Terms and Conditions of Use of Digitised Theses from Trinity College Library Dublin

Copyright statement

All material supplied by Trinity College Library is protected by copyright (under the Copyright and Related Rights Act, 2000 as amended) and other relevant Intellectual Property Rights. By accessing and using a Digitised Thesis from Trinity College Library you acknowledge that all Intellectual Property Rights in any Works supplied are the sole and exclusive property of the copyright and/or other IPR holder. Specific copyright holders may not be explicitly identified. Use of materials from other sources within a thesis should not be construed as a claim over them.

A non-exclusive, non-transferable licence is hereby granted to those using or reproducing, in whole or in part, the material for valid purposes, providing the copyright owners are acknowledged using the normal conventions. Where specific permission to use material is required, this is identified and such permission must be sought from the copyright holder or agency cited.

Liability statement

By using a Digitised Thesis, I accept that Trinity College Dublin bears no legal responsibility for the accuracy, legality or comprehensiveness of materials contained within the thesis, and that Trinity College Dublin accepts no liability for indirect, consequential, or incidental, damages or losses arising from use of the thesis for whatever reason. Information located in a thesis may be subject to specific use constraints, details of which may not be explicitly described. It is the responsibility of potential and actual users to be aware of such constraints and to abide by them. By making use of material from a digitised thesis, you accept these copyright and disclaimer provisions. Where it is brought to the attention of Trinity College Library that there may be a breach of copyright or other restraint, it is the policy to withdraw or take down access to a thesis while the issue is being resolved.

Access Agreement

By using a Digitised Thesis from Trinity College Library you are bound by the following Terms & Conditions. Please read them carefully.

I have read and I understand the following statement: All material supplied via a Digitised Thesis from Trinity College Library is protected by copyright and other intellectual property rights, and duplication or sale of all or part of any of a thesis is not permitted, except that material may be duplicated by you for your research use or for educational purposes in electronic or print form providing the copyright owners are acknowledged using the normal conventions. You must obtain permission for any other use. Electronic or print copies may not be offered, whether for sale or otherwise to anyone. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement.
Trinity College Dublin

School of Medicine

Department of Medical Gerontology

An investigation of the incidence of falling and risk factors for falls in adults with advanced cancer

Dr Carol Stone MB ChB MRCP(Glas) MSc

Student ID: 08129622

Submitted in fulfilment of the requirements of the degree of Doctor of Philosophy

2012
Declaration:

I declare that this work has not been submitted as an exercise for a degree at this or any other University. It is entirely my own work. I agree that the library may lend or copy the thesis upon request.

Carol Stone

Date: 24.8.12
# CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Introduction and summary</strong></td>
<td>9</td>
</tr>
<tr>
<td>Chapter 1</td>
<td>How to identify cancer patients at risk of falling; a review of the evidence.</td>
<td>13</td>
</tr>
<tr>
<td>Chapter 2</td>
<td>Pilot phase of study of the risk factors for falls in patients with advanced cancer.</td>
<td>39</td>
</tr>
<tr>
<td>Chapter 3</td>
<td>A prospective study of the incidence of falls in patients with advanced cancer.</td>
<td>43</td>
</tr>
<tr>
<td>Chapter 4</td>
<td>The prevalence of vitamin D deficiency in inpatients with advanced cancer.</td>
<td>55</td>
</tr>
<tr>
<td>Chapter 5</td>
<td>Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment.</td>
<td>63</td>
</tr>
<tr>
<td>Chapter 6</td>
<td>Reliability testing of hand-held dynamometry when used to test knee-extensor strength in patients with advanced cancer.</td>
<td>85</td>
</tr>
<tr>
<td>Chapter 7</td>
<td>A prospective study of falls and risk factors for falls in adults with advanced cancer</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td><strong>Acknowledgements</strong></td>
<td>119</td>
</tr>
<tr>
<td></td>
<td><strong>References</strong></td>
<td>121</td>
</tr>
</tbody>
</table>
Publications from thesis


Presentation of results from thesis

1. 12th Congress of the European Association for Palliative Care, Lisbon, May 2011:
   a) Stone CA, Lawlor PG, Nolan B, Bennett K, Kenny, RA. Falls: is this geriatric giant an even bigger issue in palliative oncology? Eur J Pall Care 2011: 57
   b) Stone CA, Lawlor PG, Healy M, Walsh JB, Kenny RA. Vitamin D deficiency in advanced cancer; the prevalence and its relevance. Eur J Pall Care 2011: 87

2. 6th Congress of the European Union Geriatric Medicine Society, Dublin, October 2010:
INTRODUCTION AND SUMMARY

The principal aims of this doctoral investigation were to identify the incidence of falls and risk factors for falling in adults with advanced cancer.

