order to establish the efficacy of magnetic resonance spectroscopy in oncology.

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# The Autopsy: Its Role in Oncology

IT APPEARS from the recent literature that in several Western countries for which data are available the autopsy rate in hospitals has been steadily declining during the last few decades. In the US [1] and in Germany [2] the rate is currently below 15%; in the UK only the increase in the coroner's autopsy rate compensated for the hospital rate decline [3]. A variety of causes of this worrisome phenomenon have been taken into consideration. As far as the US in particular is concerned, minimum mandatory autopsy rates are no longer part of the accreditation requirements for hospitals, as they were until 1972 [4]. After the publication of the *Accreditation Manual for Hospitals* of the US in 1971, there was an immediate decline in the autopsy rate below the previously fixed quota rate.

The autopsy is often viewed as a time-consuming exercise whose technique has not changed over almost two centuries, and will hardly ever change, and that cannot expect any benefit from automation or other sophistications except for encoding and data retrieval in the future [5]. Autopsy is also financially unrewarding. The quality of anatomical diagnoses produced by young assistants or young trainees with reference to inaccuracy, lack of documentation or even carelessness [6] and the frequent delay in communication of the anatomical findings have been heavily criticised by clinicians. Also, the usefulness of the autopsy after the introduction of many sophisticated antemortem diagnostic paraphernalia, especially in oncology, has been seriously questioned and this has lowered clinicians' interest and curiosity in unexpected findings—at least in unselected autopsies [7].

Additional negative factors, other than the thanklessness of the task and the apathy of clinicians, are the debatable cost-effectiveness of the whole performance including the postmortem histology assessment [8], the fear of malpractice litigation arising from autopsy findings, medicolegal constraints, the

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reluctance of doctors to obtain permission to perform the autopsy from relatives (possibly because of an unconfessed difficulty in accepting the patient's death) and that of relatives to give their consent. Last but not least, the emotional loss of favour among the lay public should be also mentioned [9]. Several of the above listed factors influence each other in a negative way, producing a descendent spiral which may eventually lead to a dangerously low historical minimum of the autopsy rate. The current decline of, or even the opposition to, the autopsy procedure has been interpreted also within the framework of the crisis that developed in health care [10], or in the general context of a social environment perspective to which political, cultural, social and economic interacting forces contribute in many ways [11].

To modify this tendency several actions might be taken at national level by the appropriate bodies or professional organisations, such as: to provide an adequate and specific training to anatomical pathologists (at least partly different from that of surgical pathologists), to give criteria to physicians for the decision to request an autopsy; to give guidelines on how to obtain consent from relatives or, alternatively, to make consent unnecessary as it is—even though with some exceptions—currently in Italy or Scandinavia; to take care of the financial costs of the procedure providing the direct monetary support for the service; to prepare forms for quick, readily usable and qualitatively uniform reports. The elimination or modification of the concept that all autopsies must be complete might also help to revive interest in autopsies [12].

The contributions of autopsy to the improvement of patient care (*mors gaudet docere vitam*!), quality assurance, education of medical professionals and even to research have been elucidated on various occasions [12]. In particular, in spite of some shortcomings, the role of autopsy in modern quality control and assurance of medical diagnostics appears to be central [13]. It is widely accepted that autopsy can be an accurate and reproducible check of the clinical diagnoses including the various forms of medical, surgical and radiological therapy. Autopsy also clarifies real or potential medicolegal deaths [14] in spite of the existence of a 1–5% of negative or obscure necropsies [15]. Autopsy provides valuable data on vital statistics for epidemiological studies as it almost guarantees the accuracy of death certificates [16, 17]. Autopsies also provide organs, tissues and extracts for transplantation. Furthermore, they provide information beneficial to the deceased's family [12]. In general terms the autopsy should also fulfill part of the moral obligations of physicians and administrators in the practice of medicine [10].

In oncology the autopsy plays various roles. It discloses unsuspected, clinically occult malignancies [18], it is relevant for the assessment of the extent of the disease, it may detect second neoplasms, it allows to investigate the effects of new therapeutic regimens and identify associated non-neoplastic events which may have contributed to the terminal event. Examples of these multivalent contributions of autopsy were the assessment of (1) the dissemination of Kaposi's sarcoma in patients with acquired immunodeficiency syndrome; (2) the multicentricity of tumours of the upper respiratory tract in heavy smokers; (3) the multiplicity of neoplastic events in patients with oesophageal cancer; (4) the ascertainment of the efficacy of current therapy of Hodgkin's disease and the high frequency of coexistent infections [19].

