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The Value of Necropsy in Oncology

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The effectiveness of diagnostic procedures in cancer patients was evaluated by comparing clinical with necropsy findings. Necropsy and clinical records of 102 patients were reviewed for primary site and histology of tumour, metastatic sites, presence of second neoplasms, associated non-neoplastic diseases, terminal illness and cause of death. Major discordances between clinical and postmortem findings were found in 34 (33%) cases: in 10 of these a correct clinical definition of site and histology of the primary tumour would have resulted in a change of management and prognosis; in 4 cases in which a major non-neoplastic pathology had been responsible for death, correct diagnosis might have resulted in prolongation of survival. Spread of disease was generally underestimated, even for metastases in clinically accessible organs. Even more disappointing were the clinical data related to terminal illness and cause of death (43% overall concordance).
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INTRODUCTION

THE INTEREST of physicians in necropsy continues to decline, although the importance of this procedure for research and education of medical staff is confirmed by virtually all studies in this field [1–11]. In recent years several techniques have become available with which improvement of diagnostic accuracy should be expected. Nevertheless, Goldman *et al.* [8] showed that diagnostic advances have not reduced the percentage of incorrect clinical diagnoses, which has remained virtually unchanged throughout the past three decades. Whilst this inaccuracy is detrimental to the individual patient, it also limits the reliability of death certificates, the main source of information for epidemiologists [2, 12–14]. Gobbato *et al.* [15], in analysing 1405 cases of patients who died in a general hospital, with a necropsy diagnosis of cancer, reported a proportion of clinically undiagnosed cancer as high as 27%, with an inaccuracy rate similar to that previously reported [16–18]. Here we analyse the role of necropsy in assessing the reliability of clinical diagnosis among a population of cancer patients who died in a university department of medical oncology.

PATIENTS AND METHODS

We reviewed the necropsy and clinical records of 102 consecutive cancer patients who died in the Department of Clinical Oncology, University of Ancona, between 1980 and 1988. During this period new non-invasive diagnostic measures, such as ultrasonography, computed tomography and magnetic resonance imaging, were made routinely available for diagnosis and/or staging. For each patient the following data were reviewed: primary site and histology of tumour, number and site of metastases, presence of second neoplasms, associated non-neoplastic diseases, terminal illness and cause of death. Clinical records were reviewed blind by two independent physicians, and necropsy records by a pathologist. Discordances were classified [8] into four categories: class I, major error with consequences for management and prognosis; class II, major error with little influence on management of the patient and no expected difference in survival; class III, minor error related to the terminal disease process but not directly contributing to death; and class IV, either important unrelated diagnoses that might eventually have affected prognosis or processes that contributed to death in a terminally ill patient.

RESULTS

Missed major diagnoses were discovered in 34 cases of the 102 examined (33.3%, Table 1). 15 of these were classified as class I errors and 19 as class II errors. Wrong definition of primary site and/or histology of the tumour accounted for 29 of these major errors. Extension of disease was completely underestimated in 1 patient, while in 4 patients a major non-neoplastic disease responsible for death was clinically unsuspected.

Concordance between clinical and necropsy judgement on primary site (Table 2) was found in 82 cases, and a similar degree of concordance was found for histology (Table 3). In 13 cases discordance occurred in primary site and histology. In 10 cases a correct clinical diagnosis would have lead to a different

Table 1. Clinically missed major diagnoses discovered at necropsy

	No. of cases
Class I	15
Primary site of tumour	3
Histology	1
Site and histology	6
Extension of disease	1
Non-neoplastic disease	4
Class II	19
Primary site of tumour	3
Histology	7
Site and histology	9

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Table 2. Concordance between clinical and necropsy diagnosis by primary site

	Concordance	Disproved at necropsy	Diagnosed at necropsy
Lung	29	1	6
Breast	11	0	1
Stomach	7	0	2
Colon/rectum	8	1	0
Haematopoietic system	5	0	2
Unknown origin	4	11	0
Ovary	2	0	2
Uterus	2	1	0
Prostate	3	0	1
Hepatobiliary	0	0	4
Pancreas	0	0	1
Soft tissues	2	1	1
Genitourinary tract	4	2	0
Pleura	0	1	0
Others	5	2	0
Total	82 (80.4%)	20 (19.6%)	20

Table 3. Concordance between clinical and necropsy diagnosis by histological type

	Concordance	Disproved at necropsy	Diagnosed at necropsy
Carcinoma	30	7	5
Adenocarcinoma	40	3	11
Haematological neoplasm	5	0	2
Seminoma	2	0	1
Sarcoma	3	1	1
Melanoma	0	2	0
CNS neoplasm	1	0	0
Unknown histology	0	6	0
Carcinoid	1	0	0
Mesothelioma	0	1	0
Total	82 (80.4%)	20 (19.6%)	20

CNS = central nervous system.

clinical management with expected consequences on prognosis (class I).

Metastatic spread at various sites was underestimated, even for metastases in accessible organs (lung, liver). Frequently missed metastatic sites were adrenals, bone marrow, effusions and pulmonary lymphangitic carcinomatosis. In 22 cases the overall spread of disease at death was largely underestimated. However, in only 1 case this could be interpreted as a major miss: a death due to metastatic colon cancer in a patient considered free of disease after 8 years off-therapy.