Review of existing literature identified a small number of papers reporting high rates of falls in inpatient oncology and palliative care settings. Whilst only two of the studies identified factors independently associated with an inpatient fall (cognitive impairment, low systolic blood pressure and a comorbid diagnosis of chronic obstructive pulmonary disease), results pertaining to factors associated with falls in univariate analyses provided useful information on possible risk factors or confounding variables.

I conducted a prospective study with adults with advanced cancer admitted to inpatient and outpatient palliative care services provided by Our Lady’s Hospice and Care Services, whereby patients participated in a research assessment at baseline and were followed-up at weekly intervals for a maximum of six months or until the time of fall or death. Interim analysis identified that approximately half of participants, regardless of age, experienced a fall during follow-up; the corresponding incidence density of falls was more than double that of healthy community-dwelling older persons.

Serum vitamin D concentrations were measured in inpatients recruited to the study; vitamin D depletion is a risk factor for falls in older persons and findings from laboratory-based and clinical research suggests that vitamin D plays an important role in maintaining muscle structure and function. Eighty-eight percent of inpatient participants had vitamin D deficiency, and all had serum concentrations below that required for optimal muscle functioning.

Autonomic dysfunction is a risk factor for falls in other populations and, as it has been shown to be prevalent in advanced cancer, was measured as an independent variable in this study, using standard bedside clinical tests. However, 45% of participants were unable to complete the tests. Post hoc analyses identified that non-completion was associated with scoring high on
clinical indicators of frailty, highlighting the need to explore novel methods of assessment of autonomic function in this population. In analysis of cross-sectional data, severity of fatigue was independently associated with having definite or severe autonomic dysfunction.

It is widely reported that hand-held dynamometry is reliable when used to measure muscle strength in frail or older persons. We conducted an assessment of test-retest and inter-rater reliability of hand-held dynamometry to measure knee-extensor strength in study participants. Measurement error was significant and increased in magnitude with increasing mean muscle strength. Critical re-appraisal of the literature identified that many studies had employed statistical measures which provide unconventionally conservative estimates of measurement error.

Factors independently associated with falls in adults with advanced cancer were having a primary brain tumour or brain metastasis, number of falls in the preceding three months, severity of depression and daily benzodiazepine dose. Forty-two percent of falls resulted in physical injury.

This is the first prospective study to measure the incidence of falling over a clinically meaningful time period and the risk factors for falling in independently mobile patients with advanced cancer. The results of this study highlight a significant and under recognized symptom in adults with advanced cancer.

In addition, we identified an association between autonomic dysfunction and fatigue in patients with cancer; preliminary work in other populations suggests that correction of associated orthostatic hypotension may have therapeutic potential in the management of cancer-related fatigue. Severe vitamin D deficiency is common in independently mobile patients with advanced cancer. Further research is required to determine whether vitamin D deficiency plays as significant a role in mediating falls risk in patients with advanced cancer as it does in older people, or how cancer-related sarcopenia, muscle fatigue and vitamin D deficiency interact in mediating cancer-related muscle dysfunction.
Chapter 1: How to identify cancer patients at risk of falling; a review of the evidence.

ABSTRACT

BACKGROUND
Clinical experience and a limited number of studies suggest that a cancer diagnosis confers a high risk of accidental falls. The negative sequelae of falls in older persons are well documented; risk factors for falls in this population have been extensively investigated and evidence for the efficacy of interventions to reduce falls is steadily emerging. It is not known whether the risk factors for falls and effective interventions for falls risk reduction in patients with cancer are different from those in older persons.

