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Causes of Deaths in an Oncology Unit

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Abstract—*The medical records of 102 autopsies performed in Royal Prince Alfred Hospital on patients treated by a medical oncology unit between January 1977 and May 1979 were analysed. Organ failure was the recorded cause of death in 42%; infection in 23%; carcinomatosis in 18%; haemorrhage in 15%; and metabolic derangement in 2%. 27% of patients had autopsy evidence of severe coexistent non-neoplastic disease, predominantly widespread atheroma and coronary artery disease. The immediate cause of death was unrelated to cancer in 19% and treatment-related in 19%. In 13%, death accompanied a high intake of narcotic analgesia during the pre-terminal 24 hours. A terminal care policy was adopted for 56 (55%) patients during their last month and three-quarters of narcotic-related deaths occurred in this group. 55% of the patients received some form of aggressive anti-tumour therapy in their terminal month and 30% of these died of treatment-related causes. 25% of the patients underwent an invasive investigation during their terminal month. Correlation of death certificate, clinical and autopsy causes of death showed the death certificate to be wrong in 41% of cases, with 29% of these errors being of potentially epidemiological importance. Pre-mortem assessment of the cause of death was in error in 26% of patients.*

INTRODUCTION

THE CARE of the dying patient is a major role of the medical oncology unit. The recognition of factors contributing to the cause of death and their correction or prevention where appropriate and feasible is an essential part of terminal care. Also essential is an ongoing review of the oncologist's ability to recognise the pre-terminal state and manage it humanely. This includes identifying that group of patients for whom hospice-type care is most appropriate[1]. We have correlated autopsy findings with pre-mortem management policies in 102 patients in an attempt to assess the quality of our pre-mortem care in patients with advanced cancer.

MATERIALS AND METHODS

Between January 1977 and May 1979, 1917 patients were seen in consultation or cared for by this unit. Of these, 297 died in Royal Prince Alfred Hospital (RPAH) and permission was granted for autopsy on 102, giving an autopsy rate of 34%. The case histories of these patients were carefully reviewed and data, including clinical history and physical examination, laboratory and X-ray findings, recorded intentions of management, ante-mortem diagnoses, therapy and findings at autopsy, were tabulated. Equivocal cases (<1%) were settled by concensus within the author group.

Definitions†

Septicaemia was considered to be the cause of death (COD) if a positive blood culture was obtained during the final seven days of life, or if a positive heart blood culture with a single organism was obtained at post-mortem examination in a patient who had shown clinical signs of severe infection prior to death. In the absence of positive blood cultures, septicaemia was also considered to be the COD if, at autopsy, pathological evidence of widespread infection (such as visceral abscesses or intravascular bacterial invasion) was found in a patient who had shown clinical signs of severe infection prior to death. Pneumonia was considered the COD if clinical signs and symptoms plus pathological evidence of severe extensive pulmonary infection were present. Infection was also considered the COD if it severely affected a vital organ.

Haemorrhage was considered the COD if it was widespread or massive and associated with

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†Derived from those used by Inagaki *et al.* [2].

pre-terminal hypotension and shock, or if it severely affected a vital organ.

Organ failure was defined as a severe impairment, incompatible with life, in the function of a vital organ, due to drug toxicity or a disease process other than those specified above.

Carcinomatosis was considered the COD in those patients having a severe metabolic or nutritional abnormality which precipitated death in addition to widespread malignancy, without any of the other causes already mentioned.

The COD was regarded as metabolic if a fatal metabolic abnormality was present in the absence of widespread malignancy and it was regarded as non-cancer-related if it was incidental and unrelated to the presence of cancer, or if no cancer was found at autopsy.

Death was considered treatment-related if it occurred as a result of medical management, the death being unlikely had the treatment not been given or the investigation not performed. A death could be both treatment-related and cancer-related.

Death was regarded as analgesic-related if the patient received at least 60 mg of methadone (or equivalent narcotic dose) during the pre-terminal 24 hours and died a respiratory mode of death.

Patients were regarded as having had specific active management withdrawn only if there was a positive statement to this effect in the medical records. These patients were not subsequently given cytotoxics, hormone therapy or antibiotics, but had symptoms palliated and all care administered in keeping with the principles of terminal care [1].

Investigations performed during a patient's terminal admission were regarded as invasive if they caused more than minimal patient discomfort or carried a risk of morbidity or mortality.

