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# Mortality within 30 Days for Patients Older than 70 Years Receiving Chemotherapy: a Single-institution Retrospective Analysis

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## ABSTRACT

***Objective:*** *The average life expectancy in western populations is increasing, as is the incidence of malignancy in older people. Historically, most chemotherapy clinical trials exclude patients older than 70 years from enrolment, so information on complications and outcomes is sparse. This study examined mortality rates within 30 days of administration of chemotherapy to patients older than 70 years in routine clinical practice.*

***Methods:*** *The medical records of all patients older than 70 years who received chemotherapy at the Cancer Centre, Belfast City Hospital, Belfast, UK, during 2006 were retrospectively reviewed. Patients' baseline demographics, characteristics, treatment, complications, death occurring within 30 days of chemotherapy, and overall survival were recorded. Actuarial survival was estimated using the Kaplan-Meier method.*

***Results:*** *284 patients were enrolled. The median age was 74 years (range, 70-88 years). The most frequent tumour sites were colorectal (25.0%), lung (22.2%), ovary (12.0%), and oesophagus (11.3%). Median survival was 17.7 months for all patients (95% confidence interval, 14.4-20.9 months) and 12.1 months for patients receiving palliative chemotherapy (95% confidence interval, 9.7-14.5 months; n = 182); median survival has not been reached for patients receiving neo-adjuvant, radical, or adjuvant chemotherapy (n = 102). Mortality within 30 days was 3.5% (n = 10). All patients who died were receiving palliative chemotherapy (5.5% of all palliative patients) and 1 death was treatment related.*

***Conclusions:*** *These results compare favourably with previously published non–clinical trial outcome data for similar age groups. Further investigation is required regarding the optimal assessment and management of elderly patients receiving chemotherapy.*

***Key Words:*** *Aged; Drug therapy; Treatment outcome*

# 中文摘要

## 70歲以上患者在化療後30天內的死亡率：一個單一機構的回顧性分析

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**目的：**隨著西方人口的平均預期壽命增加，老年人的惡性腫瘤發病率也在上升。以往，大多數有關化療的臨床試驗的病人招收均沒有包括70歲以上的病人，因此其化療併發症及化療效果的資訊很少。本項研究將調查70歲以上病人在日常臨床治療時實施化療後三十天內的死亡率。

**方法：**回顧性分析英國貝爾法斯特市立醫院癌症中心2006年70歲以上所有老年腫瘤病人的病歷。記

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錄病人的基本統計資料，特徵，治療，併發症，化療開始30天內死亡及整體生存期。統計生存期用Kaplan-Meier評估。

**結果：**共284名病人入選，中位年齡為74歲(範圍：70-88歲)。最常見腫瘤部位為大腸直腸(25.0%)，肺(22.2%)，卵巢(12.0%)及食道(11.3%)。所有病人中位生存期為17.7個月(95%可信區間：14.4-20.9個月)，接受緩解化療的病人的中位生存期為為12.1個月(95%可信區間：9.7-14.5個月，n = 182)；接受引導化療，根治性化療及輔助化療的病人的中位生存期並未達到(n = 102)。30天內死亡率為3.5% (n = 10)。 所有死亡病人均為接受緩解化療的病人(佔所有緩解治療病人的5.5%)，其中一例病人死亡與治療相關。

**結論：**本研究的結果比以往發表的相似年齡組的非臨床試驗結果要好。有關老年病人化療時的最理想評估及處理須要進一步研究。

## INTRODUCTION

The average life expectancy in western populations is increasing, as is the incidence of malignancy in older people. In the UK and Ireland, 74% of all cancers are diagnosed in people aged 60 years and older, and more than one-third of cancers are diagnosed in people aged 75 years and older.[1-4] It has been estimated that 50% of cancer deaths occur in people older than 68 years.[2] The number of elderly people being assessed for and receiving anticancer therapy will increase during the next few decades as the age distribution in the population changes.[5] Despite the anticipated increase in patients with cancer in the older age group, outcome data for this patient population is lacking across most disease sites. Historically, chemotherapy clinical trials have excluded those patients who are older than 70 years from routine enrolment, hence information on complications and outcomes in this patient population has not been widely documented.[6,7]

