Re-discovery of the oldest tool

Extended utilization of Autopsy/Forensic pathology

Hyejong Marshall/ 송혜정

▸ 2006-2011   Intern, Anatomic Pathology Resident/Fellow, Samsung Medical Center, Korea

▸ 2011-2012   Visiting Scholar, Miami-Dade County, FL

▸ 2014-2017   Anatomic Pathology Resident, Jackson Memorial Hospital/ University of Miami, FL

▸ 2017-2018   Forensic Pathology Fellow, Miami-Dade County, FL

▸ 2018-   Assistant Medical Examiner, Cook County, IL

Autopsy

▶ Postmortem examination

  ▶ cf. External inspection only

Hospital setting	Forensic setting
	Under law
Family's permission necessary	Family's permission not necessary (may accommodate tradition)
	Individual identification

The oldest tool for pathologists

▸ Autopsy
  - academic dissection by Herophilus of Alexandria (circa 300 B.C.)
  - correlated with symptoms by Galen of Pergamum (late 2nd century)

▸ Microscope
  - first microscope by Hans and Zacharias Janssen (1590)
  - observing "cells" by Robert Hooke (1667)

▸ Hematoxylin stain
  - may have been tried (around late 1600)
  - widely spread after Wilhelm von Waldeyer's publicatin (1863)

▸ Polymerase chain reaction(PCR)
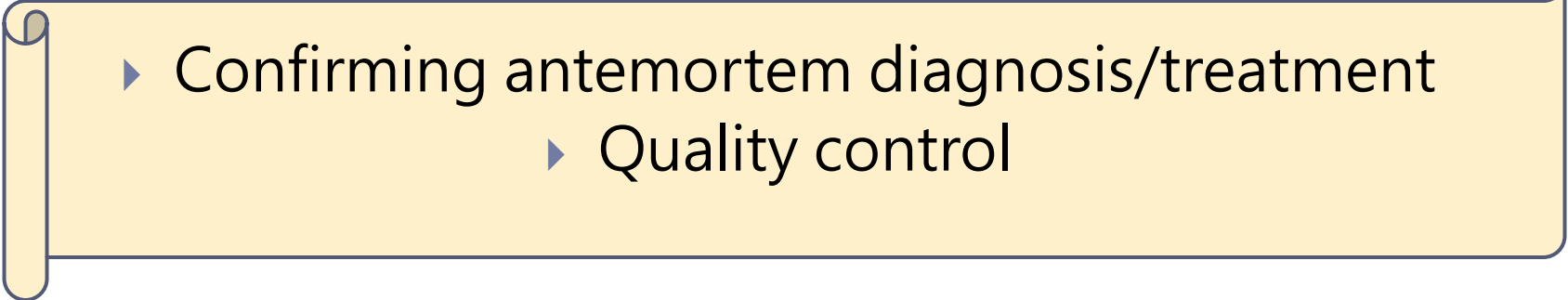 - Kary Mullis (1983)

"But is it still useful?"

Benefits of Nonforensic Autopsies

▸ Education for practitioners and trainees
(e.g., demonstration of pathological findings in advanced illness and uncommon conditions)

▸ Identification and elucidation of emerging and re-emerging diseases

▸ Local quality assurance for all aspects of antemortem diagnoses, procedure performance, and functioning of medical devices

▸ More accurate vital statistics

▸ More accurate ascertainment of causes of death in research studies

▸ Improved postmarketing surveillance for adverse effects of drugs, devices, and procedures

▸ Identification (or exclusion) of conditions of interest to family members

- Confirming antemortem diagnosis/treatment
  - Quality control

Comparison of Clinical Diagnoses and Autopsy Findings

Six-Year Retrospective Study

Hyejong Song Marshall, MD; Clara Milikowski, MD

● *Context.*—The frequency of autopsies has declined in most developed countries beginning in the latter half of the 20th century. During this time period the technology of medicine made significant advances; however, it is important to regularly reevaluate the role of the autopsy to confirm suspected diagnoses and identify unsuspected findings.

Objective.—To determine what portion of autopsies reveal clinically meaningful unexpected findings.

Design.—Reports that included clinical histories of autopsies performed at Jackson Memorial Hospital during the 6 years between 2009 and 2014 were reviewed by 2 pathologists. Each case was classified using the Goldman Classification.

Results.—In the given time period, 923 autopsies were performed; 512 patients (55.5%) were adults. A total of 334 cases were subject to review after excluding those with a short (<1 day) hospital stay, restriction to a single organ or body cavity, and cases referred from other facilities. A total of 33 of 334 cases (9.9%) were identified as class I discrepancy, where the autopsy revealed a discrepant diagnosis with a potential impact on survival or treatment. Critical findings, such as untreated infection (15 of 33 cases; 45.5%), pulmonary embolism (8 of 33 cases; 24.2%), and undiagnosed malignancy (6 of 33 cases; 18.2%), were found in these cases. Major significant findings that had not been clinically detected, whether clinically manageable or not (class I and II), were found in 65 of 334 cases (19.5%).

Conclusion.—Despite intensive modern clinical investigations, autopsies continue to reveal major antemortem diagnostic errors in a significant number of cases.

(*Arch Pathol Lab Med.* 2017;141:1262–1266; doi: 10.5858/arpa.2016-0488-OA)

Material

‣ Inclusion criteria

  - autopsies of adults (18 year old or older)
  - perfomed at Jackson Memorial Hospital
  - in last six years (2009-2014)

‣ Exclusion criteria

  - patient under 18 years of age
  - referred from outside hospital
  - hospital stay shorter than 1 day
  - single organ/cavity only autopsy

Method

▸ **Reviewing autopsy reports and clinical records if necessary**

▸ **Classification of cases**
 : Goldman classification

Type of error	Class	Definition
Major	1	Directly related to death; if recognized, may have altered treatment or survival
Major	2	Directly related to death; if recognized, would not have altered treatment or survival
Minor	3	Incidental autopsy finding not directly related to death but related to termianl disease process
Minor	4(i)	Incidental autopsy finding unrelated to cause of death
Minor	4(ii)	Incidental autopsy finding contributing to death in an already terminally ill patient
No error	5	Clinical and autopsy diagnoses in complete agreement

▸ **Reaching agreement between two pathologists**

Results

year	2009	2010	2011	2012	2013	2014	total
cases of autopsy	204	151	140	154	137	137	923
cases of age over 18	107	66	76	105	74	84	512
outside case	6	2	4	6	6	5	29
short(<1day) stay	20	13	8	23	13	16	93
single organ or single cavity only	6	4	8	9	13	13	53
	75	47	56	67	42	50	337

Results

Classification		
1	39	11.6%
2	31	9.2%
3	12	3.6%
4	108	32.0%
5	147	43.6%
	337	100.0%

Type of error	Class	Definition
Major	1	Directly related to death; if recognized, may have altered treatment or survival
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No error	5	Clinical and autopsy diagnoses in complete agreement

Results

▸ Findings which could change clinical management

Infection		18	46.2%
	pneumonia	4	
	fungal pneumonia	6	
	viral pneumonia	2	
	meningitis	3	
	toxoplasma	1	
	candida	1	
	perirectal abscess	1	
	renal abscess	1	
Pulmonary embolism		10	25.6%
Cardiovascular		3	7.7%
	retroperitoneal and/or intraabdominal hemorrhage	2	
	cartilagenous emboli	1	
Malignancy		6	15.4%
	lymphoma	3	
	pulmonary carcinoma	2	
	gastric carcinoma	1	
Immunological		1	2.6%
	anaphylactic laryngeal edema	1	
Miscellenous		1	2.6%
	acute interstitial pneumonia	1	
		39	100.0%

Case 1

- 54 year old female
- Previous history of asthma
- Cough, chest pain, diarrhea
- Chest x-ray: lung opacity concerning for infection
- Tx: Antibiotics

Ascites 2.5 L
Multiple nodules
in omentum and mesentery.