METHODS
Electronic databases Medline, Embase and CINAHL were searched for studies of risk factors for falls or effective interventions for falls risk reduction in patients with cancer. Assessment of study quality was performed. Data analysis was descriptive.

RESULTS
Seven studies designed to identify the risk factors for falls in patients with cancer and one study to determine the predictive validity of a screening tool for falls in patients with cancer were included. All had methodological
shortcomings, precluding the generation of a new synthesis from this review, but highlighting important design and statistical issues.

CONCLUSIONS
Further research is needed to identify patients at risk and inform the design of an interventional model to reduce falls risk. Investigators should be cognisant of the limitations of using cross-sectional study design to answer this research question, should employ validated tools to measure exposure variables, use reliable methods to ascertain the occurrence of falls and appropriate statistical models to adjust for confounding variables.
BACKGROUND

Much of the body of knowledge pertaining to falls: risk factors, consequences and effective methods of risk reduction originates from studies of older persons.

Falls represent a serious problem in older people; one-third of community dwelling persons aged ≥65 years fall annually and approximately 10% of falls result in fracture, head injury or serious soft tissue injury.¹² Even non-injurious falls have significant negative consequences for the individual with up to 40% of those who fall subsequently experiencing a fear of falling. Fear of falling is associated with self-imposed activity restriction, which although in the short term may protect against falls, ultimately leads to decline in physical performance, independent of baseline function, and to development of gait and balance problems.³

The high incidence of falls in older persons is attributed to a complex interaction of intrinsic and extrinsic risk factors, and the risk of falls increases with each additional risk factor. Intrinsic risk factors include cognitive impairment, neurological conditions, polypharmacy, the use of psychotropic or cardiovascular medications, impairment in balance, gait and functional mobility, muscle weakness, decline in visual function, and low blood pressure states such as orthostatic hypotension and carotid sinus hypersensitivity.⁴
Evidence of effective interventions for reducing falls risk in selected or unselected populations of older persons, is steadily emerging. Multicomponent interventions that target multiple risk factors, targeted exercise interventions, home hazard modification, reducing psychotropic medication and correction of vitamin D depletion have all been shown to be effective interventions for community-dwelling older persons.\textsuperscript{5,6} 

Do patients with cancer have a high incidence of falls?

In the course of our experience of provision of palliative care services we observed falls to be a common occurrence in people with advanced cancer. A preliminary look at the literature revealed evidence of an association between a cancer diagnosis and falling; in a longitudinal study of 146,959 postmenopausal women, Chen \textit{et al} found the hazard ratio for falling after incident breast cancer diagnosis to be 1.15 (CI=1.06-1.25) and 1.27 (CI= 1.18-1.36) after other cancer diagnosis.\textsuperscript{7} In a study of falls risk factors in hospital inpatients, a diagnosis of cancer was associated with a relative risk of falling of 2.7.\textsuperscript{8} Based on analysis of incident forms over a one year period, researchers in the United Kingdom (UK) reported fall rates of 15.6 falls per 1000 bed days in palliative care inpatient units (IPU) within a single cancer network.\textsuperscript{9} This far exceeds the average rates of falling in acute and community hospitals in the UK of 4.8 falls per 1000 bed days and 8.4 per 1000 bed days respectively.\textsuperscript{10}
The susceptibility of cancer patients to falling has not gone unrecognised. There are many references in nursing literature to the need to recognise and address the high risk of falling associated with a cancer diagnosis. Authors advocating evidence-based practice have made recommendations pertaining to identification of at risk cancer patients and modification of risk factors based on the risk factors for falls in older people. However, it is not clear if risk factors for falls, the strength of their association or the profile of reversible risk factors are the same in patients with cancer as in older people. To enable us to design effective interventions to reduce the risk of falls in patients with advanced cancer, we need to know what the risk factors and modifiable risk factors are in this population.

Our objective was to conduct a systematic review of published literature to identify research designed to (i) ascertain the risk factors for falls in adults with cancer or (ii) demonstrate effectiveness of falls prevention strategies in this population. We wished to identify the extent and validity of current evidence, common challenges to researching falls in this population and to offer guidance, based on these, for researching in this area.