The ageing process is usually accompanied by alterations in pharmacodynamics, pharmacokinetics, and tolerance of normal tissues, and this has implications for the safe delivery and tolerability of chemotherapy in older people.[8] There are many age-related physiological changes that may cause altered tolerance among elderly people, and these changes may affect absorption, distribution, metabolism, and excretion of cytotoxic agents.[9] Absorption may be altered by the administration of concomitant medication (e.g., $H_2$-receptor agonists, antacids, proton pump inhibitors), compliance, reduced gastric secretion, emptying and motility, diminished splanchnic blood flow, and decreased surface absorption. The distribution of cytotoxic drugs may be altered by the following factors that change with increasing age: doubling of fat content; decreased intracellular water; reduction in serum albumin concentrations; presence of anaemia; increase in volume of distribution; and lower peak concentration and prolonged terminal half life. The ageing process may also lead to altered metabolism due to reduced liver blood flow, decreased liver size, changes in P450 microsomal systems, and the increased likelihood of polypharmacy, leading to competition for rate-dependant enzyme systems. Pharmacokinetic changes include declining glomerular filtration rate with increasing age, which results in reduced excretion of chemotherapeutic agents such as methotrexate and cisplatin.[10,11]

In addition to the general physiological changes described above, ageing may lead to specific changes that increase the toxicity associated with the administration of chemotherapy. A reduction in the reserve of haematopoietic stem cells and increasing age is known to be an independent risk factor for treatment-related neutropenia and neutropenic sepsis, prompting the recommendation of the routine use of colony-stimulating support factors in older patients.[12,13] Increasing age has been identified as an independent risk factor for mucositis associated with the use of intravenous fluorinated pyrimidines.[14] Mucositis may be fatal, and its increased severity in this age group may be due to a decreased reserve of stem cells or a declining concentration of dihydropyrimidine dehydrogenase within the cells. Other studies have suggested that intravenous fluorinated pyrimidines are as well tolerated in the elderly population as they are in younger populations.[15] In contrast to the intravenous fluorinated pyrimidines, the pharmacokinetics of capecitabine appear not to be affected by increasing age.[16] Anthracyclines are also associated with increased toxicity in elderly people, with an increasing incidence of congestive cardiac failure in people older than 70 years.[17] Increased plasma levels of cyclophosphamide and the other alkylating agents appear to be associated

with declining renal function, but not with age alone.[18] Gemcitabine, despite an increase in plasma half-life, does not appear to be related to increased toxicity with increasing age.[19] Both paclitaxel and docetaxel are highly protein bound. Reduced plasma protein levels, coupled with alterations in liver cytochrome activity, can lead to altered drug levels in elderly people.[20] This list is by no means exhaustive, but illustrates many of the alterations in pharmacokinetics that may occur with age and the resultant potential complications.

Data for death rates related to chemotherapy are scarce beyond that reported in published clinical trials, and there is little guidance as to acceptable rates of early treatment-related mortality.[21] The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a report *For better, for worse?* in November 2008.[22] The NCEPOD study aimed to explore "the process of care of patients who died within 30 days of receiving systemic anticancer therapy";[22] the report has outlined key findings and recommendations for patient care. One recommendation is that outcomes of systemic anticancer therapy should be monitored and regularly audited within treatment centres.

The Cancer Centre, Belfast City Hospital, Belfast, UK, is the regional cancer centre for Northern Ireland. The centre provides all oncological treatments for patients with cancer in Greater Belfast and provides specialist treatment for Northern Ireland. With the increasing use of systemic chemotherapy for patients older then 70 years at the Cancer Centre, assessment of the morbidity and, in particular, the mortality associated with the delivery of systemic chemotherapy to elderly patients is needed. This retrospective review was performed to examine the tolerability and outcomes of chemotherapy among elderly people with a range of tumour sites and treatments.

## METHODS

This audit was conceived, developed, and approved by the Oncology and Haematology Clinical Audit Department of the Belfast Health and Social Care Trust. Patients were identified from the Cancer Centre's Clinical Oncology Information System registry, which includes electronic patient records.