Liver

Lung

Spleen

Omentum

Lymph node

CD3

CD4

CD5
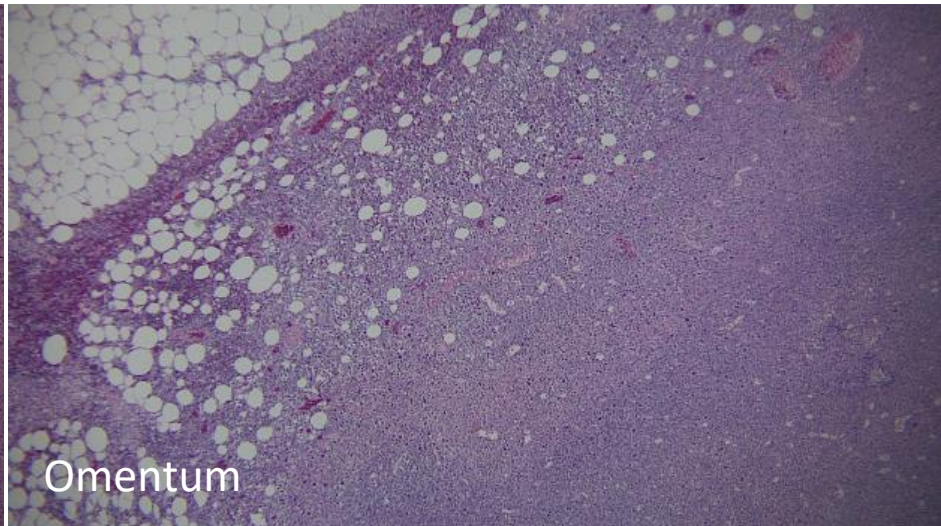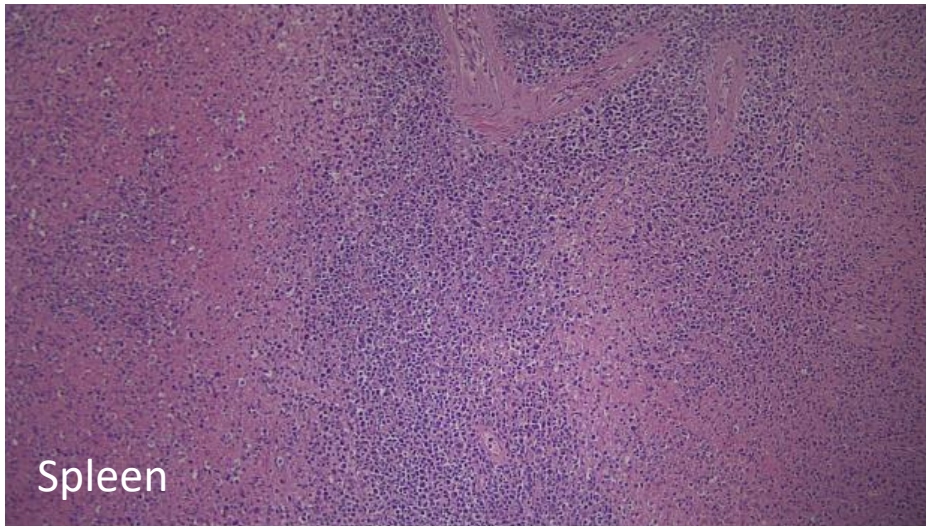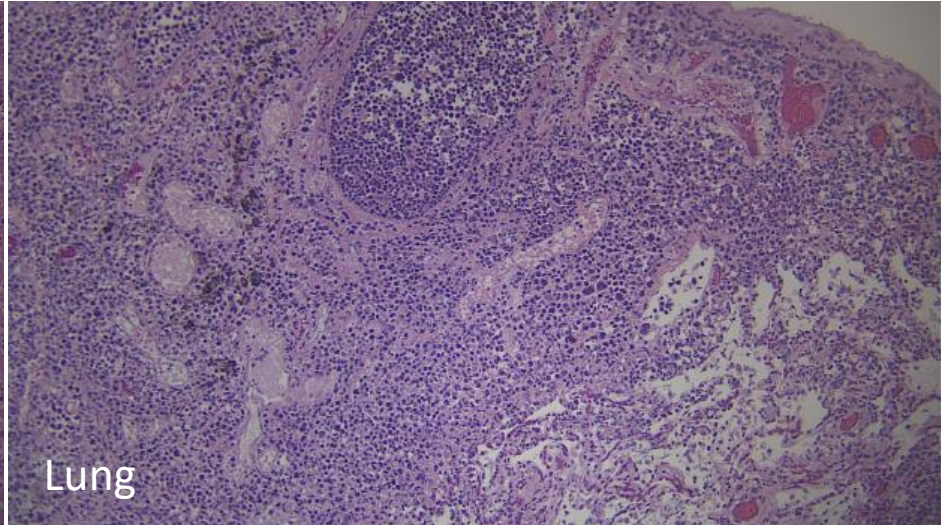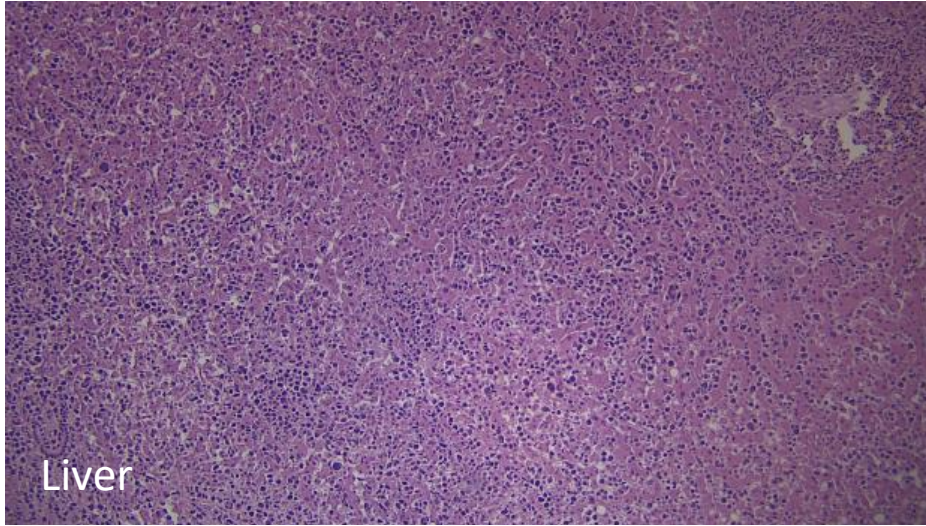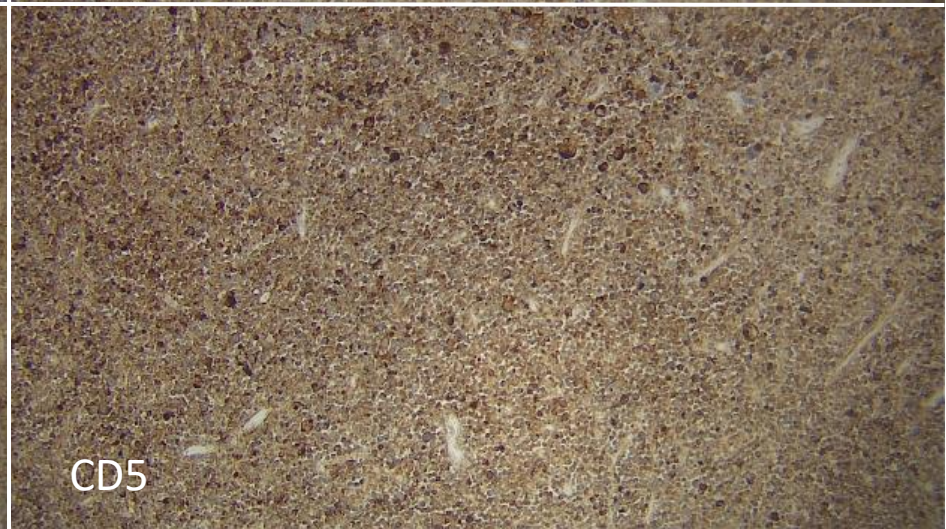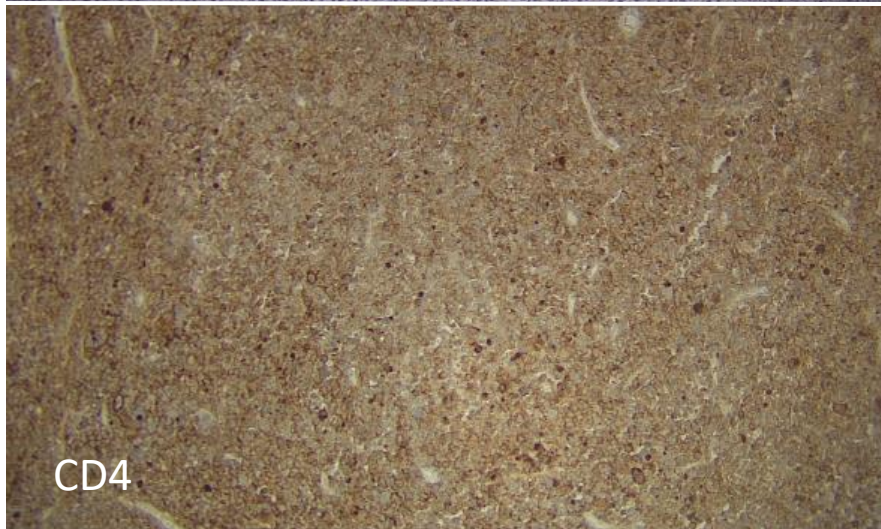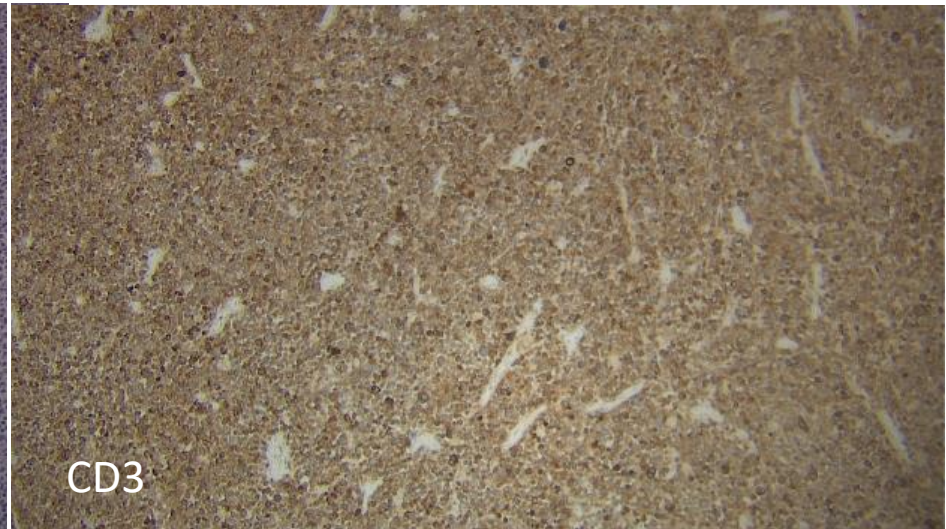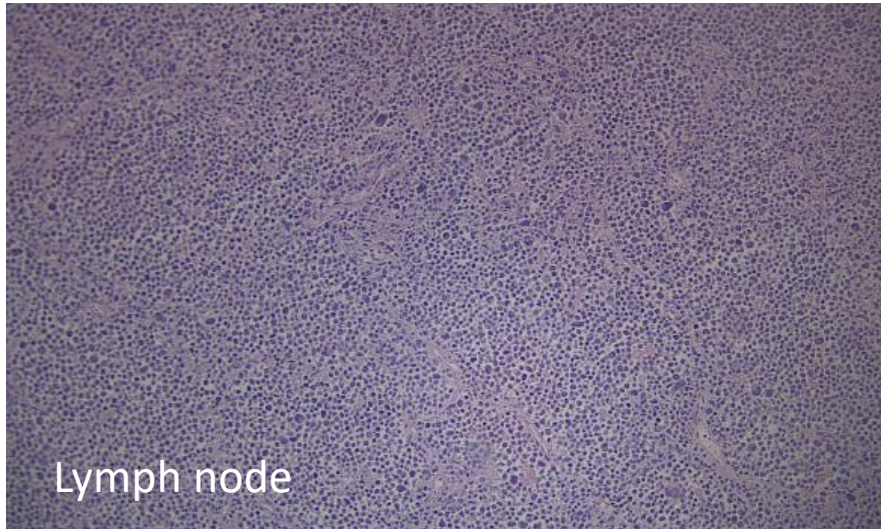
▸ Diagnosis:

