APMIS 109: 774–80, 2001
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APMIS
ISSN 0903-4641

Malignant neoplasms: discordance between clinical diagnoses and autopsy findings in 3,118 cases

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Avgerinos DV, Björnsson J. Malignant neoplasms: discordance between clinical diagnoses and autopsy findings in 3,118 cases. APMIS 2001;109:774–80.

Background. During the past few decades, hospital autopsy rates have steadily declined throughout the Western world. This decline is mainly attributed to the introduction of advanced diagnostic techniques. Despite technological developments, discrepancy rates between clinical diagnoses and autopsy findings remain high. Few studies have addressed discrepancy rates exclusively with regard to malignant neoplasms. In the present study, we reviewed the records of 3,118 autopsies performed at Mayo Clinic during a 6-year period (1994–1999) and identified clinically undiagnosed malignancies found at autopsy and clinically diagnosed cancers not confirmed at postmortem examination. *Materials and Methods.* Autopsy protocols, provisional and final anatomic diagnoses, and data from the Mayo Autopsy Pathology Quality Assurance program were reviewed in an attempt to identify discrepancies between clinical diagnoses and autopsy findings regarding malignant neoplasms. *Results.* In 3,118 autopsies performed at Mayo Clinic between 1994 and 1999, a malignant tumor was identified in 768 cases (25%). In 128 of 3,118 cases (4.1%), the malignancy was not diagnosed clinically. In 14 of 3,118 cases (0.45%), autopsy failed to confirm a clinically diagnosed cancer. A review of the literature is presented. *Conclusions.* Autopsy remains an effective tool for the confirmation and refutation of clinical diagnostic findings regarding malignant neoplasms.

Key words: Autopsy; clinical discrepancy; malignancy; quality assurance.

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Beginning in the middle of the 20th century, hospital autopsy rates entered on a steady decline throughout the Western world (1, 2). This trend will undoubtedly continue in the 21st century despite ongoing debate regarding the usefulness of the autopsy and its role in patient management, quality assurance, medical education, and research (3, 4). Various explanations have been offered for this decline: recently introduced laboratory and imaging techniques (e.g. magnetic resonance) and the conviction that these may, in part or totally, have supplanted the autopsy as a diagnostic tool. Equally important, but less frequently mentioned, may be

TABLE 1. *Number of clinically undiagnosed malignant neoplasms found at autopsy, by site*

Malignant neoplasm site	Neoplasms	
	No.	%
Genitourinary tract	37	28
Respiratory tract	23	18
Endocrine	20	15
Heme/lymph	18	14
Gastrointestinal tract	17	13
Hepatobiliary	6	5
Central nervous system	4	3
Pleura	2	1
Other*	4	3
Total	131	100

* Adenocarcinoma of unknown primary (2), carcinoid tumor of unknown primary (1), Kaposi sarcoma of unknown primary (1).

Received July 7, 2001.
Accepted August 16, 2001.

disinterest in, and disdain for, the autopsy among pathologists.

Despite technological advances, discrepancy rates between clinical diagnoses and autopsy findings have remained constant, ranging from 20% to 40%, depending on definitions and methodologies (1, 5–10). Only a limited number of these studies have specifically addressed, and been limited to, discrepant diagnoses of malignant tumors (1, 5, 6, 11–17), whereas most have investigated discrepant diagnoses where malignant tumors have represented one of several disease categories (2, 7–10, 18–29). Most of the studies limited to malignancies have investigated cancers unsuspected during the patient's life and first identified at postmortem examination (1, 5, 6, 11–17). In contrast, only a few investigators have addressed clinically diagnosed cancers that

TABLE 2. *Distribution by organ and histologic type of clinically undiagnosed malignant neoplasms*

Organ	Histologic type	Neoplasm, no.
Lung	Adenocarcinoma	12
	Squamous cell carcinoma	4
	Small cell carcinoma	4
	Non-small cell carcinoma	1
	Neuroendocrine carcinoma	1
	Carcinoid	1
Pancreas	Adenocarcinoma	5
	Islet cell carcinoma	1
	Cystadenocarcinoma	1
	Papillary cystadenocarcinoma	2
Kidney	Renal cell carcinoma, clear cell type	10
	Renal cell carcinoma, papillary variant	1
Adrenal gland	Pheochromocytoma	3
Prostate	Adenocarcinoma	23
Thyroid	Papillary carcinoma	7
	Medullary carcinoma	1
Pleura	Mesothelioma	2
Esophagus	Adenocarcinoma	1
Stomach	Adenocarcinoma	1
	Stromal tumor	1
	Gastroesophageal junction	1
Ileum	Carcinoid	1
Colon	Adenocarcinoma	10
Rectum	Adenocarcinoma	2
Liver	Hepatocellular carcinoma	2
Biliary tree	Cholangiocarcinoma	4
Urinary bladder	Transitional cell carcinoma	2
Uterus	Endometrial carcinoma	1
Malignant lymphoma	Hodgkin lymphoma	2
	Large cell lymphoma	6
	Lymphoplasmacytic lymphoma	1
Leukemia	Acute myeloid	1
	Chronic lymphocytic	2
Myeloid metaplasia		1
Myelodysplastic syndrome		1
Plasma cells	Multiple myeloma	3
	Plasma cell proliferative disorder	1
Nervous system	Glioblastoma multiforme	1
	Gliomatosis cerebri	1
	Leptomeningeal carcinomatosis	2
Other*		4
Total		131

* Adenocarcinoma of unknown primary (2), carcinoid tumor of unknown primary (1), Kaposi sarcoma of unknown primary (1).