All patients who received chemotherapy at the Cancer Centre between 1 January 2006 and 31 December 2006 and who were aged 70 years and older at the date of their first chemotherapy cycle were enrolled. Patients undergoing both inpatient- and outpatient-based treatments were included. Chemotherapy was delivered as per the institutional protocol. Full doses of chemotherapy are given at the first cycle unless the patient has impaired performance status or major organ dysfunction. The dose for subsequent cycles is based on any toxicity encountered during previous cycles. A retrospective review of the medical records of eligible patients was undertaken by the medical staff working in the medical and clinical oncology departments. Baseline patient demographics, tumour site, pretreatment comorbidities, Eastern Cooperative Oncology Group performance status, details of treatment received, treatment intent, and any treatment-related complications were recorded.

Survival and follow-up were recorded from day 1 of the first cycle of chemotherapy. The date of death was obtained from the patient's electronic medical record, which is automatically updated for any death occurring in the Belfast Health and Social Care Trust hospitals. Any death occurring outside of the Trust is notified to the relevant consultant by the patient's general practitioner (GP) or local hospice team and documented on the electronic medical record. Cause of death was determined from the electronic medical records, paper medical charts, or contact with the patient's GP. Death was categorised where possible as being treatment-related, non–treatment-related, or inconclusive if information was lacking. Survival was estimated using the Kaplan Meier method and calculations were performed using the Statistical Package for the Social Sciences, version 15.0.1.1 (SPSS, Inc., Chicago, USA).

## RESULTS

284 patients aged 70 years or older received cytotoxic chemotherapy at the Cancer Centre. The median age of the patients was 74 years (range, 70-88 years), and 8.4% of the patients were aged 80 years or older (Figure 1). The male-to-female ratio was 1.38:1. The most frequent tumour sites were colorectal (25.0%), lung (22.2%), ovary (12.0%), and oesophagus (11.3%) [Table 1]. Twenty six patients (9.2%) received neo-adjuvant treatment, 17 (6.0%) received treatment with radical intent (patients receiving primary chemotherapy with curative intent or concurrent chemoradiotherapy with curative intent), and 59 (20.8%) received adjuvant chemotherapy. The remaining patients (182; 64.1%) received treatment with palliative intent. Of the patients receiving palliative chemotherapy, 144 (50.1%) received first-line treatment, 33 (11.6%) received second-line treatment,