Peripheral T-cell lymphoma involving:

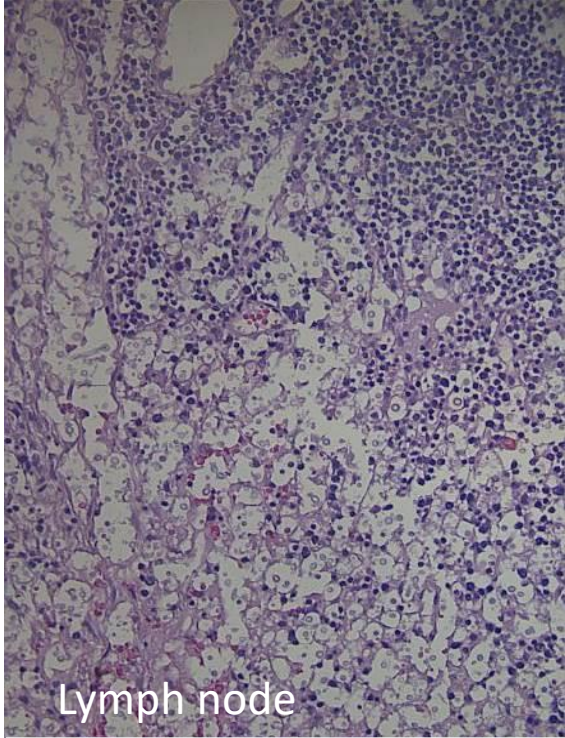parao-aortic, paraesophageal, and mesenteric nodes, spleen, liver, lungs, gastrointestinal tract and omentum

Case 2

- 28 year old male
- Headache, abdominal pain
- HIV negative three months ago

- Elevated LFTs, low WBC
- Acute pansinusitis on brain CT