METHODS

Criteria for selection of studies

Table 1 shows the criteria for selecting studies to be included in this review.
Table 1. Criteria for selecting studies

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Studies to identify risk factors for falls</th>
<th>Studies of interventions to reduce falls risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study designs which</td>
<td>Study designs which provide level I-IV</td>
<td>Study designs which provide level I-IV</td>
</tr>
<tr>
<td>provide level I-IV</td>
<td>evidence on the NHMRC Evidence</td>
<td>evidence as per the NHMRC Evidence</td>
</tr>
<tr>
<td>evidence on the</td>
<td>Hierarchy for studies of aetiology, with the exception of case series, will be included.</td>
<td>Hierarchy for studies of interventions, with the exception of case series, will be included.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Adults aged 18 or over with a diagnosis of cancer, of any stage.</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Setting</th>
<th>Any community or health care setting</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Not applicable</th>
<th>Studies of any intervention to reduce falls risk, with or without concurrent controls.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>A measure of risk (adjusted or unadjusted), appropriate to study design</th>
<th>A measure of risk reduction (adjusted or unadjusted), appropriate to study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic Database</td>
<td>Search Terms</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Medline via Ovid</td>
<td>Medical Subject Headings (MeSH terms): terminal care, palliative care, hospice care, oncology service hospital, medical oncology, radiation oncology, neoplasms and accidental falls (MeSH terms were exploded and all subheadings included). Keywords: palliative, falls, advanced cancer and supportive care</td>
<td></td>
</tr>
<tr>
<td>Embase</td>
<td>Emtree terms: hospice, hospice care, hospice nursing, hospice patient, palliative therapy, terminal care, advanced cancer, neoplasm, oncology and falling</td>
<td></td>
</tr>
<tr>
<td>CINAHL via EBSCOhost services</td>
<td>Subject Headings: accidental falls, fall prevention, safety behaviour: fall prevention, safety status: falls occurrence, oncology care units, oncologic care, radiation oncology, oncologic nursing, radiation oncology nursing, rehabilitation cancer, terminal care, palliative care, hospices, hospice and palliative nursing, hospice patients, hospice care and neoplasms. Key words: falls, oncology, terminal care, palliative care, hospice, cancer and neoplasms.</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. Flow chart to show selection of studies

- Medline: 241 citations
  - 170 excluded based on title
  - 57 excluded based on abstract
  - Full text of 14 articles retrieved for further evaluation

- Embase: 551 citations
  - 512 excluded based on title
  - 26 excluded based on abstract
  - Full text of 13 articles retrieved for further evaluation

- Cinahl: 94 citations
  - 52 excluded based on title
  - 29 excluded based on abstract
  - Full text of 13 articles retrieved for further evaluation

Total of 21 full text articles retrieved

13 articles excluded as they do not meet inclusion criteria
8 articles included in analysis
Search strategy

Electronic databases Medline (1950-June week 3 2010), Embase ('all years') and CINAHL (1982-June 2010) were searched. The final searches of the databases were carried out on 30th June 2010. See table 2 for details of search strategy. All searches were restricted to studies of humans. ‘Falls’ was included as a keyword in the Medline and Cinahl searches in order to maximise the sensitivity of the search, albeit at the expense of specificity. Hand searching of the reference lists of relevant articles was also carried out.

Study selection

A single reviewer (CS) examined the titles of all retrieved articles and subsequently the abstracts of potentially relevant articles. In the next step, the full texts of all relevant articles were obtained. These were reviewed by both CS and PL. Articles were excluded if they did not meet the criteria for selection of studies. See Fig. 1 for more detail of results of search strategy and study selection.

Data extraction and quality assessment

Data were extracted from the reports of included studies on risk factors into a standardised table. Using the table, information from the studies was reported under the following headings: Publication details, Cohort details, Outcome measure used in analysis and Risk factors identified. This was carried out by
CS and verified by PL. Further details pertaining to individual studies including those on variables measured in each study were included in a descriptive analysis.