Management objectives

The therapeutic aims during their final admission were assessed for each patient in terms of the objectives of chemotherapy, invasive investigations, withdrawal of specific active care aimed at prolonging life and the use of narcotic analgesics. The objectives of chemotherapy were assessed as being either "cure", "prolongation of life" or "palliation of symptoms".

Death certificates

The COD after autopsy was compared with the death certificate COD and the clinical assessment of COD as determined by review of each patient's final admission medical record. In this comparison, major discrepancies were defined as those of epidemiological significance, such as death wrongly attributed to a coincidental cancer and wrongly placed primary tumour site. Minor discrepancies were errors of omission or inclusion as to the immediate COD but where a cancer was correctly stated to be the underlying COD. The Medical Certificate of Cause of Death in use in the state of New South Wales is identical to the international form published in the International Classification of Diseases [3].

Performance status at the time of terminal admission was graded 0–4 according to the scale of the Eastern Cooperative Oncology Group (ECOG; Appendix 1).

RESULTS

There were 41 females and 61 males, with a median age of 59 years (range 22–80). The distribution of primary tumour types is shown in Table 1.

The median survival time of patients from time of diagnosis of cancer was 22 weeks, whilst median survival from time of referral to the medical oncology unit was 11 weeks. The median duration of terminal admission was 14 days (range, 1–80 days). These figures indicate that this group of patients was selected, since the median survival of the first 500 patients seen by the unit in 1978 was 44 weeks, and the median time from cancer diagnosis to referral to the unit was 6 weeks.

Causes of death

Figure 1 shows the major causes of death, determined by the clinical and pathological findings.

Organ failure. Organ failure was the most common COD, accounting for 42% of deaths. The factors causing organ failure are shown in Table 2. Twenty-one patients (49%) died of respiratory failure, ten (23%) of cardiac failure or infarction, six (14%) of liver failure and three each of renal failure and central nervous system disease. Ten of the patients dying of respiratory failure had extensive pulmonary metastases, eight had pulmonary thromboembolism, two died of aspiration pneumonia and one of pneumothorax. None of these were clearly related to treatment. Six of the patients dying cardiac deaths had a myocardial infarction, three had a cardiac tamponade due to pericardial metastases, and one died of unexplained cardiac arrhythmia.

Infection. Twenty-four patients (23%) died of infection. Of these, 15 (63%) died of pneu-

Table 1. Distribution of primary tumour sites

Site of primary tumour	No.
Non-small cell lung	16
Gastrointestinal	16
Small cell lung	15
Breast	12
Head and neck	10
Non-Hodgkin's lymphoma	6
Ovary	6
Leukaemia	4
Testicular Germ Cell	3
Other solid tumours	14
Total	102

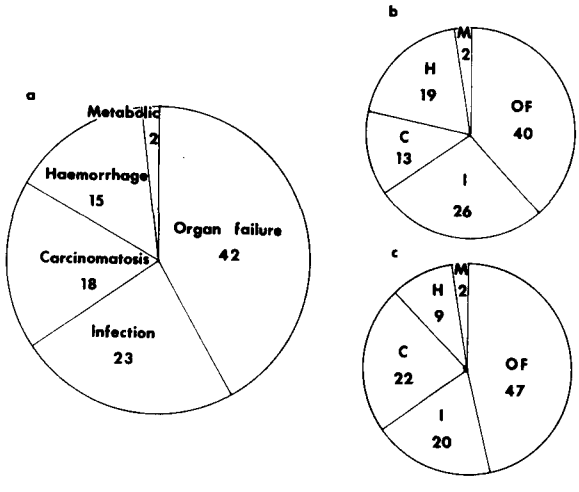

Fig. 1. Causes of death in autopsied cancer patients expressed as a percentage. (a) Total group (102 patients); (b) group receiving aggressive antitumour therapy in the preterminal month (56 patients); (c) untreated group (46 patients). OF: Organ failure; I: Infection; C: Carcinomatosis; H: Haemorrhage; M: Metabolic.

monia, seven (29%) of septicaemia, one of peritonitis and one of acute bacterial endocarditis. Causative organisms were isolated ante-mortem in only eight patients (1 with 2 organisms) and no further organism was identified post-mortem, giving an isolation rate of 9/24 (38%). The organisms were *Staphylococcus aureus* (4) *Escherichia coli* (3), *Clostridium welchii* (1) and *Mycobacterium tuberculosis* (1). Infection was diagnosed clinically and/or microbiologically ante-mortem in 16 cases (67%), and 14 of them were treated appropriately. Ten of the infected patients (42%) were granulocytopenic ($<1.0\times10^9$/l) at the time of death and this was due to chemotherapy in nine.