Lymph node
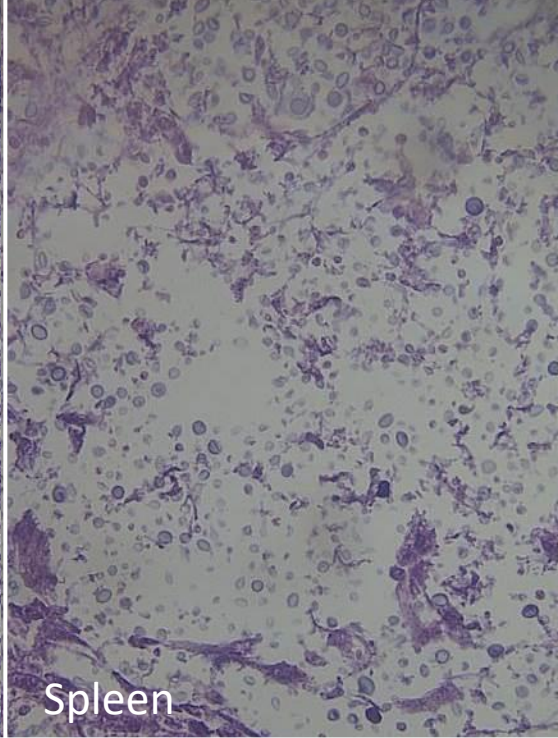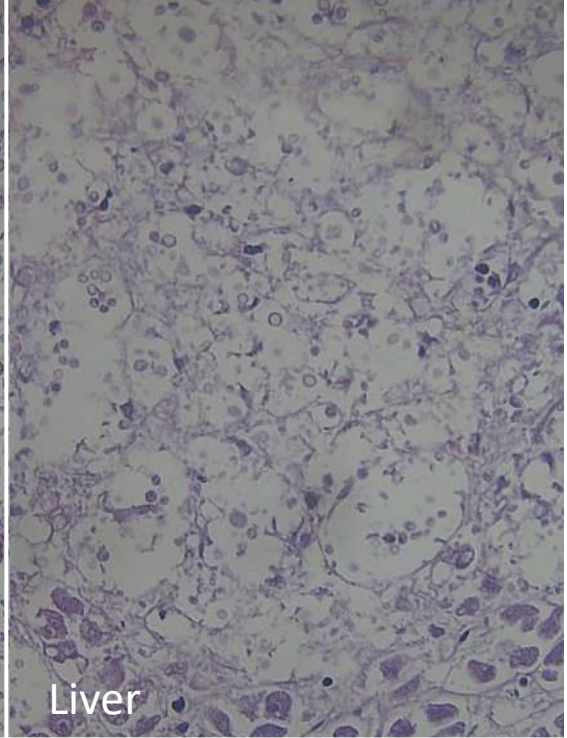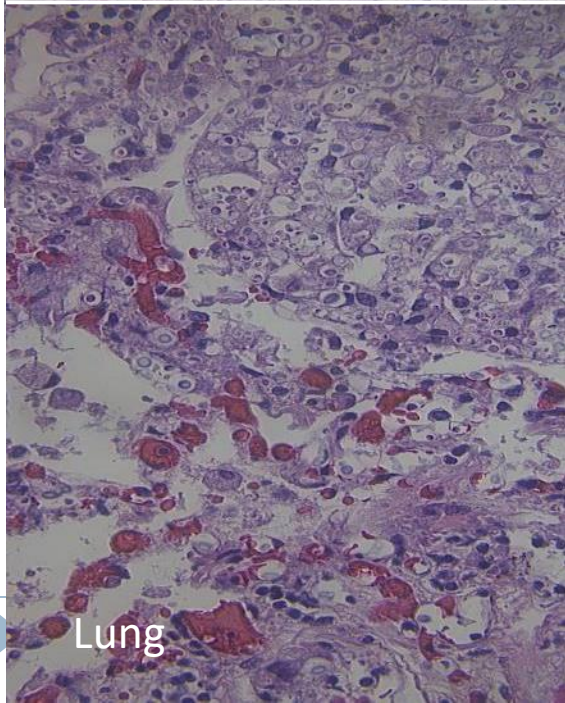
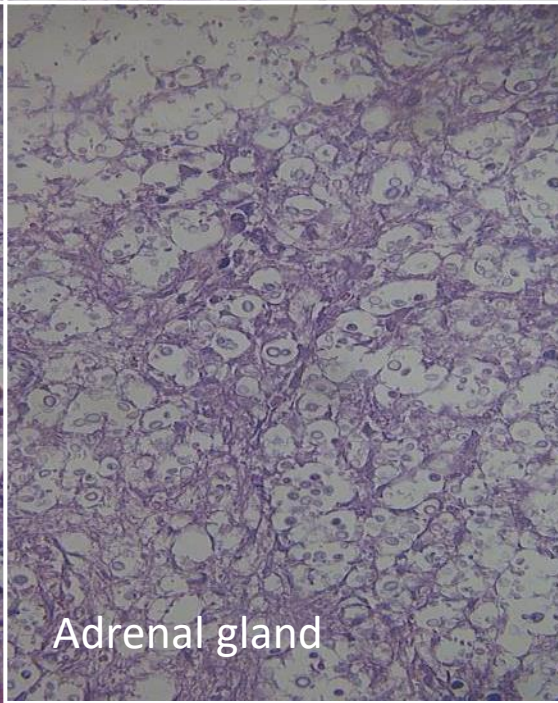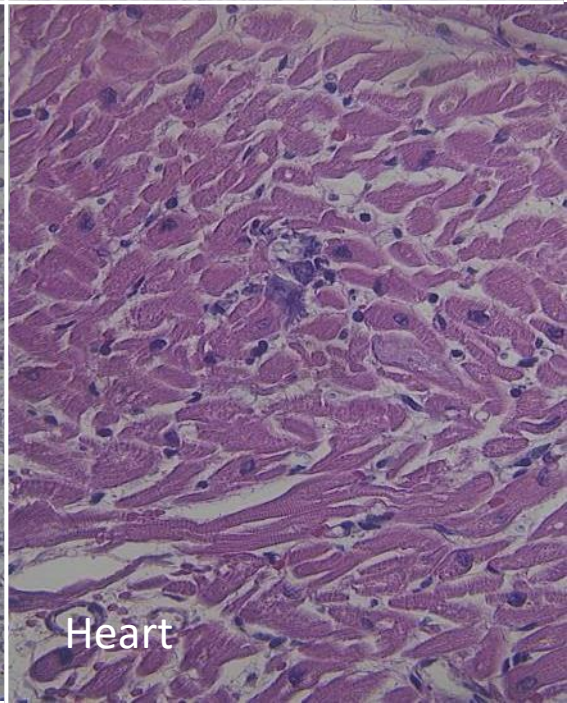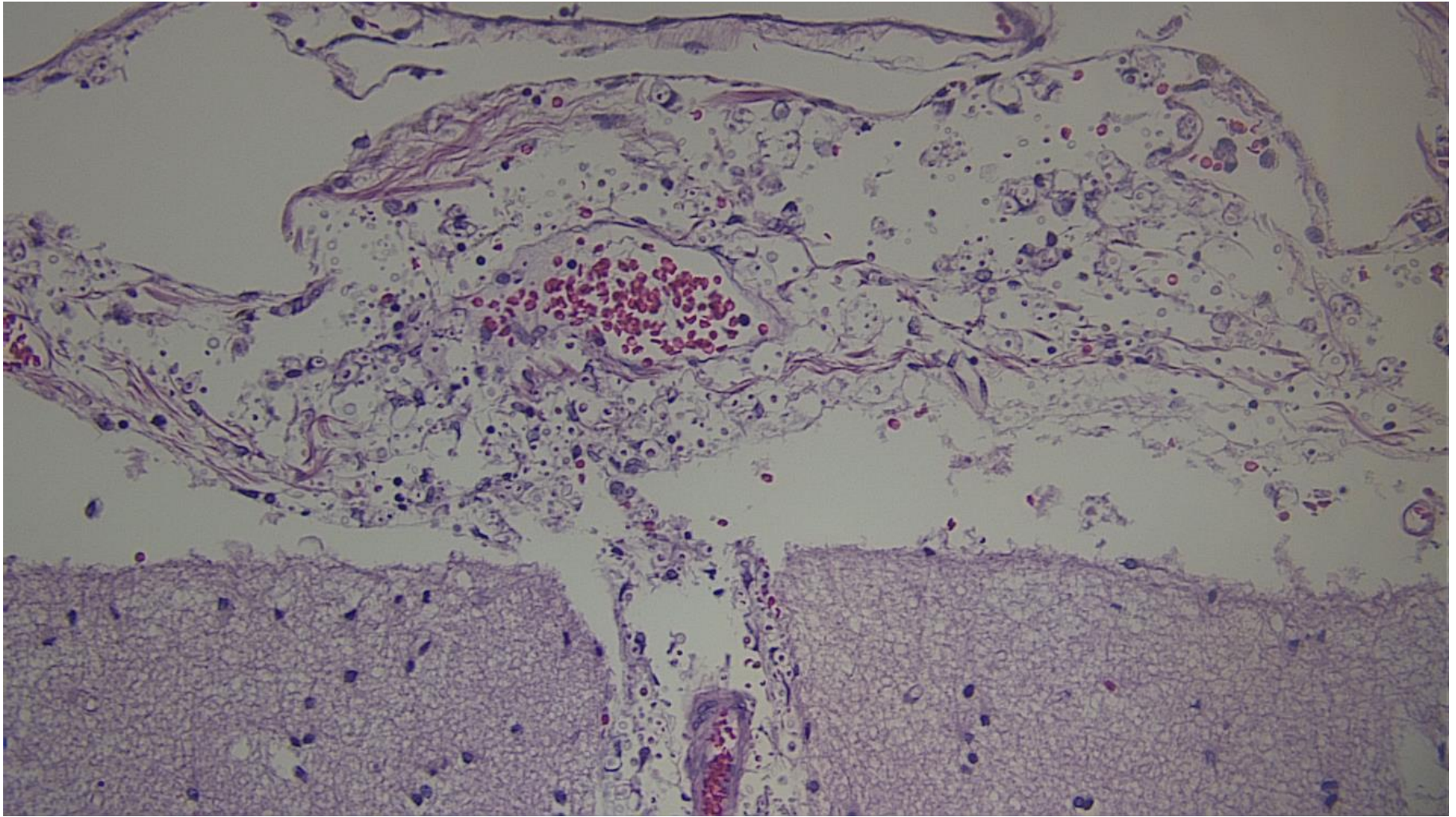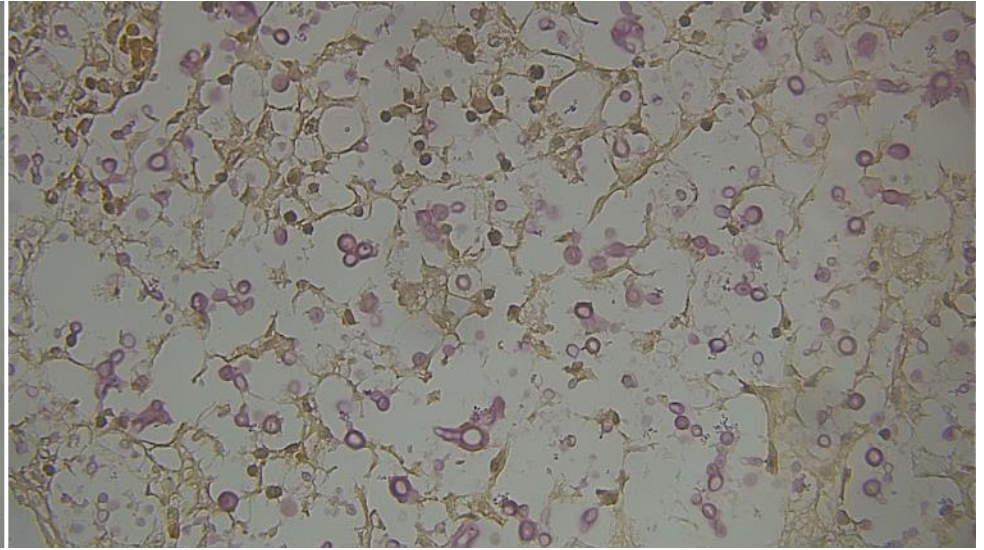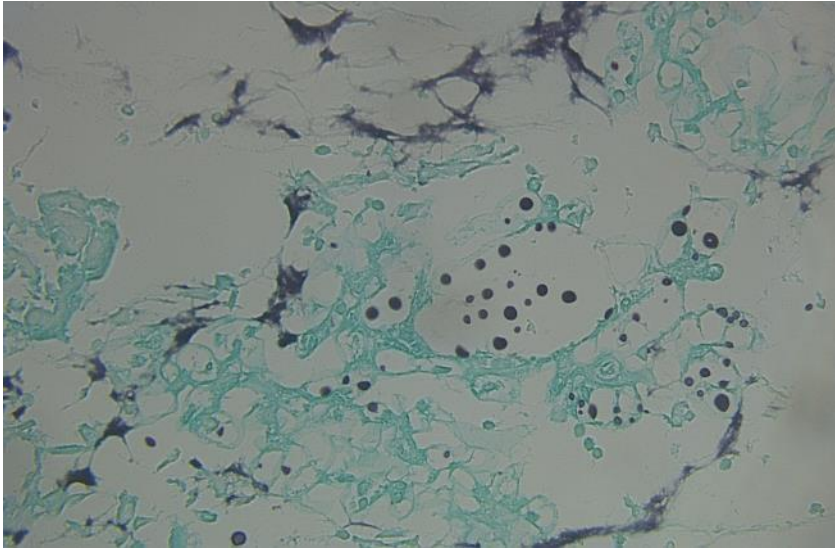Spleen

