5% (-12-2)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-2-64)	98% (92-100)	100% (94-100)	2% (-1-5)
4. Other (n=8)	88% (48-100)	88% (48-100)	0% (-35-35)	97% (90-100)	94% (86-98)	-3% (-7-1)

[a] Autopsy was not able to establish the involved type of pathology and anatomical system in eight cases. [b] Not applicable.

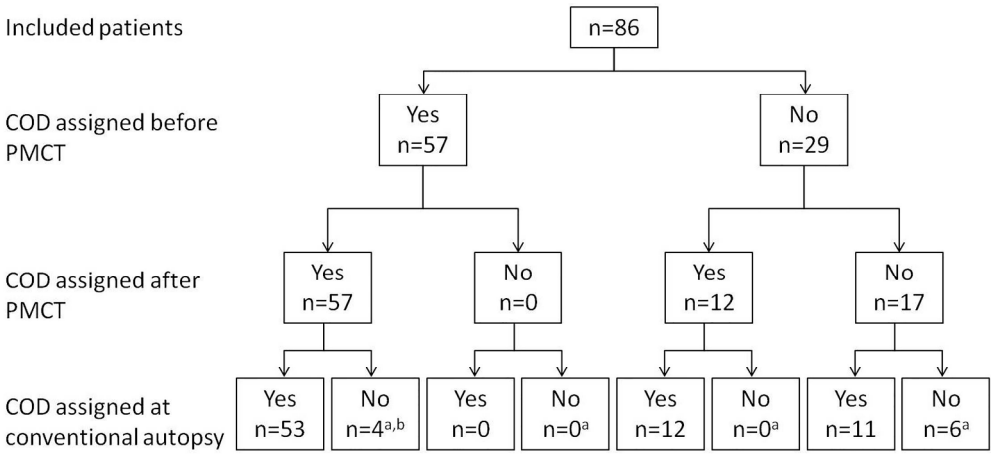

Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.
a No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. b In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

379x172mm (300 x 300 DPI)

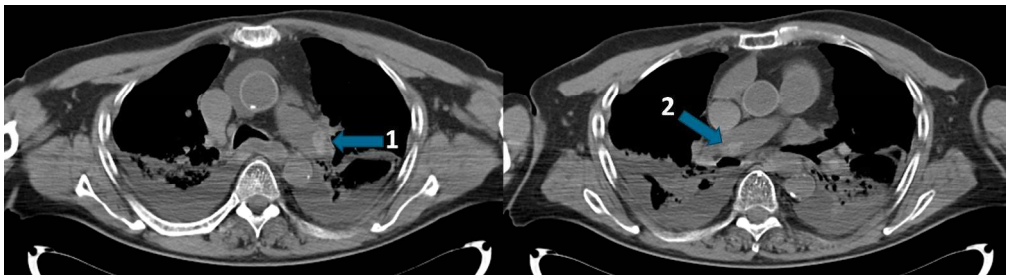

Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy. ‼ ┼ This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

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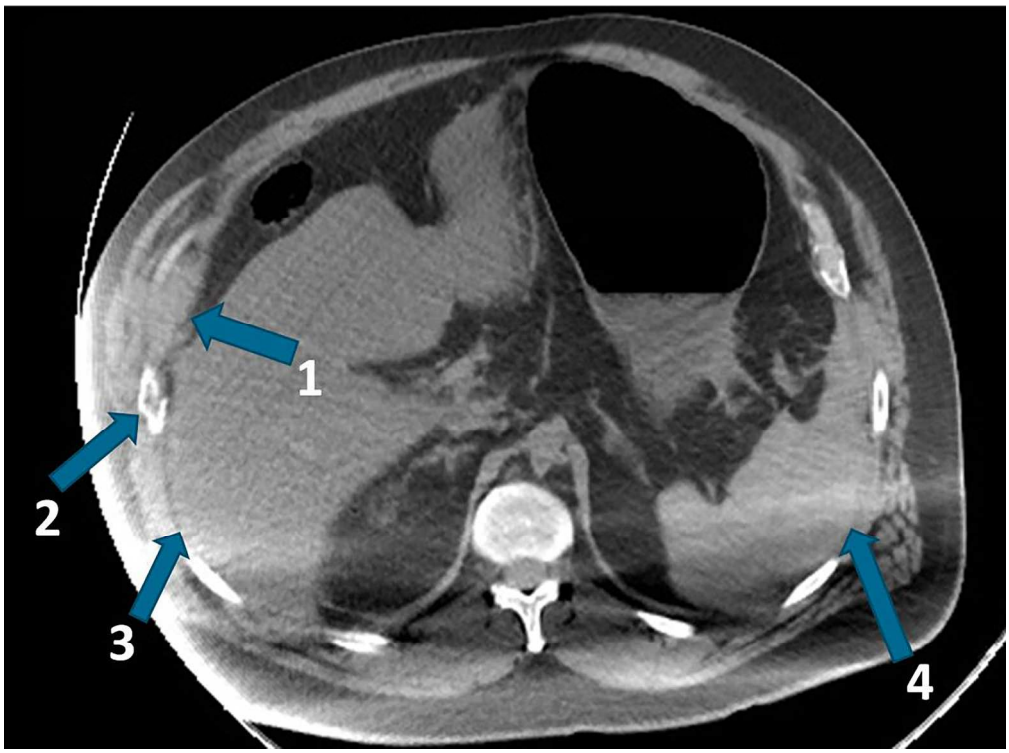

Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.‼ ┼ This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