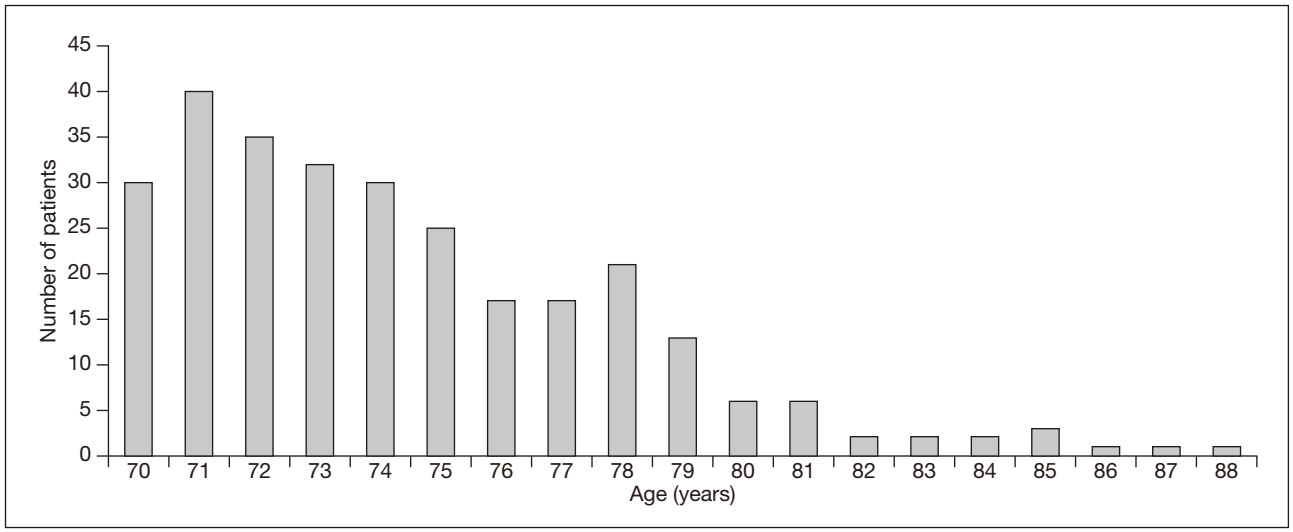


**Figure 1.** Age of patients older than 70 years who received chemotherapy.

**Table 1.** Tumour type and mortality (n = 284).

| | Bladder | Breast | Cervix and uterus | Colorectal | Gastric | Lung | Melanoma | Oesophagus | Ovary | Pancreas | Prostate | Other* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number of patients | 9 | 17 | 7 | 71 | 18 | 63 | 5 | 32 | 34 | 10 | 6 | 12 |
| Treatment | | | | | | | | | | | | |
| Neoadjuvant | 3 | 0 | 0 | 5 | 5 | 2 | 0 | 10 | 1 | 0 | 0 | 0 |
| Adjuvant | 1 | 11 | 0 | 25 | 4 | 3 | 0 | 9 | 4 | 0 | 0 | 2 |
| Radical | 0 | 0 | 2 | 0 | 1 | 9 | 0 | 3 | 0 | 0 | 0 | 2 |
| Palliative | | | | | | | | | | | | |
| First-line | 4 | 5 | 4 | 30 | 7 | 41 | 3 | 9 | 22 | 10 | 4 | 5 |
| Second-line | 1 | 1 | 1 | 9 | 1 | 8 | 2 | 1 | 5 | 0 | 2 | 2 |
| Third-, fourth-, and fifth-line | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 1 |
| Death within 30 days of administration of any chemotherapy cycle | 0 | 0 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 | 0 | 0 |
| Death overall | 5 | 5 | 3 | 28 | 12 | 51 | 5 | 15 | 18 | 10 | 4 | 8 |
| Treatment-related | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 |
| Disease-related | 5 | 5 | 3 | 19 | 11 | 45 | 5 | 12 | 16 | 7 | 4 | 7 |
| Death from other cause | 0 | 0 | 0 | 4 | 1 | 3 | 0 | 3 | 0 | 1 | 0 | 0 |
| Death from unknown cause | 0 | 0 | 0 | 5 | 0 | 2 | 0 | 0 | 1 | 2 | 0 | 1 |

* Includes unknown primary, central nervous system tumours, cholangiocarcinoma, head and neck tumours, renal tumours, and peritoneal primary tumours.

3 (1.1%) received third-line treatment, 1 (0.4%) received fourth-line treatment, and 1 (0.4%) received fifth-line treatment. Pretreatment morbidity was documented, and the most common morbidities were ischaemic heart disease/peripheral vascular disease or hypertension (80.2%) [Table 2]. Thirty two patients (11.3%) had had a prior malignancy at a different primary site. 154 patients (54.2%) had a pretreatment performance status of 0 or 1, and 32 (11.3%) had a pretreatment performance status or 2 or more. Ninety eight patients (34.5%) had no pretreatment performance status recorded.

The number of intended cycles of chemotherapy varied with tumour type, chemotherapy regimen, and treatment intent. Eighty two patients (28.9%) did not receive all of the intended treatment cycles, and 15 patients (5.2%) only received 1 cycle of chemotherapy.

Ten patients (3.5%) died within 30 days of starting any chemotherapy cycle (Table 3) and 19 (6.7%) died within 60 days of starting any chemotherapy cycle. The median age of the patients who died was 73.5 years (range, 70-81 years), with 1 patient older than 80 years.

**Table 2.** Pretreatment morbidity and performance status (n = 284).

| Factor | Number of patients (%) |
|---|---|
| Pretreatment comorbidities | |
| Diabetes mellitus | 34 (12) |
| Ischaemic heart disease or peripheral vascular disease | 78 (27.5) |
| Hypertension | 91 (32.0) |
| Previous malignancy of separate origin | 32 (11.3) |
| Other comorbidity, not otherwise specified | 150 (52.8) |
| ≥2 comorbidities | 121 (42.6) |
| Performance status | |
| 0 | 49 (17.3) |
| 1 | 105 (37.0) |
| 2 | 30 (10.6) |
| 3 | 2 (0.7) |
| 4 | 0 (0.0) |
| Unrecorded | 98 (34.5) |