Liver

Lung

Adrenal gland

Heart

- Diagnosis:

  Disseminated cryptococcosis involving:

 lungs, lymph nodes, spleen, kidneys, adrenals, liver, heart, gastrointestinal tract, sinuses

- HIV result became available postmortem and was positive.

Discussion

▸ ## Most recent and largest meta-analysis

  ▸ Of 53 autopsy series from 1966 to April 2002

  ▸ Median error

    ▸ 23.5% (range, 4.1%-49.8%) for major errors

    ▸ 9.0% (range, 0%-20.7%) for class I errors

  ▸ Analyses of diagnostic error rates yielded relative decreases per decade of 19.4% for major errors and 33.4% for class I errors.

  ▸ Despite these decreases, contemporary US institution could observe a major error rate from 8.4% to 24.4% and a class I error rate from 4.1% to 6.7%.
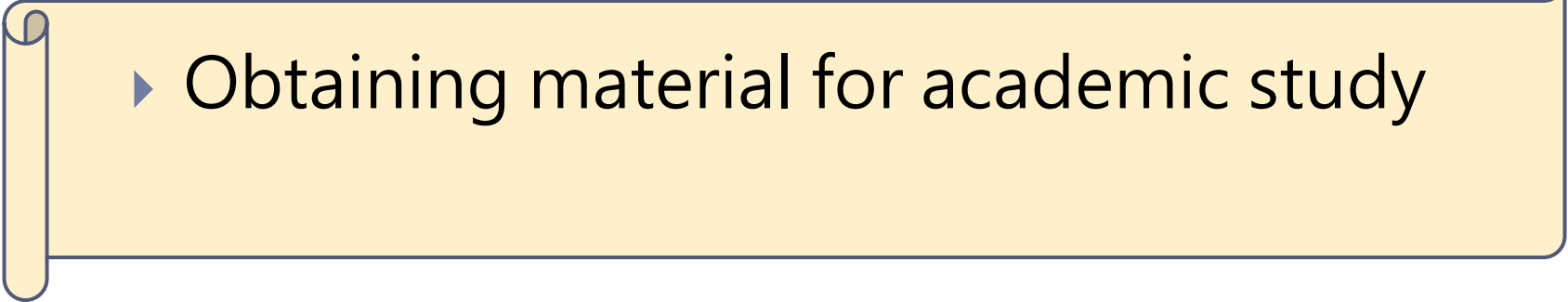
Discussion
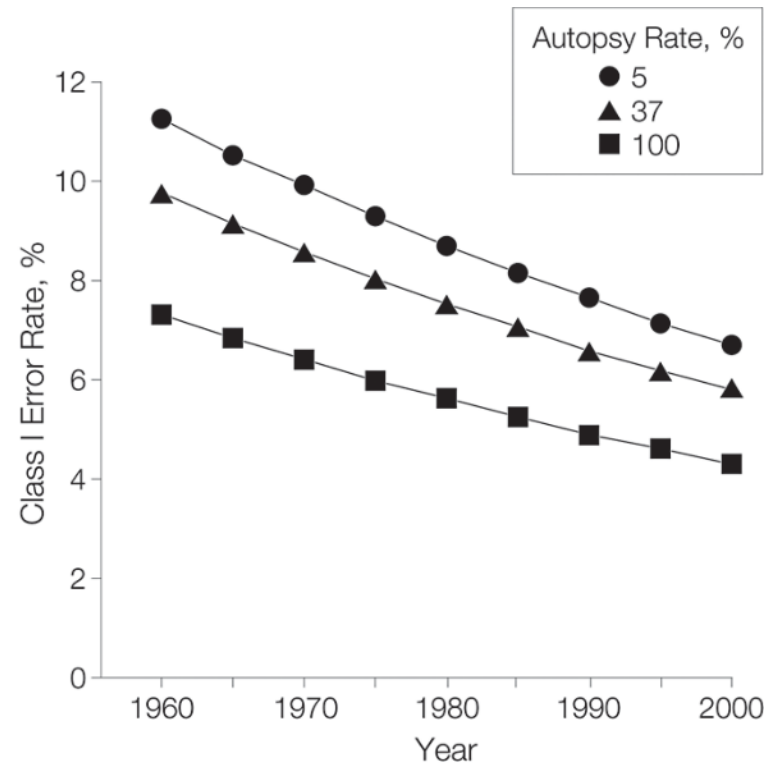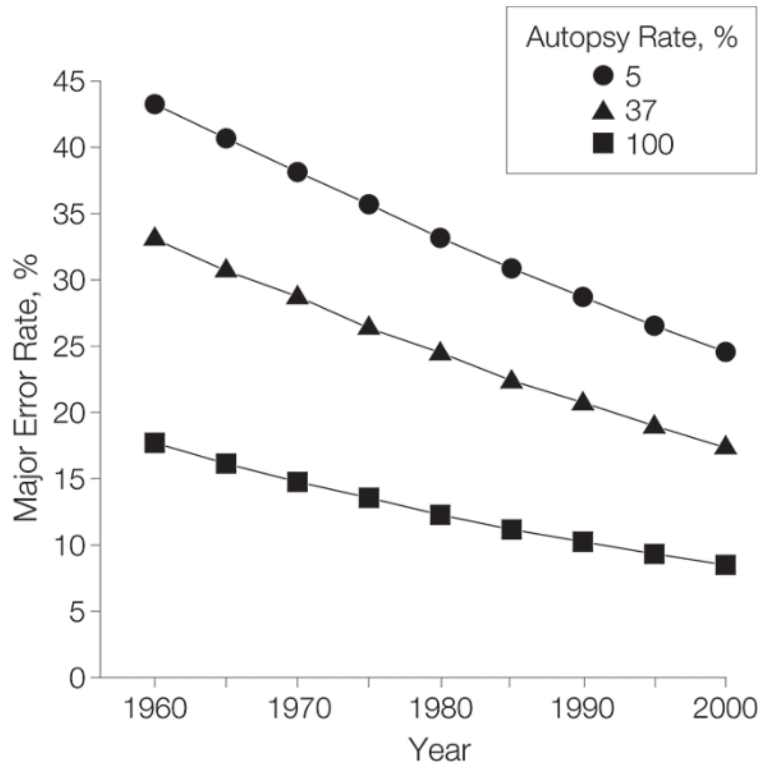
Discussion

▸ Mutiple follow up data from one institution

▸ Autopsy rate declined from 90% in the years from 1972 to 1992 to 54% in the present study.

▸ Major diagnostic errors (class I and II) declined significantly from 30 to 7% over the last 30 years.

▸ Class I errors decreased from 16 to 2% in the year 2002.
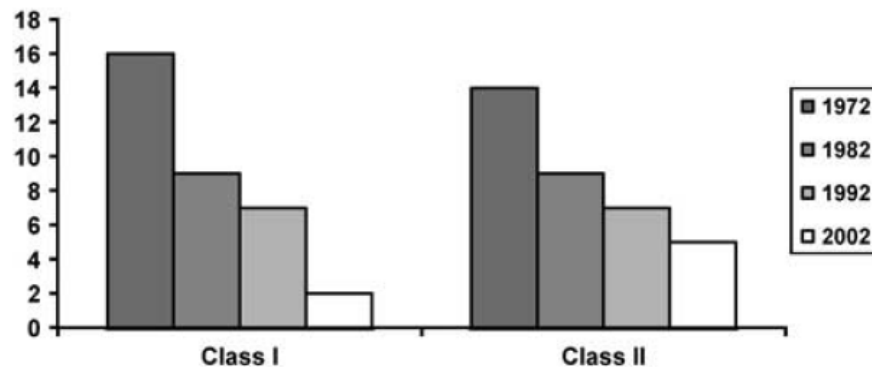
▸ Obtaining material for academic study

- Normal variation
  - Weight, shape, branching…

- Abnormal/Disease
  - Common benign disease prevalence
  - Early disease prevalence
  - Brain

Rapid autopsy

▸ Patient with cancer or certain disease

▸ Consent in advance

▸ Autopsy as soon as possible after death

▸ Obtain specimen with aseptic technique

▸ Advantage
  ▸ Good quantity from various organs
  ▸ Good for preserving DNA/RNA
  ▸ No invasive intervention to alive patient

▸ Disadvantage
  ▸ Needs special techniques and facility
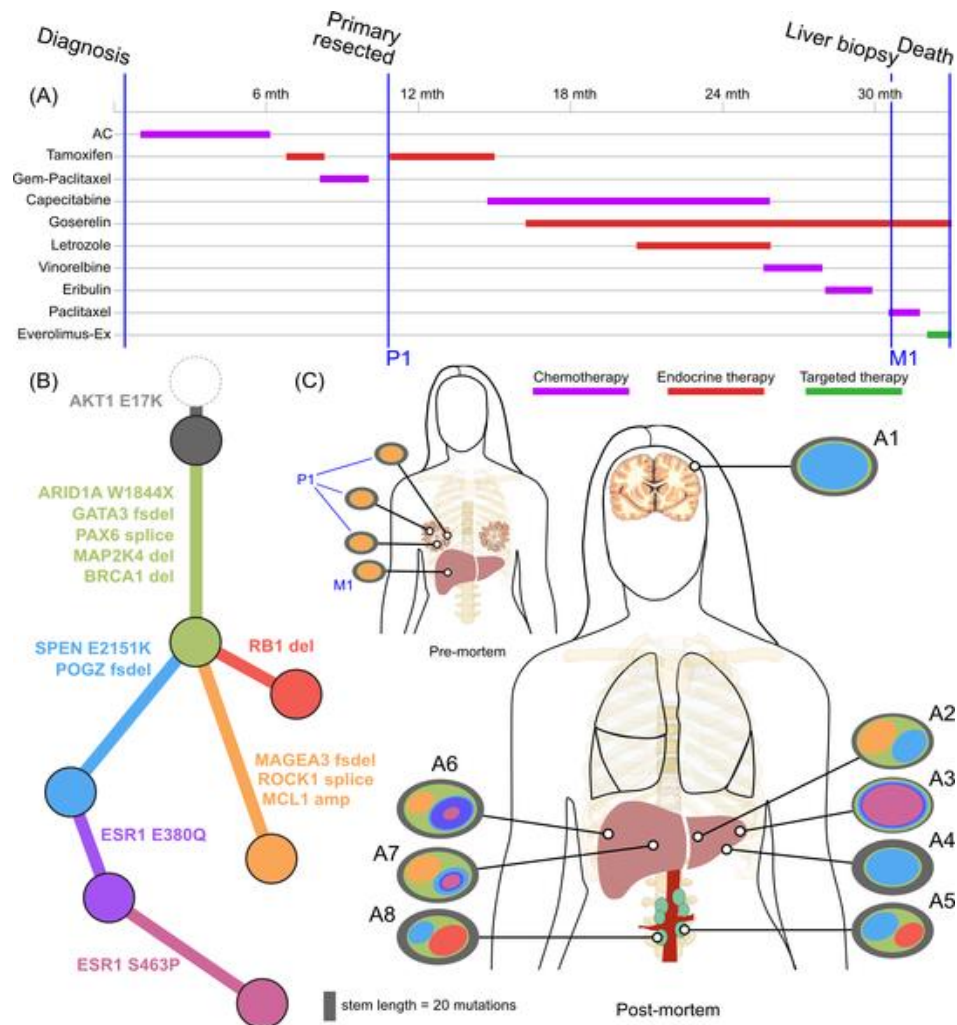
Savas P, Teo ZL, Lefevre C, Flensburg C, Caramia F, et al. (2016) The Subclonal Architecture of Metastatic Breast Cancer: Results from a Prospective Community-Based Rapid Autopsy Program "CASCADE". PLOS Medicine 13(12): e1002204. https://doi.org/10.1371/journal.pmed.1002204

87% are willing to donate tissue

Metastatic breast cancer patients: attitudes toward tissue donation for rapid autopsy.

Achkar T[1], Wilson J[2], Simon J[3], Rosenzweig M[3], Puhalla S[3].

⊕ Author information

Abstract

Rapid autopsy (RA) offers a unique opportunity to obtain a large amount of metastatic tissue at death in order to deepen existing understanding of cancer evolution and heterogeneity. In breast cancer, understanding metastasis is particularly valuable given that treatment regimens are based on the traditional hormone and HER2 receptor status as well as evolving genomic data of the primary tumor. We aimed to elucidate the attitudes and interests of patients with metastatic breast cancer (MBC) toward RA, and to identify associated demographic or disease characteristics that may influence patient attitudes and interest. Ninety-seven patients with MBC were surveyed over the course of 12 months at a large, urban comprehensive cancer center's breast cancer outpatient clinic. 93/97 patients completed the survey sufficiently to be included in the analysis. Fisher's exact test was employed for categorical variables, and t test and rank-sum tests for continuous variables. p values ≤0.05 were considered statistically significant. Of the 93 patients with MBC analyzed, 87 % were willing to donate tissue at death. Marital status and younger age were associated with willingness to donate (p = 0.000, p = 0.025, respectively). Race, employment status, religion/spirituality, and cancer subtype were not associated with likelihood of donating. Forty-five percent of patients felt that doctors should ask about RA at diagnosis of early-stage breast cancer rather than during late-stage disease. These data provide evidence that an RA program would be welcomed by patients and requires initiative by providers.