Haemorrhage. Haemorrhage accounted for 15 deaths (15%). Sites of haemorrhage are shown in Table 3. The haemorrhage was attributed to the patient's cancer in eight cases, but only one of these patients was thrombocytopenic ($<50\times10^9$/l). In three patients, haemorrhage was secondary to thrombocytopenia caused by treatment. In two thrombocytopenic patients, haemorrhage was considered to be due to both treatment and cancer. One of these patients bled into a retroperitoneal teratoma which was regressing rapidly with chemotherapy and the other died of an intracranial haemorrhage, following biopsy of a cerebral metastasis. Two further patients died of incidental haemorrhage unrelated to either cancer or treatment.

Metabolic derangement. Metabolic derangement was primarily responsible for death in only two patients, both of whom had minimal tumour evident at autopsy. One patient died in a profound hypoglycaemic coma and the other died of convulsions and cardiac arrest associated with severe hypercalcaemia.

Non-cancer related deaths

Overall, 19 patients (19%) were considered to have died of causes unrelated to their cancer. Ten were iatrogenic deaths, with eight patients dying of infection or haemorrhage resulting from drug-induced pancytopenia and two patients dying anaesthetic deaths. The remaining nine non-cancer deaths were due to incidental causes, including six cases of myocardial infarction. Ten of the 19 patients dying non-cancer-related deaths had no evidence of tumour at autopsy and six were treatment-related deaths.

Treatment-related deaths

Nineteen patients (19%) died treatment-

Table 2. Major factors causing organ failure

Type of failure	Number patients	Per cent due to: Tumour	Other*
Respiratory	21	48	52
Cardiac	10	30	70
Hepatic	6	100	—
Central nervous system	3	100	—
Renal	3	100	—
Total	43	58	42

*See text.

Table 3. Fatal haemorrhage in cancer patients

Site	No. of patients (%)
Intracranial	5(33)
Gastrointestinal	4(27)
Rupture of major blood vessel	4(27)
Retroperitoneal	2(13)
Total	15

related deaths. The median age of these patients was 59 yr (range 22–76) and small cell lung cancer, germ cell tumours and head and neck carcinoma contributed 10 cases (53%), compared to only 27% of the total series. Chemotherapy was the precipitating treatment in 15 patients and radiotherapy was in one; three patients died following an investigative procedure. Table 4 shows the causes of death in this group of patients and pre-terminal leukocyte counts. Two anaesthetic deaths occurred in patients with squamous cell carcinoma of the head and neck in remission undergoing follow-up examination and two patients died of pulmonary oedema following rapid intravenous infusion of fluids after administration of cytotoxics. The remaining patients died of infection (ten patients) or haemorrhage (five patients). The final cancer chemotherapy treatment was given at a mean of 12 days prior to death (range 2–44) and a summary of the regimens responsible is given in Table 5.

The therapeutic intention in patients dying of treatment-related causes was "cure" in three patients, "prolongation of life" in eight, "palliation of symptoms" in five and "purely investigative" in the other three patients. The patients dying of treatment-related causes were further analysed in terms of their performance status at the time of their final hospitalization and remission status at time of death (Fig. 2).

Terminal care patients

Thirty-three patients (32%) were recognised as terminal at the time of their final admission. The median period from admission to death for this group was five days, compared with a median period of 18 days for those not so recognized. A positive statement to withdraw specific active treatment to prolong life was present in the medical records at some point during the terminal admission of a further 23 patients, giving a total of 56 patients (55%) for whom terminal care was adopted. 80% of these patients had performance status ECOG 3 or 4 at the time of hospitalization, compared with 56% of the other patients (Fig. 3). The median age of the terminal care group of patients was 56 years and for the others, 60 years. The median distribution of causes of death in the terminal care group was similar to the other patients, with 25 (45%) of dying of organ failure, 13 (23%) of carcinomatosis, 11 (20%) of infection, six (11%) of haemorrhage and one of metabolic causes. The death certificate gave the wrong primary COD in 22 (39%) of these patients, but in only two patients was death wrongly attributed to cancer where correct ante-mortem diagnosis and treatment may have prolonged life: one patient, aged 30, with advanced carcinoma of the breast, died of unrecognized massive gastrointestinal haemorrhage while pancytopenic after chemotherapy; her death was wrongly attributed to septicaemic shock; one patient, aged 66, died of unrecognised disseminated miliary tuberculosis following chemotherapy and hemibody radio-