Seven of the 10 patients who died within 30 days of any chemotherapy were men. No patients receiving treatment with radical, adjuvant, or neo-adjuvant intent died within 30 days of treatment. All 10 patients who died were receiving palliative chemotherapy (5.4% of all patients receiving palliative chemotherapy). Four deaths occurred within 30 days of starting the first cycle of chemotherapy; all other patients received at least 2 or 3 of the intended number of cycles. The median time to death was 7 days (range, 2-26 days) from the start of chemotherapy. Eight patients died in hospital, 1 died at home, and the place of death was not recorded for 1 patient. One death was treatment related. This occurred in a 78-year-old man receiving first-line palliative chemotherapy for small cell lung cancer. The patient developed neutropenic sepsis following the first cycle of chemotherapy. The other deaths that occurred within 30 days of chemotherapy were due to disease progression or disease-related factors. Two of the 10 patients who died within 30 days of chemotherapy had a glomerular filtration rate of <50 mL/minute, but the carboplatin dose was adjusted accordingly.

**Table 3.** Demographics of patients dying within 30 days of any cycle of chemotherapy (n = 10).

| Characteristic | Number of patients (%) | Chemotherapy regimen |
|---|---|---|
| Median age (range) [years] | 73.5 (70-81) | |
| Sex (M:F) | 7:3 | |
| Median time to death* (range) [days] | 7 (2-26) | |
| Treatment intent | | |
| Radical | 0 (0) | |
| Neoadjuvant | 0 (0) | |
| Adjuvant | 0 (0) | |
| Palliative first-line | 8 (80) | |
| Palliative second-line | 2 (20) | |
| Tumour type | | |
| Small cell lung cancer | 3 (30) | Carboplatin, etoposide, cisplatin |
| Gastro-oesophageal | 2 (20) | Epirubicin, cisplatin, 5-fluorouracil, capecitabine |
| Colorectal | 1 (10) | Oxaliplatin, 5-fluorouracil‡ |
| Melanoma | 1 (10) | Temozolamide |
| Ovarian | 1 (10) | Carboplatin |
| Pancreatic | 1 (10) | Gemcitabine |
| Uterine | 1 (10) | Carboplatin |
| Place of death | | |
| Hospital | 8 (80) | |
| Home | 1 (10) | |
| Not recorded | 1 (10) | |
| Cycle in which death occurred | | |
| 1 | 4 (40) | |
| 2 | 5 (50) | |
| 3 | 1 (10) | |
| Pretreatment performance status† | | |
| 0 | 0 (0) | |
| 1 | 3 (30) | |
| 2 | 2 (20) | |
| Not recorded | 5 (50) | |
| Pretreatment comorbidities | | |
| None documented | 2 (20) | |
| 1 | 4 (40) | |
| ≥2 | 4 (40) | |

* From day 1 of last chemotherapy cycle received.
† Eastern Cooperative Oncology Group.
‡ Modified De Gramont schedule.

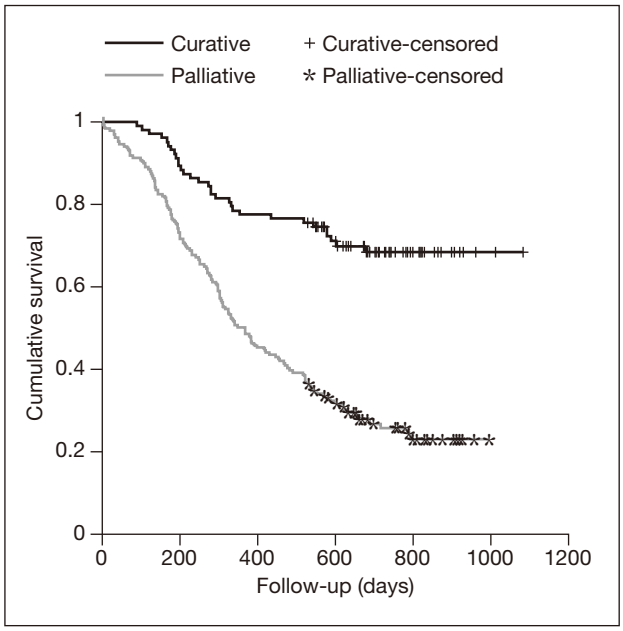


**Figure 2.** Kaplan-Meier estimates of cumulative survival by treatment intent. Patients receiving neoadjuvant, radical, or adjuvant therapy were categorised as treatment with curative intent. All other treatments were palliative in nature.