▸ Supporting forensic science study

The Potential Use of mRNA to Determine the Postmortem Interval

Any help for postmortem interval?

- Body temperature
- Electrical stimulation of the facial muscles
- Potassium
- Amino acids
- Neurotransmitters
- Decompositional by-products

Possible use of RNA in forensics

- Detection of cell-specific gene expression
    - Identification of body fluids
- Quantification of RNA degradation
    - Determination of post-mortem interval
    - Determination of the age of stains
    - Assessment of RNA quality
- Reactive changes of gene expression
    - Wound age determination
    - Determination of vitality and survival time
- Functional status of cells and organs
    - Diagnosis of cause and mechanism of death

If mRNA is

▸ Unstable,

▸ AND degrades in a constant rate,

▸ AND the quantity can be properly measured,

it may be used to estimate
the postmortem interval (PMI).

Previous studies

Previous studies

Previous studies

qPA$_{act}$ vs. age: 0 - 59 months

(a)

M. Bauer et al. Forensic Science International 138 (2003) 94–103
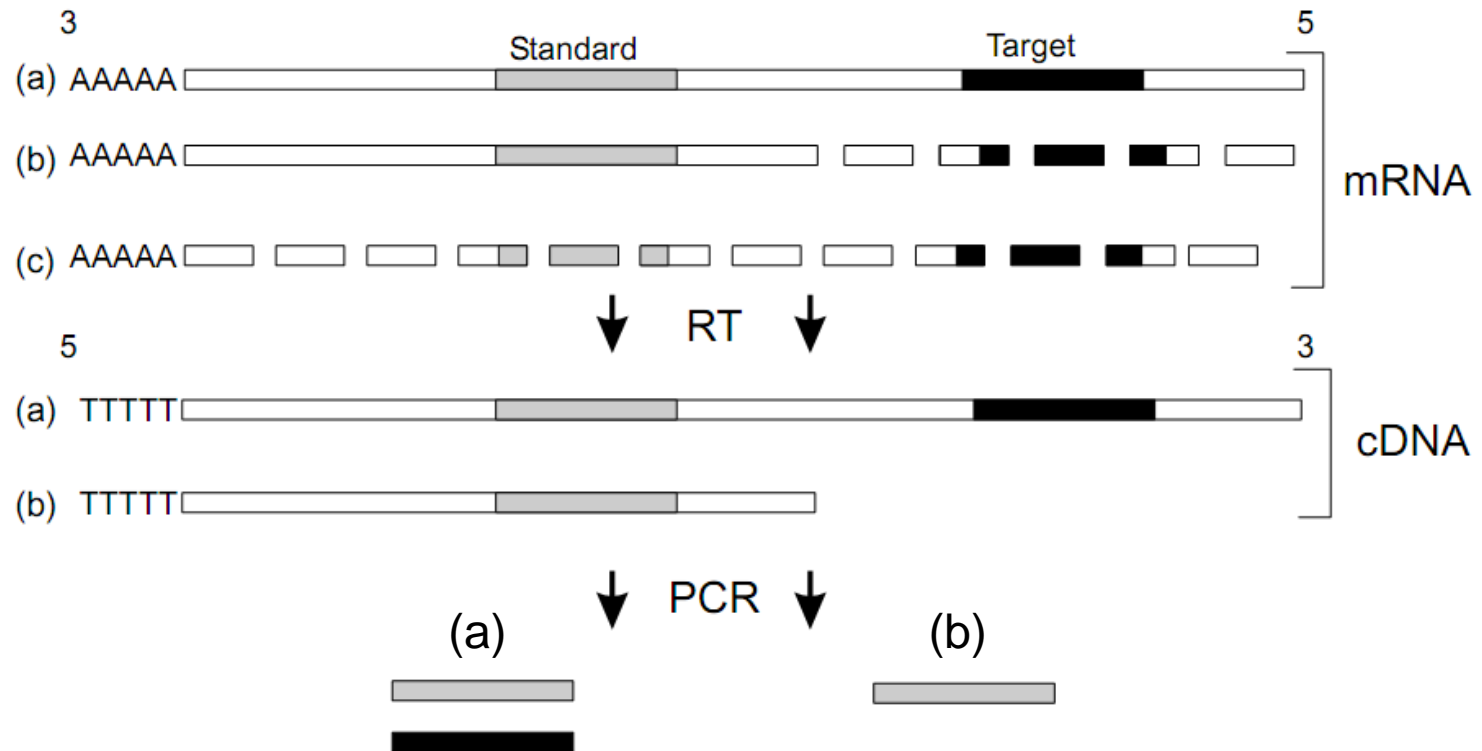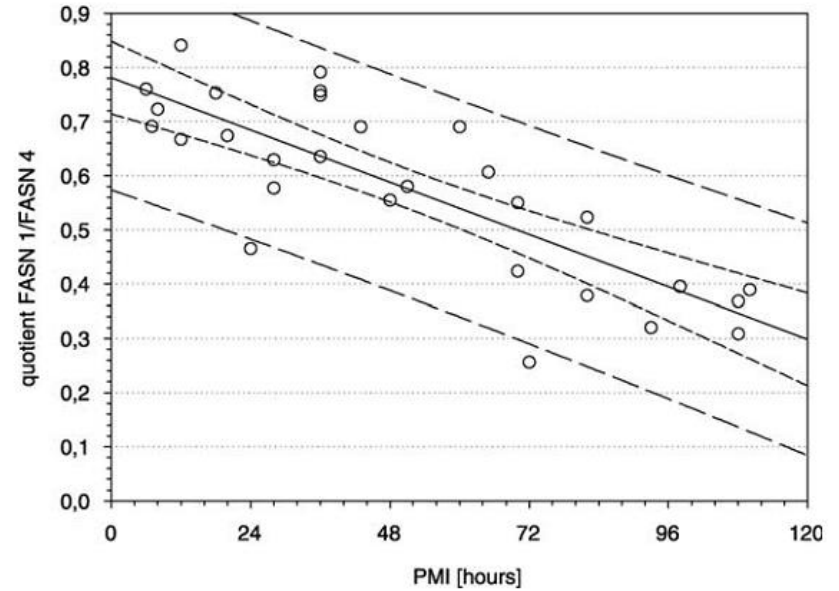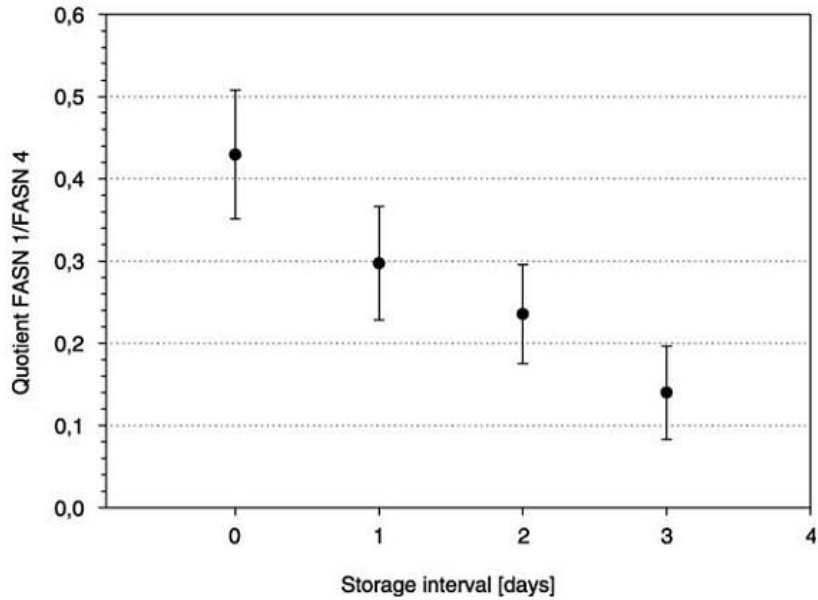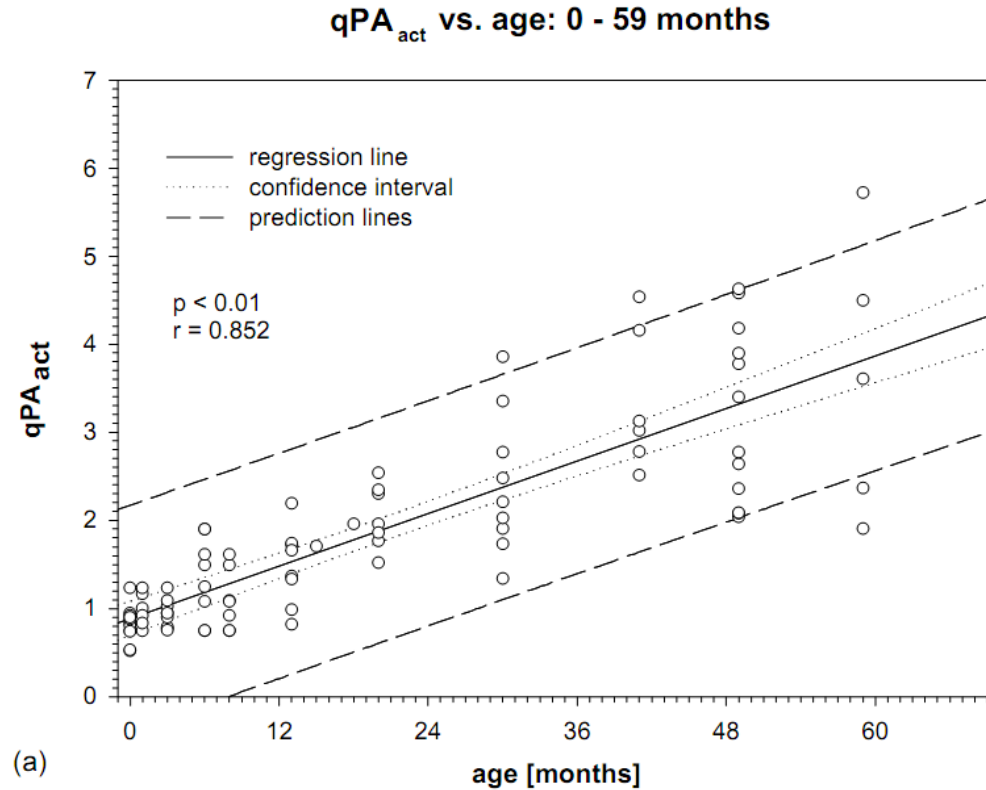
Previous studies
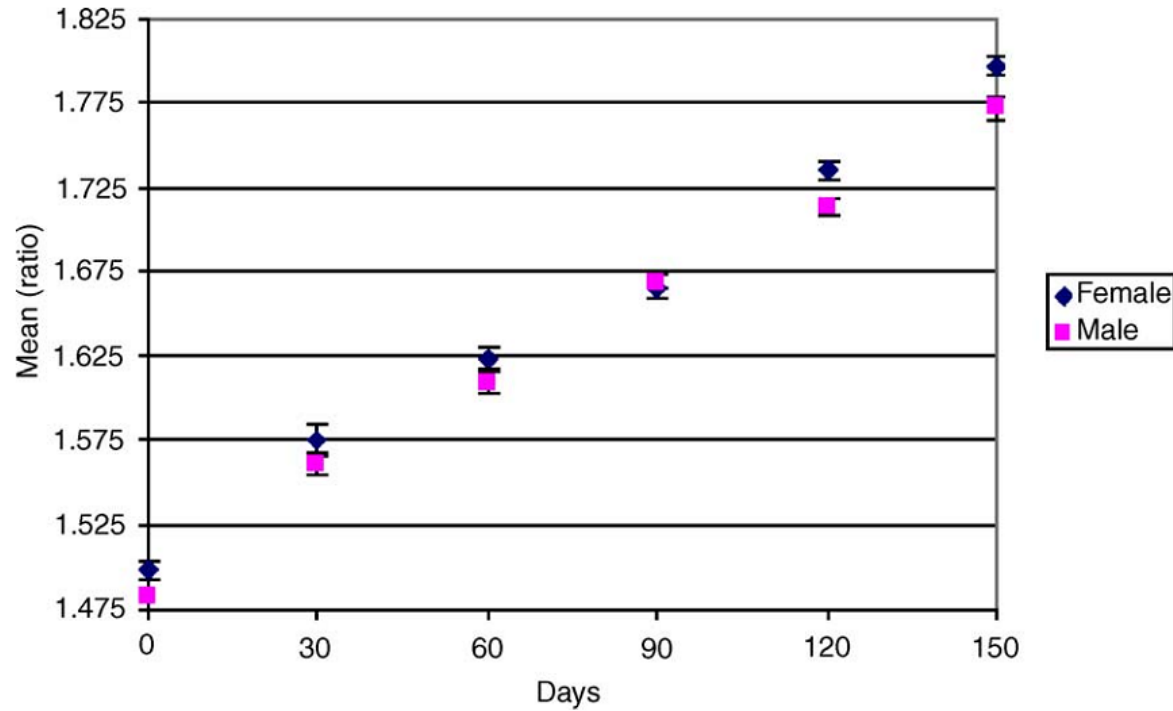
Material and Method