Table 4. Cause of death in patients dying treatment-related deaths vs haematological parameters prior to death

Haematological parameters	No. of Patients	Cause of death: Infection	Haemorrhage	Pulmonary Oedema	Anaesthetic
Granulocytopenia alone ($< 1.0 \times 10^9$/l)	6	5	0	0	1
Granulocytopenia and Thrombocytopenia ($< 50 \times 10^9$/l)	7	4	3	0	0
Normal	6	1*	2†	2	1
Total	19	10	5	2	2

*Disseminated tuberculosis after upper hemibody irradiation.

†One patient died from massive haemorrhage into responding tumour and one patient died from intracranial haemorrhage after brain biopsy.

Table 5. Chemotherapeutic regimens resulting in treatment-related deaths

Drug combination	No. of deaths
Cis-platinum, vinblastine, bleomycin	5
Adriamycin, cyclophosphamide	2
High-dose methotrexate (5 g/m^2)	2
High-dose fluorouracil (2 g/m^2)	2
Cyclophosphamide, methotrexate, fluorouracil	1
Daunorubicin, cytosine-arabinoside	1
Fluid overload	2
Total	15

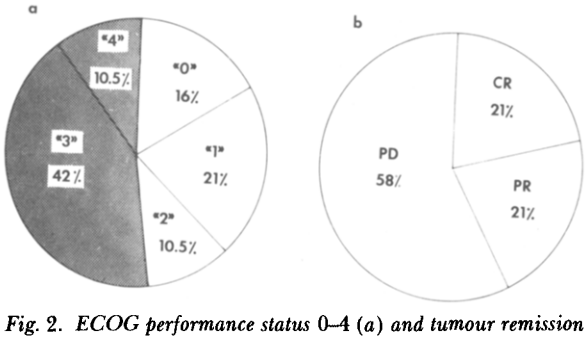

Fig. 2. ECOG performance status 0–4 (a) and tumour remission status (b) in 19 patients dying of treatment-related causes. Hatched segment: non-ambulant patients; CR: complete remission; PR: partial remission; PD: progressive disease.

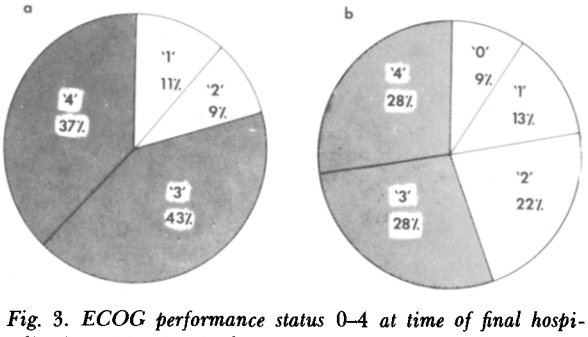

Fig. 3. ECOG performance status 0–4 at time of final hospitalization. (a) Terminal care group (56 patients); (b) non-terminal care group (46 patients). Hatched segments: non-ambulant patients.

therapy for a small cell carcinoma of the lung which was in complete remission at autopsy; his death was wrongly attributed to progressive tumour.

Altogether, seven of the 56 terminal care patients died non-cancer-related deaths, four caused by previous chemotherapy and three of correctly identified other coexistent disease.

Overall, 13 patients (13%) died analgesic-related deaths and ten were terminal care policy patients (Fig. 4).

Aggressively treated patients

Aggressive anti-tumour therapy, which caused more than minimal toxicity to normal tissues, was administered to 56 patients (55%) during their pre-terminal month. Forty were treated with cytotoxic drugs, 13 with radiotherapy and six with surgery. The median survival from diagnosis for these patients was 22 weeks, compared to 25 weeks for those not treated. The causes of death in the two groups are shown in Fig. 1. There was an excess of infective and haemorrhagic deaths in the treated group and 17 (30%) were regarded as having died of treatment-related causes (mostly with pancytopenia), compared to only two patients in the group not treated aggressively.