TABLE 3. *Clinically diagnosed malignant neoplasms not confirmed at autopsy, by site*

Malignant neoplasm site	Neoplasms	
	No.	%
Heme/lymph	4	29
Respiratory tract	3	22
Genitourinary tract	2	14
Gastrointestinal tract	2	14
Endocrine	1	7
Central nervous system	1	7
Unknown primary	1	7
Total	14	100

autopsy failed to confirm (12, 14, 20, 21, 24). In the current study, we reviewed 3,118 postmortem examinations performed at one institution during the 6-year period from 1994 through 1999. We identified and tabulated malignant neoplasms unknown during the patient's lifetime and first diagnosed at autopsy and postmortem examinations that failed to confirm cancers diagnosed during life.

MATERIAL AND METHODS

This study was approved by the Mayo Foundation Institutional Review Board. The study covered the period from 1 January, 1994, through 31 December, 1999. We reviewed autopsy protocols and provisional and final anatomic diagnoses. We further reviewed data from the Mayo Autopsy Pathology Quality Assurance program (MAPQA). MAPQA is an internal quality audit in which several variables are tabulated at final sign-out of each postmortem examination. These include the identification at autopsy of clinically unsuspected significant diseases, and the failure to confirm clinical and imaging diagnoses rendered during the patient's lifetime. All of these databases were available electronically for the period covered by the study. For the purposes of this review, we excluded small incidental tumors – i.e. occult prostate cancers, only identified on microscopic examination and limited to the prostate gland, and thyroid neoplasms smaller than 1 cm. When tabulating patients whose cancers were not found at autopsy, we excluded all who had received tumor-specific therapy – i.e. surgical procedure, chemotherapy, or radiotherapy. In addition to demographic information (age, sex), we tabulated primary tumor sites and histologic type.

RESULTS

During the 6-year period from 1 January, 1994, to 31 December, 1999, a total of 3,118 autopsies were performed at Mayo Clinic. For this period, autopsy rates at Mayo Clinic hospitals ranged from 28.3% to 34.4%, with a mean of 31.1%. Of these 3,118 patients, 768 (25%) had a malignant tumor identified at autopsy. Of these 768 patients, 128 (17%) harbored a malignancy unknown during the patient's life. These 128 patients represent 4.1% of the 3,118 autopsies performed during the period. A total of 131 neoplasms were identified in these 128 patients. Sixty-eight patients (53%) were men and 60 (47%) were women. The patients' ages ranged

TABLE 4. *Distribution by organ and histologic type of clinically diagnosed malignant neoplasms not confirmed at autopsy*

Organ	Histologic type	Neoplasm, no.
Lung	Small cell carcinoma	1
	Malignant lymphoma	1
	Pulmonary metastases of transitional cell carcinoma	1
Pancreas	Carcinoma	1
Prostate	Adenocarcinoma	1
Urinary bladder	Transitional cell carcinoma	1
Esophagus	Adenocarcinoma	1
Stomach	Adenocarcinoma	1
Myelodysplastic syndrome		1
Malignant lymphoma	Large cell lymphoma	2
	Non-Hodgkin lymphoma, NOS	1
Nervous system	Dysgerminoma	1
Cancer of unknown primary		1
Total		14

NOS, not otherwise specified.

TABLE 5. *Studies of clinically undiagnosed malignant neoplasms*

Author (Year)	Country	Autopsy rate, %	Autopsies reviewed, no.	Cases with cancer found at autopsy, no. (%)	Undiagnosed malignancies, no. (%)	Three most frequent sites of undiagnosed malignant neoplasms
Present study	USA	31	3,118	768 (25)	128 (4.1)	Genitourinary tract Respiratory tract Endocrine
Burton et al. (1) (1998)	USA	42	1,105	225 (20)	111 (10)*	Respiratory tract Gastrointestinal tract Genitourinary tract
Stanta et al. (16) (1997)	Italy	65	507†	139 (27)	61 (12)	Not specified
Manzini et al. (6) (1995)	Italy	40	1,036	457 (44)	228 (22)	Urogenital apparatus Gastroenteric apparatus Respiratory apparatus
Mayordomo et al. (15) (1993)	Spain	Not specified	1,656	582 (35)	201 (12)	Not specified
Karwinski et al. (13) (1990)	Norway	75	21,530	6,384 (30)	700 (3)	Prostate Kidney Lung
Mollo et al. (14) (1986)	Italy	17	4,972	1,000 (20)	162 (3)	Lung Hemopoietic system Liver
Gobbato et al. (5)(1982)	Italy	65	Not specified	1,405	377	Not specified
Suen et al. (17) (1974)	USA	Not specified	3,535†	1,149 (33)	324 (9)	Prostate Kidney Colon
Bauer & Robbins (11) (1972)	USA	47	10,977	2,734 (25)	721 (6.5)	Prostate Lung–bronchus Colon
Wells (12) (1923)	USA	Not specified	3,712	545 (15)	178 (4.8)	Stomach Central nervous system Esophagus