Processes related to terminal illness and cause of death were correctly identified in 44 cases. In 4 cases a major unsuspected non-neoplastic disease was responsible for death: 2 cases of massive digestive haemorrhage, 1 disseminated mycosis and 1 thromboembolic disease with pulmonary embolus. In all these cases the tumour was localised and controlled by treatment. In other cases, clinically unsuspected non-neoplastic diseases were considered related to the terminal disease process but not directly contributing to death (class III) or terminal events responsible for death in a terminally ill patient (class IV). Pneumonia was present in 33 cases, 13 of which were detected clinically.

9 of 102 patients were affected by second benign neoplasms, only 2 of which had been clinically diagnosed.

DISCUSSION

Necropsy data were used for comparison with clinical diagnoses in a group of patients who died of a neoplastic disease in a medical oncology unit. This comparison, like similar studies, was retrospective. Clinical variables had, although blind, to be interpreted, and it is possible that clinical records did not exactly reflect the true thinking of doctors in all instances. Furthermore, there was some degree of case selection by clinicians in submitting cases to necropsy.

Our data showed a poor correspondence between clinical and necropsy definition of both tumour characteristics and associated diseases. In 15 of 102 cases we believe that a more appropriate clinical approach would have lead to a major change in the patient's management, with substantial consequences for prognosis. Patients with haematological neoplasms and potentially curable solid tumours (such as ovarian, testicular, mammary, prostatic carcinoma and small cell lung cancer) were denied an aggressive treatment and possibly a better prognosis. For example, in a case of colorectal cancer who presented years after radical surgery with disseminated disease, biopsy would have led to the diagnosis of prostatic cancer and to a more specific therapeutic approach.

However, definition of histology and primary site in our patients was only one aspect of clinical diagnosis. The spread of neoplasm was usually underestimated. Missed associated non-neoplastic diseases and wrongly identified causes of death were the rule rather than the exception.

Many studies have reported little improvement in diagnostic accuracy with the use of new techniques [8, 15, 17, 18] compared with old studies [16]. However, we believe that in all the studies where clinical and necropsy findings are compared, the overall diagnostic attitude of the clinician, rather than the role of single diagnostic techniques, is under evaluation. In our patients, for example, an instrumental diagnosis of pneumonia or of spread of the tumour to adrenals or liver was easily achievable with available techniques. There is no doubt that diagnostic procedures are more sophisticated and sensitive than in the past. Necropsy helps us to give a more correct interpretation of instrumental findings, and may reveal a high frequency of pathologies of which the clinician is, in most cases, unaware. Our data agree with the warnings [10, 19, 20] that the fall in necropsy rate is unjustified, and underline the role of necropsy in neoplastic diseases to improve clinical practice, to evaluate new diagnostic and therapeutic techniques and to contribute to clinical and epidemiological research.

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Tropisetron plus Haloperidol to Ameliorate Nausea and Vomiting Associated with High-dose Alkylating Agent Cancer Chemotherapy

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Tropisetron is a novel antiserotoninergic drug with potent and specific activity against cancer chemotherapy-induced emesis. High-dose cyclophosphamide or high-dose melphalan are chemotherapeutic regimens associated with severe nausea and vomiting refractory to current antiemetic medications. We compared in a randomised open label study the antiemetic efficacy of tropisetron and alizapride in a first group of 32 consecutive patients treated with high-dose alkylating agent chemotherapy with or without autologous bone marrow transplantation. Tropisetron was more effective than alizapride in reducing vomiting episodes. In the first 24 h of treatment the median number of episodes in patients treated with tropisetron was 5 compared with 9 episodes in the alizapride group ($P = 0.005$). In the 72 h study period the median number of emetic episodes was 6 in the tropisetron group and 12 in the alizapride group ($P = 0.004$). In a second group of 26 consecutive patients, a combination of tropisetron plus haloperidol, a dopamine antagonist, was employed for prevention of emesis. This combination was more effective than tropisetron as single agent in preventing emetic episodes, as the median number of emetic episodes in the 72 h of observation was only 3, while they were 6 in the tropisetron group. The side-effects of tropisetron were mild and reversible upon discontinuation of the drug. We conclude that tropisetron is an effective antiemetic drug when employed in high-dose alkylating agent chemotherapy, and that its activity is potentiated by the association with haloperidol.
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INTRODUCTION

NAUSEA AND VOMITING are side-effects associated with cancer chemotherapy [1]. Vomiting may produce malaise, dehydration and electrolyte imbalance. The diminished quality of life induced by vomiting may lead to a refusal of anticancer therapy or to reduced compliance for medications. Current medications for prevention of vomiting are effective against strongly emetogenic drugs but are not devoid of side-effects, particularly in younger patients [1]. In recent years there has been considerable interest in increasing dose and/or dose intensity of cancer chemotherapy [2], and notably this increase has been associated with increase of severity and frequency of vomiting. Our group has been exploring the effectiveness and the toxicity of a sequential high-dose chemotherapy regimen employing high-dose cyclophosphamide and high-dose melphalan in patients with stage II breast cancer at high risk of relapse or with high-grade diffuse non-Hodgkin lymphoma [3]. Both chemotherapeutic agents induce severe vomiting which is only partially ameliorated by current antiemetic regimens, including continuous intravenous

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