Invasive investigations

Twenty-seven invasive investigations were performed on 26 (25%) patients during their terminal hospitalization (Table 6) and 11 of these patients (42%) were subsequently included in the terminal care group.

Death certificates

When compared to the autopsy findings, the death certificate (DC) was inaccurate in 41 (40%) of the patients (Table 7). Twelve of these errors were of epidemiological significance, with eight deaths being wrongly attributed to cancer. Three DCs recorded the wrong primary tumour site and in each case chemotherapy in the terminal month had been directed at the wrong tumour type. Clinical assessment of cause of death was also inaccurate in 25 of these 41 cases.

Evidence of severe co-existent non-neoplastic chronic disease was present at autopsy in 28 patients (27%). The median age of these patients was 66 yr (range, 49–80) and only three were female. Widespread atheroma or severe coronary disease was found in 21 patients, four had severe chronic airways disease, two had renal failure (one polycystic disease and one secondary to diabetes) and one had malignant hypertension from scleroderma. The presence of this co-existent disease was recognised antemortem in 16 patients.

DISCUSSION

Autopsied cancer patients are a selected group, the characteristics of which are likely to

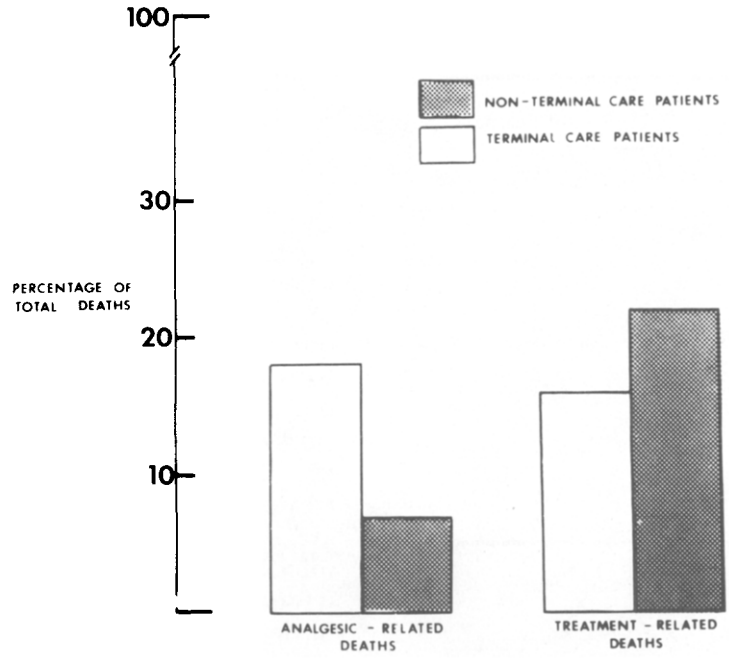

Fig. 4. Analgesic and treatment-related deaths as a percentage of total deaths in terminal care group (56 patients) and non-terminal care group (46 patients).

Table 6. Invasive investigations during terminal hospitalization

Type of investigation	No.
Radiological (Barium or angiographic studies)	9
Tissue biopsy	5
Bone marrow biopsy	4
Lumbar puncture	4
Laparotomy	3
Bronchoscopy	1
Sigmoidoscopy	1
Total	27

be biassed towards the unusual, the unexpected and the unexplained. For this reason they may serve only as a guide to mortality factors in the cancer population. Nonetheless, we have determined a number of clear messages from this analysis.

Firstly, infection remains a major COD in cancer patients, whether or not they are neutropenic[2, 4–7]. The prevention, detection and appropriate treatment of infection, particularly in the setting of drug-induced neutropenia, requires continual vigilance by the medical oncology team and deserves the attention currently being paid it by international study groups [8].

Secondly, iatrogenic events make an unacceptable contribution to morbidity and mortality in cancer patients. A high percentage of treatment-related deaths may be tolerated if the tumour is potentially curable or likely to respond to therapy, provided the patient is otherwise in good general health. By these standards, it may be concluded that treatment attitudes were too aggressive in some cases, since only three of the 19 patients who died of treatment-related deaths were being treated with "curative intent", only eight had signs of tumour response at autopsy and more than half were not ambulatory at the time of final hospitalisation (Fig. 2). A comparison between patients treated and not treated during their final month of life shows an expected increased frequency of death due to treatment-related infection and haemorrhage, but no significant difference in median survival time from referral. The use of invasive investigations may be justified in individual cases, but the fact that nearly half of these investigations were performed on patients judged to be terminal suggests that treatment aims within the unit were at times confused. Three iatrogenic deaths were the result of investigative procedures and while one of these, a patient undergoing biopsy of cerebral metastatic melanoma, was unavoidable, the other two patients undergoing progress examinations under anaesthesia for head and neck cancers in remission are a warning that this procedure may be unwarranted in patients in poor general health.