* Undiagnosed and misdiagnosed malignant neoplasms.
† Limited to geriatric patients.

from 25 to 102 years, with a mean of 72.4 years. Table 1 shows the distribution of the 131 tumors by site, and Table 2 shows the histologic types of tumor identified in each organ. The most commonly diagnosed cancers were adenocarcinoma of the prostate (23), adenocarcinoma of the lung (12), and renal cell carcinoma (10). The lungs (23), prostate (23), kidneys (11), pancreas (9), and hematolymphoid (9) were the organ systems most commonly affected.

During the same period, 14 of 3,118 autopsies (0.45%) failed to confirm a malignant neoplasm diagnosed during life. Of these 14 patients, 9 (64%) were men and 5 (36%) were women. These 14 patients ranged in age from 25 to 89 years, mean 68.7 years. Table 3 shows the distribution of tumors by site, and Table 4 shows the distribution by organ system and histologic type. The organ systems most commonly affected were the hematolymphoid system (4), the respiratory tract (3), and the genitourinary tract (2).

DISCUSSION

Autopsy rates continue to decline throughout the Western world (2, 4, 18, 24). Anderson &

TABLE 6. *Studies of clinically diagnosed malignant neoplasms not confirmed at autopsy*

Author (Year)	Country	Autopsy rate, %	Autopsies reviewed, no.	Cases not confirmed by autopsy, no. (%)	Three most frequent sites of clinically diagnosed malignant neoplasms
Present study	USA	31	3,118	14 (0.45)	Heme/lymph Respiratory tract Genitourinary tract
Kirch & Schafii (24) (1996)	Germany	36–88	400	7 (1.8)	Not specified
Mollo et al. (14) (1986)	Italy	17	4,972	78 (1.6)	Hemopoietic system Gastrointestinal tract Respiratory tract
Cameron & McGoogan (20) (1981)	Scotland	25	1,152	62 (5.4)	Gastrointestinal tract Respiratory tract Endocrine
Munck (21) (1952)	Denmark	78	1,000	15 (1.5)	Gastrointestinal tract Respiratory tract Central nervous system
Wells (12) (1923)	USA	Not specified	3,712	33 (0.9)	Not specified

Hill (30) reported hospital autopsy rates from 5% to 70% during the 1980s. Undoubtedly, these numbers continued their decline during the 1990s. During the same period, the percentage of clinically significant and potentially lethal disease states unknown during life and first identified at autopsy has remained constant (1, 5–10).

Few studies have focused on clinical and postmortem discrepancies limited to malignant neoplasms. Table 5 represents a compilation of studies limited to malignancies. The most recent of these, from Louisiana State University Medical Center, identified clinically unsuspected cancers in 10% of 1,105 postmortem examinations (1). The present study found clinically unsuspected tumors in 4.1% of 3,118 autopsies. This low total percentage in the present series may in large measure be explained by the fact that Mayo Clinic is a tertiary care center, where a large proportion of the patients have received extensive clinical evaluation before their admission.

We identified only five studies in the English literature specifically addressing the failure of postmortem examination to confirm clinically diagnosed cancers (Table 6) (12, 14, 20, 21, 24). Again, the lower percentage identified in the current study is a selection bias because Mayo Clinic is a specialized referral facility. The hematolymphoid system was the site most frequently harboring clinically diagnosed neoplasms not confirmed at autopsy.

Several apparently unrelated factors influence premortem and postmortem discrepancy rates. Battle et al. (31) identified several. First, the type of hospital may exert a significant influence, with nonacademic facilities having higher discrepancy rates than academic ones. Second, an inverse relationship appears to exist between the size of the facility and the discrepancy rate. Third, women and geriatric patients appear to carry a higher risk of dying with a clinically occult neoplasm. In contrast, hospital autopsy rates and the duration of hospitalization appear to play a minor role.

During the past few decades, sophisticated diagnostic modalities have improved diagnostic accuracy in clinical medicine (24). Nevertheless, the introduction of these techniques has not appreciably lowered the number of malignancies missed during clinical evaluation. Therefore, postmortem examination remains unchallenged as the standard for the confirmation or refutation of clinical diagnostic findings (32, 33).

Several factors may account for the decline of hospital autopsy rates. These include the perception by attending physicians that autopsies provide little information beyond that acquired during clinical investigation. Second, some at-

tending physicians believe (probably erroneously) that unexpected autopsy findings may provide grounds for malpractice litigation. Finally, and importantly, pathologists themselves tend to ascribe scant priority or prestige to the performance of autopsies (4). It is nevertheless the contention of this study that the autopsy remains an indispensable tool for the detection and confirmation of malignancies that would otherwise remain undiagnosed (32, 33).

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