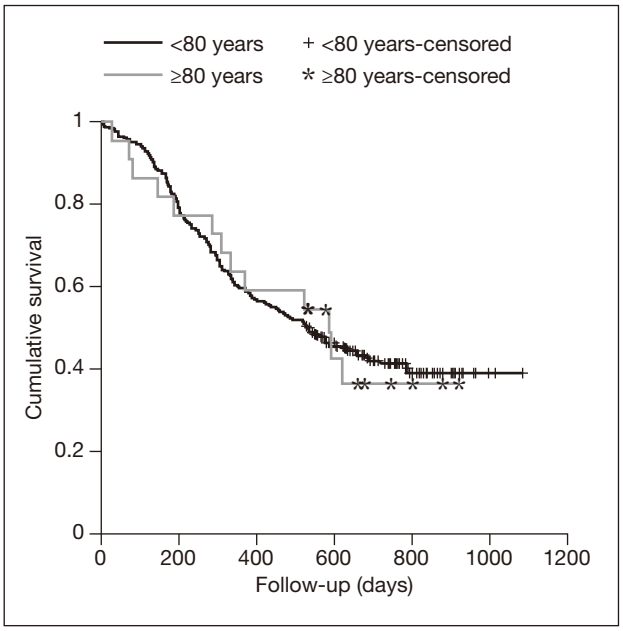


**Figure 3.** Kaplan-Meier estimates of cumulative survival by age.

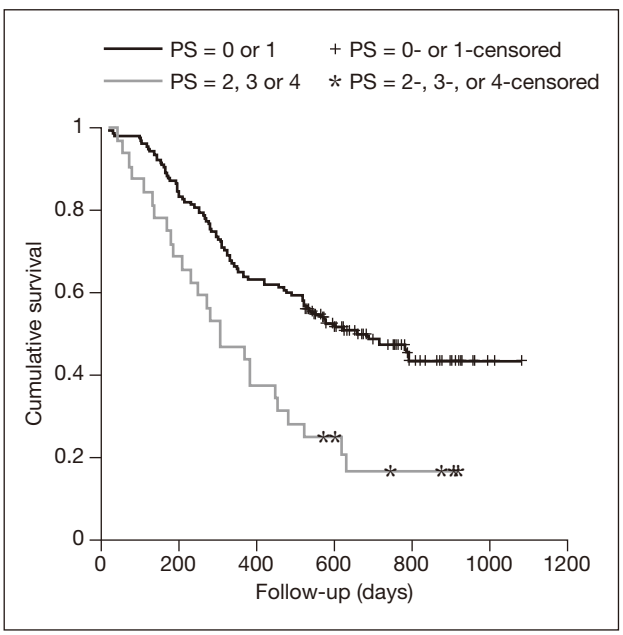


**Figure 4.** Kaplan-Meier estimates of cumulative survival by Eastern Cooperative Oncology Group performance status. Abbreviation: PS = performance status.

The median survival was 17.7 months for all patients (95% confidence interval [CI], 14.4-20.9 months) and 12.1 months for patients receiving treatment with palliative intent (95% CI, 9.7-14.5 months); median survival was not reached for patients receiving radical or adjuvant/neo-adjuvant treatment (Figure 2). As expected, there was a significant difference in survival by treatment intent (Mantel-Cox log rank test, $p < 0.0001$). There was no significant difference in survival between patients aged 70 to 80 years and those older than 80 years (17.4 months [95% CI, 13.5-21.1 months] versus 19.3 months [95% CI, 9.8-28.7 months]; Mantel-Cox log rank test, $p = 0.947$) [Figure 3]. Pretreatment performance status, where recorded, correlated with survival (Figure 4). For those patients with documented pretreatment performance status, there was a significant difference in survival by performance status (0 or 1 versus 2 or 3; Mantel-Cox log rank test, $p = 0.0001$). By multivariate analysis, age, pretreatment haemoglobin, glomerular filtration rate, bilirubin, or presence of comorbidities did not correlate with either death within 30 days of chemotherapy or overall survival.