The study design and the level of evidence of aetiology that it can provide, as determined by the Australian National Health and Medical Research Council (NHMRC) was included in the data extraction table.\textsuperscript{15,16} An assessment of individual study quality was also conducted. The factors to be included in this assessment were selected based on their pertinence to the internal validity of studies which answer questions relating to risk factors and those that are most problematic in the area under scrutiny.\textsuperscript{17} CS and PL independently assessed the quality of the included studies. The results were then compared and disagreements resolved by consensus. The following quality items were considered:

Has selection bias been minimised?

Consideration was given to two particular sources of selection bias; non-random sampling bias and missing information bias. Non-random sampling can yield a non-representative sample which generates parameter estimates which differ from the target population. Moderate to high levels of missing data can also introduce selection bias if participants with complete information are not representative of the total sample.\textsuperscript{18}

Has misclassification bias been minimised?
Consideration was given to the validity and reliability of methods used to measure exposure and outcome variables, and the likelihood that misclassification may have resulted in an erroneous estimation of effect.

Is the outcome measure valid?
Consideration was given to whether the outcome measure and the corresponding method of analysis were appropriate. ‘Outcome measures’ which occur prior to the measurement of the ‘exposure’ or ‘risk factor’ were not considered to be valid.

Have adequate adjustments been made for strong confounders?
The decision to regard a factor as a confounder should ideally be based on plausibility and prior evidence. In the current context, knowledge of risk factors is limited. The options are, therefore, to adjust for confounding factors as identified in studies of older people, or to adjust for those factors shown in univariate analysis to have a substantial effect, regardless of p value, which may be large due to small sample size.

Data analysis
Data analysis was descriptive and includes analysis of the consequences of observed bias on the results obtained. Details of the studies of falls risk factors in hospital or hospice inpatients were analysed separately from community-dwelling patients.
RESULTS

Description of studies

Seven studies which examined the risk factors for falls and one study of diagnostic accuracy of a screening tool for falls in patients with cancer were included, the first of which was published in 2002 and most recent in 2009. Of the studies to identify risk factors, four examined risk factors in hospital or hospice inpatients and three studied outpatient attendees (see Table 3). Studies of interventions to reduce falls risk in patients with cancer were identified but none met the inclusion criteria (see Table 4).

Of the studies to identify risk factors for falls in patients with cancer in the inpatient setting, two were of prospective cohort design, one was a retrospective cohort study and the other a case-control study.

Pearse et al studied the risk factors for falls in a prospective study of patients admitted to three palliative care IPU's within a cancer network in the UK. In addition to those variables detailed in Table 2, the following data were collected; gender, functional impairment, use of hearing aid, use of opioids, benzodiazepines, hypotensive agents, antimuscarinics and dopamine antagonists at time of admission and the occurrence of a fall in the week preceding admission. Mean age was 67 years; 54% were female. Data pertaining to postural hypotension and impaired cognition was missing for 30% and 14% respectively of patients who did not fall. Statistical methods designed to control for the confounding effects of one or more than one variable were used; variables shown to be associated with falls in univariate analysis were
entered into a logistic regression model. However, due to participants having variable lengths of follow-up, the logistic regression model, using ‘fall’ or ‘no fall’ as a binary outcome is not an appropriate choice; patients with longer admissions are ‘at risk’ for longer. Instead, survival analysis methods, such as the Cox proportional hazards model should have been employed, using ‘time to fall’ as the outcome measure.

O’Connell et al prospectively studied the risk factors for falls in consecutive admissions to oncology and palliative care wards in a private hospital. In addition to those variables shown to be associated with the occurrence of falls, as detailed in Table 2, the following data was collected: the occurrence of a fall in the preceding year, gender, blood pressure and hand grip, arm and leg muscle strength measured manually and scored from 1-3.