Disagreement between antemortem and postmortem diagnoses has been estimated to range between 20 and 50%, depending on the selection of patients, type of institution and relevance of findings. Discrepancies between clinical and anatomical diagnoses have been repeatedly reported [20] and classified according to the cause and the magnitude [13]. One classification recognises errors ascribed to (1) inadequacy of current knowledge in medical science; (2) necessary fallibility; (3) human factors; and (4) wilful or malicious damage. It appears that the first two types of errors are almost unavoidable and that only type three errors are those to which quality control can be applied with success. Premortem and postmortem diagnostic divergencies were categorised by Goldman *et al.* [21] into various classes according to the impact on treatment failure. Class I were those missed major diagnoses for which detection before death would most likely have led to a change in management with some favourable effect on survival. Class II comprised those missed major diagnoses with equivocal influence on the management of the patient. Class III missed minor diagnoses referred to the terminal disease process even though without direct relationship to death, whereas class IV missed minor diagnoses were either of major importance but unrelated to the main disease or processes that contributed to death in terminally ill patients. The study of Goldman *et al.* showed that in a major US teaching hospital class I missed diagnoses were in the order of about 10% and class II missed diagnoses of 12%, and that these percentages had not changed over the last three decades. The authors concluded that advances in diagnostic technology had not reduced the value of the autopsy. One may also add that three decades of improvements in diagnostic technology have not ameliorated its failure rate. It should, however, be also noted that probably a shift in the type of errors that were made had taken place.

A similar study, published in this issue of the *EJC*, was conducted on 102 cancer patients by Dr Di Furia and colleagues at the University of Ancona (p. 559). The authors evaluated the primary site and the histological type of the tumour, the metastatic sites, the presence of second neoplasms and of non-neoplastic diseases, the terminal illness and the cause of death. Class I missed major diagnoses were identified in 15 cases, 10 of which would have had a different treatment since the clinical definition of site and histology proved to be at variance anatomically. In 4 cases the non-neoplastic diseases responsible of death had not been diagnosed. Class II errors were identified in as many as 19 cases. Even though the authors recognise some degree of selection of cases submitted to autopsy, they stress the poor agreement between clinical and autopsy diagnostic assessment in cancer patients including even the main features of the primary tumour, its type of spread and associated non-neoplastic conditions. Similar results were reported also by Gambino [22] whose autopsy case material showed a major missed diagnosis in 6.3% of cases due to the appropriate diagnostic test not being ordered, in 4.4% because of errors in the results of a variety of diagnostic tests, in 2.8% because of the omission of an otherwise available test and in 2.1% because of a combined clinical and instrumental error.

From an *ad hoc* prepared table on the accuracy of clinical diagnostics among autopsied persons dying with a number of diseases, it appears that sensitivity was highest for leukaemia, lowest for pulmonary embolism and intermediate for liver and gastric cancer and that specificity was beyond 97% for all causes of death [13].

In conclusion, it appears that there are several good reasons why autopsy should be revived. These reasons have been analysed in detail in a recent Symposium published in the February 1990 issue of *Human Pathology*. It has been pointed out that the value of autopsy lies not only in its significance as

a professional obligation but also derives from its immense contribution to the future of medicine if one looks at the autopsy as a "collected" autopsy experience and not as a single event [23], providing that the quality of autopsy performance is strictly monitored and under constant control.

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# Salvage Treatments in Hodgkin's Disease

DURING THE past 25 years, carefully planned strategies based on natural history as well as on cytotoxic potential of radiotherapy and chemotherapy have dramatically changed the prognosis of Hodgkin's disease from an almost invariably fatal to a highly curable malignancy. In fact, approximately 75% of all patients with this type of lymphoma can now be offered the chance of cure [1, 2]. The impact of various treatments on the 5-year to the 20-year results is now being balanced against delayed morbidity, such as organ damage and second neoplasms produced by the intensity of therapy or the prolonged delivery of alkylating agents.

In spite of the considerable evolution through innovations in the primary management of various stages, treatment of relapsing Hodgkin's disease is still incompletely defined. The frequent lack of consistent results from salvage therapy is often due to the application of the same or putatively similar treatment to different prognostic subsets. Thus, it is important to clearly define the subsets bearing different prognoses at the time of first treatment failure.

## PROGNOSTIC INDICATORS

In untreated Hodgkin's disease certain clinical presentations are widely recognised to bear unfavourable prognostic outcome. The major unfavourable prognostic indicators are tumour mass (e.g. bulky mediastinal and/or para-aortic adenopathy, multiple extranodal involvement, 5 or more splenic nodules), disease progression while on primary chemotherapy and short-term complete remission. In the above mentioned clinical situations the biological implications concern primary drug resistance to one or more classes of cytotoxic agents. Prognosis is also inversely related to age, since children and young adults fare better than older people. In particular, patients aged more than 60 years often present with advanced disease and other medical problems that cause difficulties in the proper staging and treatment of their disease [3]. Recent observations have confirmed that lymphocyte depleted Hodgkin's disease is a rare (5% or less of cases) but very aggressive form of lymphoma whose prognosis is still unfavourable because of widespread nodal and extranodal involvement [4].

The presence of systemic ("B") symptoms carries in general unfavourable prognostic significance, especially in patients with more advanced lymphoma. Patients in stage IIB managed with radiotherapy alone appear to have an adverse outcome when they manifest all three "B" symptoms; this finding is often associated with bulky mediastinal disease [5]. Finally, males almost always have a less favourable prognosis compared with that of females.

In relapsing patients prognosis is mainly related to type of primary treatment and time of treatment failure. In particular, the single most unfavourable prognostic indicator is lack of attainment of complete remission from an intensive multiple drug regimen, particularly when chemotherapy includes non-

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