## DISCUSSION

The delivery of cytotoxic drugs to older patients has been a controversial issue since the advent of chemotherapy. Previously, older patients were excluded from chemotherapy trials but, in recent years, some chemotherapy trials have not set an upper age limit, instead basing their inclusion and exclusion criteria on other indicators of likely poor tolerance of the chemotherapeutic agent under investigation, such as baseline performance status and renal function. Furthermore, studies have specifically examined the efficacy and toxicity of chemotherapy when delivered to older people.[23]

Many patients older than 70 years receive chemotherapy at the Cancer Centre. It is therefore important to document the tolerability, including early mortality, and

outcomes of chemotherapy among elderly patients receiving a range of treatments. These results on early mortality compare favourably with previously published non–clinical trial outcome data for patients of all ages.[21] Only 1 of the 10 patient deaths occurring within 30 days of chemotherapy was treatment-related, with the remainder being due to disease progression, and all deaths occurred among patients receiving palliative chemotherapy. The 30-day limit was chosen as a specific endpoint as this is used for surgical case mortality review, and is the timepoint used by a large UK study on chemotherapy mortality;[21] it was also the time interval used by the report by the NCEPOD.[22] Furthermore, death within 30 days raises the distinct possibility that either the patient is unfit for chemotherapy or that an inappropriate dose or schedule was used. As the 30-day mortality rate in the NCEPOD report was not calculated, given that the NCEPOD report only collected outcome data on those who died within 30 days,[22] direct comparison with these results is not possible. Furthermore, no detailed analysis by age distribution in the NCEPOD report occurred. The low early mortality rates following the administration of systemic chemotherapy in the current study may be a result of overcautious delivery of chemotherapy to older people (with reduced dose intensity or restrictive case selection), which would also be undesirable. Details on dose intensity and dose modification in response to toxicity were not recorded, but this information may be useful for assessing the extent of toxicity experienced by those older than 70 years in comparison with younger patients. Future evaluations of chemotherapy in elderly people could examine the appropriateness of the decision to administer chemotherapy and measure dose intensity in those who died from disease within 30 days of starting treatment.

The low mortality rate in this patient population suggests that, with appropriate selection, chemotherapy may be delivered safely to older patients. Assessment and documentation of pretreatment performance status is an important part of deciding on the suitability of a patient for a given treatment regimen, and these results have shown that pretreatment performance status does appear to predict for survival in this population. However, in approximately one-third of patients, performance status was not documented. Of those who died within 30 days, 5 patients had no performance status recorded. Pretreatment evaluation and documentation of performance status is an essential component of the assessment of fitness to receive chemotherapy and its documentation should be routine. The modest sample size and low event rate (death within 30 days) in this study prevented a meaningful assessment of the putative link between initial performance status and early mortality following chemotherapy in this patient group. The low death rate within 30 days and heterogeneous population will have mitigated against any firm conclusions on predictive factors for morbidity or mortality. Four of the 10 patients who died within 30 days of chemotherapy died after only 1 cycle and 1 of these patients died from neutropenic sepsis. The other 3 deaths were documented as disease related. If these deaths were due to disease progression, then the decision to treat these patients may not have been appropriate, given the advanced state of their disease.

With appropriate assessment guidelines older patients should be offered inclusion in relevant chemotherapy trials. This may increase the amount of information available to clinicians to guide treatment decisions in this patient population. During the past decade, there has been increasing investigation and reporting of chemotherapy outcomes in older patients. The International Society of Geriatric Oncology has provided guidelines for the safe delivery of cytotoxic agents to older people.[24] The National Comprehensive Cancer Network in the USA has recently updated its practice guidelines regarding senior adult oncology, and this provides valuable guidance for the management of cytotoxic therapy for older people.[25] The National Chemotherapy Advisory Group draft report on chemotherapy services in England advises that the leadership team charged with provision of systemic chemotherapy at institutions involve the input of care of the elderly physicians.[26]

Finally, particularly in light of the NCEPOD report, it is important that each cancer centre regularly monitors outcomes and mortality rates from chemotherapy treatments, and assesses patient care pathways to identify areas for continued improvement of patient care.[22]

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