A total of 227 patients were recruited (mean age 67±13.83 years). However, of the 34 patients who fell during the study, 18 fell prior to having the baseline research assessment. For these patients, data other than that routinely collected at admission (age, gender, cancer diagnosis, blood pressure on admission and history of falls) was missing, thus making it likely that the estimate of effect of these variables was biased towards the null hypothesis. Conversely, non-validated tools were used to measure alertness and confusion and subjective methods used to assess muscle strength; any resulting misclassification bias involving these ordinal variables may have resulted in an away from the null bias i.e. suggesting an association between the variable and falls where none exists.
In the study by Pautex et al, the charts of all patients with advanced cancer hospitalised over a one year period were reviewed and the characteristics of those who fell during admission compared with those who didn’t. In addition to those variables shown to be associated with falls, as per Table 2, the following variables were examined; demographic details, Charlson Comorbidity Index, main medical diagnoses, Mini-mental state examination (MMSE), Functional Independence Measure, incident comorbidities, haemoglobin concentration, administration of opioid, benzodiazepine, neuroleptic, antiepileptic, antidepressant, hypotensive, diuretic, respiratory system, corticosteroid and antibiotic medications, use of parenteral hydration or nutrition and administration of palliative sedation. The occurrence of falls was determined using the institutional incident report forms. The mean age of participants was 71±12.1 years; 59% were female. It was not apparent from the presentation of the results whether there was any missing data.

The criteria used to determine the occurrence of delirium or incident comorbidities during hospitalisation were not specified, nor was it clear whether their occurrence preceded the fall in the patients who fell. Similarly it was not clear whether consideration had been given to the temporal relationship between medications used during admission and the timing of the fall in those who fell. If not, the direction of the observed association between falls and delirium and falls and the use of neuroleptic medications cannot be ascertained. Patients had differing lengths of follow-up corresponding to length of admission. As per the study by Pearse et al, logistic regression, rather than
survival analysis techniques, was inappropriately used to adjust for confounding.

Goodridge and Marr conducted a retrospective analysis of falls which occurred in an IPU during 1999. The mean age of patients admitted was 70.9 years, 53.2% were male and 0.3% had a non-cancer diagnosis. Univariate analyses were conducted to investigate relationships between the occurrence of one or more falls during admission and gender, age, duration of stay and diagnosis using data from all admissions. Male gender, increasing age and longer stay were associated with falls. Cognition (measured using MMSE), symptom severity measured using the Edmonton Symptom Assessment System (ESAS) and medications on admission were compared between those who fell once and those who fell more than once during admission. There were significant levels of missing MMSE (37%) and ESAS (11%) data. Whilst ESAS scores were observed to be higher in those who fell once than those who had repeated falls, age was inversely related to total ESAS scores and hence a potential confounder given the observed correlation between increasing age and falls.

Three studies examined factors associated with falls in patients with cancer attending outpatient clinics. In two of the three patients with cancer at any tumour stage were included, whilst in the study by Bylow et al, patients with symptomatic metastatic disease were excluded. All three employed convenience sampling and were therefore subject to non-random sampling bias. The studies were cross-sectional in design, collecting information from
each subject at one point in time, but used a retrospective question i.e. have you fallen during the past 3/12 months, to ascertain the 'outcome'. As a result the 'outcome' preceded the 'exposure', the study design therefore facilitating identification of the sequelae of falls rather than risk factors for falling. See Table 5 for details of incidence of falls reported in included studies.