- Modified radical mastectomy specimens
- The recorded times of reception were designated as the starting times of each specimen
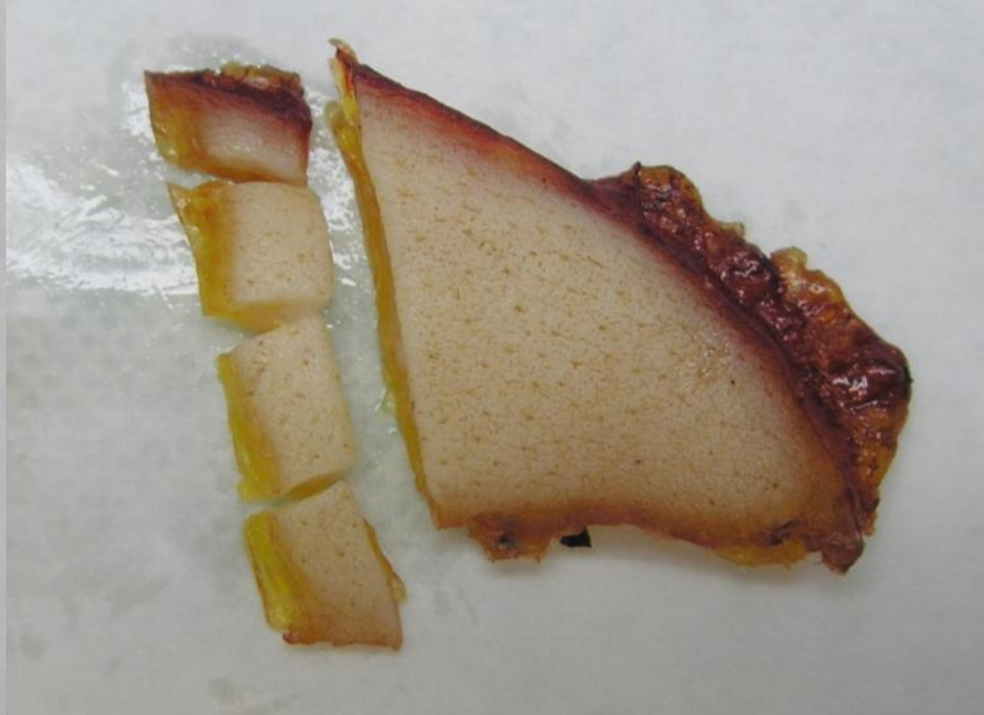
Material and Method

▸ Frozen sections

  ▸ Ten to fifteen, 20 micrometer sections

▸ RNA extraction

▸ Reverse transcription-polymerase chain reaction (RT-PCR)

  : housekeeping genes

  : two locations in fatty acid synthase (FASN)
   and two locations in β-actin
  (M. Bauer et al. Legal Medicine 5 (2003) 220–227)

▸

Material and Method

- Ct
- Delta Delta Ct

Result

- Forty-four samples from nine cases
- 3-10 samples per case
- Median of earliest elapsed times was 8.3 hours (range: 0 to 18 hours)
- Median of maximum elapsed times was 40.0 hours (range: 24.5 to 92.5 hours).

Result

Table 3. Ct Values of each RNA Segment and Relative Quantification by the $\varDelta\varDelta C_t$ Method

Case	Serial Number	Elapsed Time (h)	$\varDelta$Ct				2^-$\varDelta\varDelta$Ct (Target/Reference)		
			FASN1	FASN2	ACTB1	ACTB2	FASN1 /FASN2	FASN1 /ACTB1	ACTB2/ ACRB1
1	1	18.0	33.31	25.57	20.96	26.50	1.00	1.00	1.00
	2	21.0	33.42	26.46	21.48	27.01	1.72	1.33	1.00
	3	39.0	33.12	27.25	21.83	27.27	3.66	2.09	1.07
	4	42.0	35.38	28.06	22.44	27.91	1.33	0.67	1.06
	5	45.0	34.21	28.04	22.46	27.95	2.98	1.52	1.03
	6	48.5	35.75	28.48	22.95	28.73	1.38	0.73	0.85
	7	63.0	35.83	28.37	23.16	28.83	1.21	0.80	0.91
	8	66.0	36.79	27.91	22.46	27.92	0.45	0.25	1.06
	9	68.0	34.07	27.85	22.31	28.27	2.86	1.50	0.74
2	1	13.0	38.00	27.58	21.75	27.52	1.00	1.00	1.00
	2	16.0	34.60	27.47	22.20	27.08	9.76	14.40	1.86
	3	19.0	33.34	27.79	21.90	26.71	28.94	27.81	1.94
	4	22.0	33.27	27.94	21.98	26.39	34.00	31.05	2.56
	5	37.0	36.08	28.64	23.21	27.90	7.85	10.39	2.12
	6	40.0	31.63	27.77	22.79	27.15	93.72	169.29	2.65