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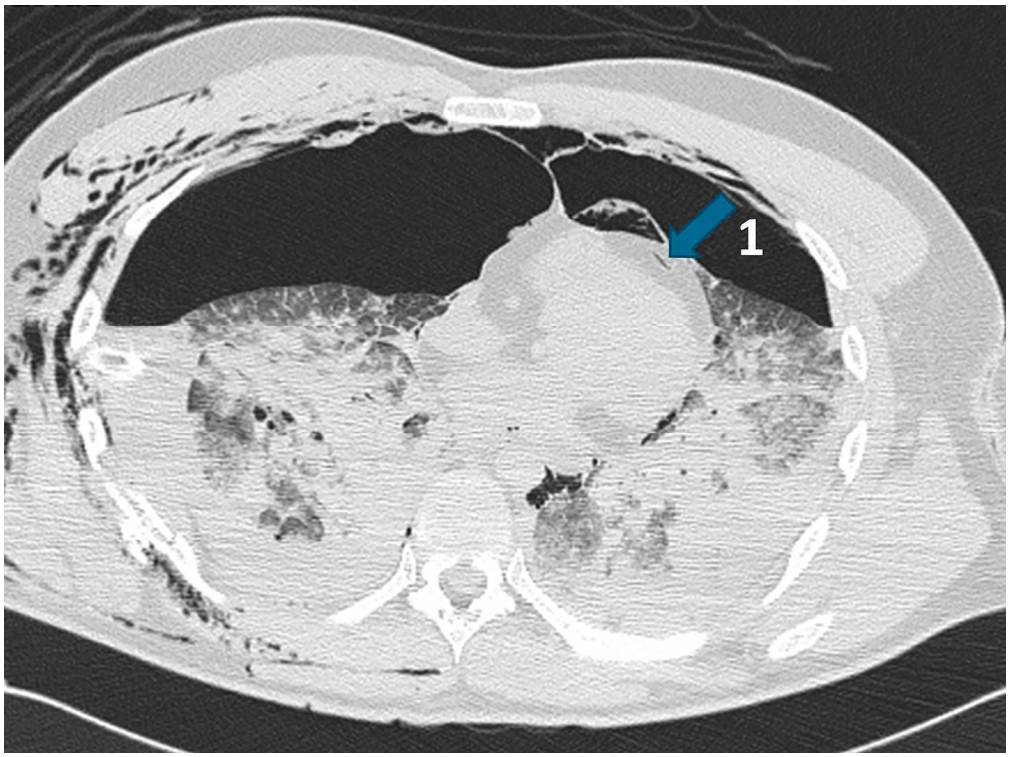

Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy. This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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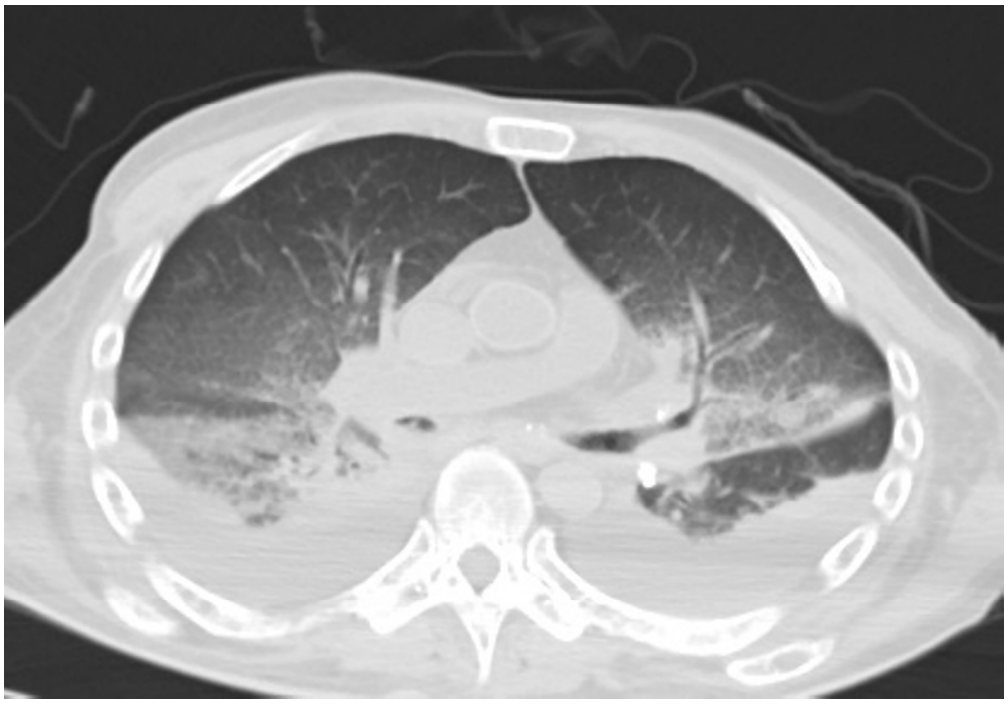

Figure 5. Normal postmortem changes could mask underlying pathology. This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

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Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
Participants	**6**	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
Test methods	**10a**	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	(6)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	8 ~~See supplementary file: 'response to editorial request'~~
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	10
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table ~~2~~3, page 22-~~23~~
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table ~~2~~3 + 5
	25	Any adverse events from performing the index test or the reference standard	
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	4, 13-1~~6~~5
	27	Implications for practice, including the intended use and clinical role of the index test	13-1~~6~~5
OTHER INFORMATION			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5

	30	Sources of funding and other support; role of funders	5

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.