Table 7. Classification of death certificate errors as determined at autopsy

Major discrepancy			
Cause of death wrongly attributed to cancer			8
Autopsy cause of death			
Myocardial infarction		3	
Gastrointestinal haemorrhage, cytotoxic-induced bone marrow hypoplasia		2	
Infection, cytotoxic-induced bone marrow hypoplasia		2	
Spontaneous pneumothorax (non-tumour related)		1	
Cancer death wrongly attributed to other cause			1*
Error of primary tumour site			3
Death certificate diagnosis	Autopsy diagnosis		
1 Adenocarcinoma of the breast	Adenocarcinoma of pancreas		
2. Non-Hodgkins lymphoma	Anaplastic carcinoma of lung		
3. Non-Hodgkins lymphoma	Carcinoma of ovary		
Total			12
Minor discrepancy			
Error of omission as to immediate cause of death			25
Autopsy immediate cause of death—			
Infection		10	
Organ failure		6	
Haemorrhage		5	
Pulmonary thromboembolism		3	
Metabolic		1	
Error of inclusion as to immediate cause of death			2
Death certificate immediate cause of death—			
Infection		2	
Error of histological type			2
Total			29

*Non-Hodgkins lymphoma death attributed to "pyrexia of unknown origin".

Whilst it is not possible to assess the degree to which large doses of narcotics are necessary for relief of pain or distress in individual cases, the majority of cancer patients taking regular narcotics achieve pain relief without drowsiness or evidence of major respiratory depression [9]. The predominance of analgesic-related deaths in patients regarded as terminal suggests an iatrogenic component, although it is emphasized that in no patient was there any evidence of administration of narcotics in excess of symptomatic requirements.

Thirdly, errors of death certification are frequent (41%) and this figure is similar to other studies [10–12]. In general, patients having acquired the diagnostic label of cancer during life are likely to carry it with them to the grave and in an analysis of 257 death certificates of 500 cancer patients referred to this unit between January and September 1978, the primary COD was given as the known cancer in 95% of patients [13]. In 16 cases in this analysis, correct clinical assessment of cause of death was not carried through to the DC. Those involved in epidemiological surveys based on DCs and medical records should make allowance for such errors. They should also be aware of the high incidence of co-existent non-neoplastic chronic disease in cancer patients and of non-cancer-related deaths in this group.

Fortunately, errors in pre-terminal diagnosis of therapeutic importance were uncommon and, in general, autopsy confirmed the correctness of the terminal care approach in patients so designated. However, two patients in this group had undiagnosed potentially treatable conditions and this serves to remind that the adoption of conservative measures must be based on careful and accurate diagnosis. One of these cases died of undiagnosed disseminated miliary tuberculosis and although this condition has a 91% mortality rate in cancer patients [14], the patient's tumour was in complete remission at autopsy.

Finally, we emphasize the value of autopsy review in assessing cancer management. The low autopsy rate of 34% in our patients, which compares to 64% for the general medical and surgical patients in the same hospital, reflects a regrettable unwillingness on the part of physicians and relatives to subject the cancer patient to the same level of scrutiny applied to other major illness in determining the primary and

contributory causes of death. While the selection of a plan of management for the patient with advanced cancer will always be governed by individual considerations, it is suggested that the periodic review of pre-terminal management policies, and an assessment of their appropriateness in relation to autopsy findings, should be routine in all units caring for cancer patients.

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APPENDIX

Grade 0	Fully active without restriction or aid of analgesic. (Karnofsky 90–100).
Grade 1	Restricted in strenuous activity, but ambulatory and able to carry out work of light or sedentary nature. (e.g. light housework, office work, Karnofsky 70–80)
Grade 2	Ambulatory and capable of self care, but unable to work. Up and about more than 50 per cent of waking hours. (Karnofsky 50–60)
Grade 3	Capable of only limited self care, confined to bed or chair more than 50 per cent of waking hours.
Grade 4	Completely disabled, unable to carry out any self care, and confined totally to bed or chair.
Grade 5	Dead.