▸ **Results**
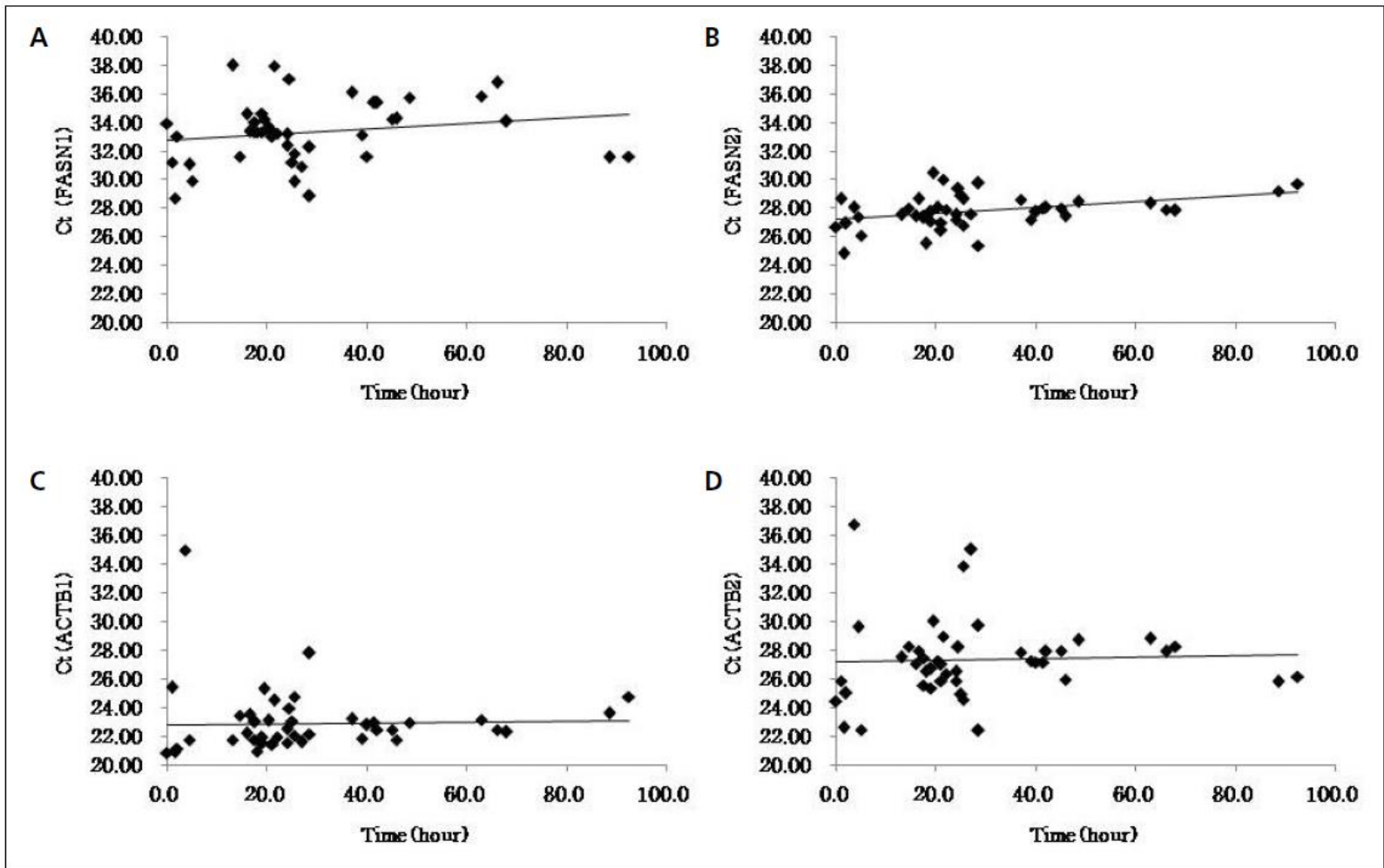
Fig. 3. These graphs show the relationship between the Ct values with elapsed time.
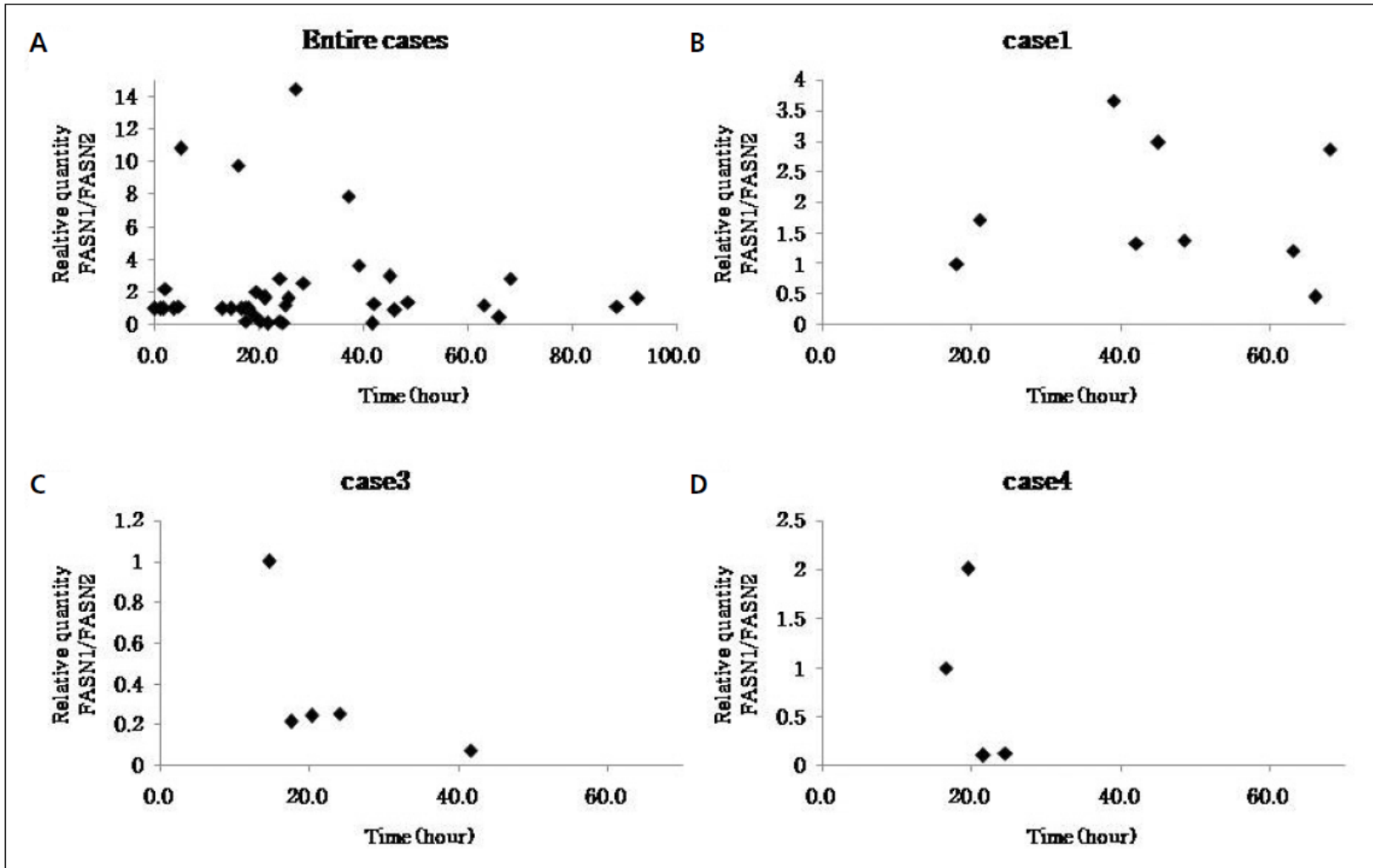
Fig. 4. These graphs show the relative quantifications of FASN1 along elapsed time (calibrator: FASN2).

Discussion
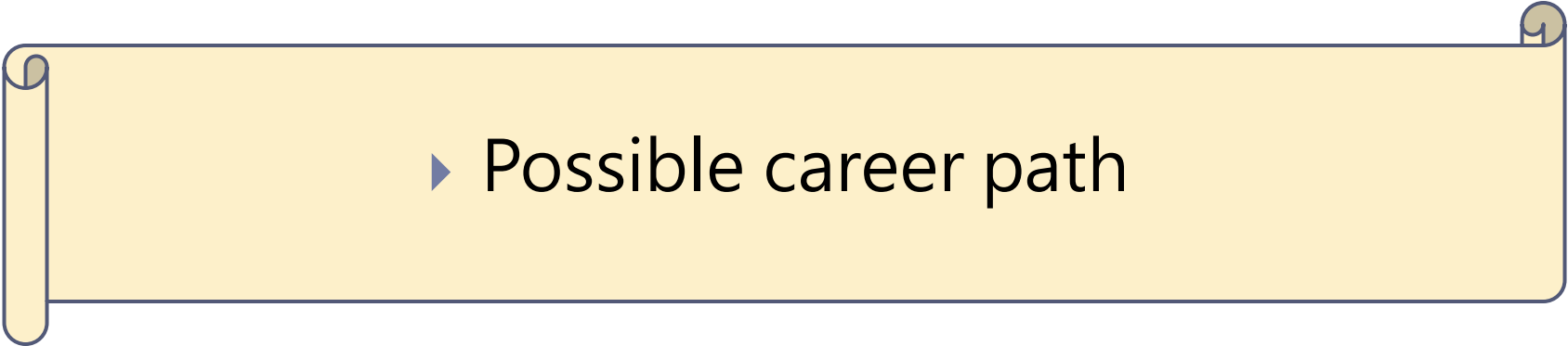
- First study in tissue
  - Skin: easier to sample/ train to sample
- Relatively homogeneous samples
- Sequential sampling from one specimen
- First study using gene specific primer

Discussion: Limitation

▸ Model study

▸ Not tightly controlled environment

▸ Not regularly sampled

▸ Possible career path

- 500 board-certified forensic pathologists in the USA
- 30-40 new forensic pathologists/ year
- Opioid crisis increased demand
  : Toxicology-related cases need autopsy

- Primary care physicians median income $202,392/yr
- Medical specialities median income $356,885/yr
- Pathologists' income survey $344,000/yr
- Forensic pathologists' first year salary $180-200K/yr

- Advantage
  - Many employment chances including part time oppotunities
  - Flexible time use

- Disadvantage
  - Decomposed bodies
  - Court testimonies

Chances for Sabbath year/ Visiting: https://www.thename.org/international-relations

Medical Examiner	Office	City	State	Contact Information
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Jon Lucas	Los Angeles County Department of Medical Examiner Coroner	Los Angeles	California	jlucas@coroner.lacounty.gov 323-343-0522
John Thornburg		Monterey	California	831-755-3761
Michael Hunter		San Francisco	California	Michael.hunter@sfgov.org
James Caruso	Office of the ME	Denver	Colorado	James.caruso@denvergov.org 720-337-7600
Roger Mitchell	OME in DC	Washington, DC	District of Columbia	Terencia.davenport@dc.gov 202-698-9000
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Take home message

▸ The oldest tool of pathology is still useful.

▸ Enjoy performing autopsy if you can.

▸ Look for a chance to collaborate with autopsy/forensic pathologist.

▸ Encourage your students/residents to consider autopsy/forensic pathology career.

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- ## Alexander Marshall
  - Born in England, 1861
  - Move to Rhode Island, USA in 1871
  - Medical Examiner of District 7 (?Providence, RI) in 1900