Quality items reflecting consideration of important sources of bias in studies of diagnostic accuracy were used to assess the study by Overcash and Rivera, whereby 2 instruments were administered to older persons with cancer, in order to establish their accuracy in predicting which patients had fallen. Critically, the utility of determining the accuracy of a test in predicting a past event is not clear. A useful lesson from this study is the susceptibility of retrospective reporting of falls to recall bias; 13 of the 20 patients reported having fallen within the preceding year, whilst 15 reported having fallen within 3 months.
Table 3. Data abstraction for studies included to identify risk factors for falls.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Publication details</th>
<th>Cohort details</th>
<th>Quality items</th>
<th>Outcome measure used in analysis</th>
<th>Risk factors identified (p≤0.5) (HR, 95%CI)</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Pearse et al 2004</td>
<td>Palliative care Inpatient Units Cancer ? +/- non-cancer diagnosis Adults aged ≥18 N=102</td>
<td>Selection bias minimised? Misclassification bias minimised? Valid outcome measure? Adjustments for confounding?</td>
<td>≥1 fall during admission</td>
<td>Age&gt;80 years Low lying systolic BP Low sitting systolic BP Require glasses Cognitive impairment Not on opioid</td>
<td>Cognitive impairment OR 12.8 (CI 1.95-84)</td>
<td>Lying systolic BP OR 0.96 (CI 0.93-0.99)</td>
</tr>
<tr>
<td>II</td>
<td>O'Connell et al 2005</td>
<td>Hospital Palliative/ Oncology Units Cancer diagnosis Adults aged≥18 N=227</td>
<td>Selection bias minimised? Misclassification bias minimised? Valid outcome measure?</td>
<td>≥1 fall during admission</td>
<td>Increased age ECOG status Confusion Upper limb strength Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-2</td>
<td>Pautex et al</td>
<td>Hospital Inpatient Palliative Care</td>
<td>Selection bias minimised?</td>
<td>≥1 fall during admission</td>
<td>Delirium OR 2.24(1.08-4.64)</td>
<td>COPD OR 5.42 (1.16-</td>
<td></td>
</tr>
<tr>
<td>Study Type</td>
<td>Year</td>
<td>Source</td>
<td>Setting</td>
<td>Diagnosis</td>
<td>Age Range</td>
<td>N</td>
<td>Selection Bias Minimised?</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------</td>
<td>------------------------------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>-------------------------</td>
<td>---------------</td>
<td>------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Retrospective</td>
<td>2008</td>
<td><em>Journal of Palliative Medicine</em></td>
<td>Cancer diagnosis unit</td>
<td>Adults aged ≥18</td>
<td>N=198</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>cohort study</td>
<td></td>
<td></td>
<td>Cancer diagnosis</td>
<td>Adults aged ≥18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-3</td>
<td>Goodridge &amp; Marr 2002</td>
<td><em>International Journal of Palliative Nursing</em></td>
<td>Palliative care Inpatient Unit</td>
<td>Cancer and non-cancer diagnosis. Adults aged ≥18</td>
<td>1a. N=437 1b. (N=98)</td>
<td>X</td>
<td>1a. ≥1 fall versus no fall during admission</td>
</tr>
<tr>
<td>Case-control study</td>
<td></td>
<td></td>
<td>Inpatient Unit</td>
<td>Adults aged ≥18</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Overcash J 2007</td>
<td><em>Oncology Nursing Forum</em></td>
<td>Oncology outpatient clinics</td>
<td>Cancer diagnosis</td>
<td>Aged ≥70</td>
<td>N=165</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Cross-sectional study</td>
<td>Overcash &amp; Beckstead</td>
<td>Oncology outpatient clinics</td>
<td>Selection bias minimised?</td>
<td>≥1 fall during past year (i.e. prior to assessment)</td>
<td>ADL Score (OR 3.4 for chemotherapy group, OR 1.4 for non-chemotherapy group)</td>
<td></td>
</tr>
<tr>
<td>----</td>
<td>-----------------------</td>
<td>----------------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Clinical Journal of Oncology Nursing</td>
<td>Cancer diagnosis</td>
<td>Misclassification bias minimised?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aged ≥70</td>
<td>N= 297</td>
<td>Valid outcome measure?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjustments for confounding?</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Cross-sectional study</td>
<td>Bylow et al</td>
<td>Urology outpatient clinics</td>
<td>Selection bias minimised?</td>
<td>X</td>
<td>≥1 fall during past 3 months (i.e. prior to assessment)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Urology</td>
<td>Prostate cancer with biochemical recurrence or asymptomatic metastatic disease. Aged ≥70 N=50</td>
<td>Misclassification bias minimised?</td>
<td>√</td>
<td>ADL OR 4.71 VES-13 score≥3 OR 5.41 Use of assist device OR=7.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Valid outcome measure?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjustments for confounding?</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III-2 (studies of diagnostic accuracy)</td>
<td>Overcash &amp; Rivera</td>
<td>Oncology outpatient clinics</td>
<td>Selection bias minimised?</td>
<td>1. ≥1 fall during past year</td>
<td>1. ROC for TUG 0.85 2a. ROC for TUG 0.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2008</td>
<td>Cancer diagnosis</td>
<td>Misclassification bias minimised?</td>
<td>2a. ≥1 fall during past 3</td>
<td>2b. ROC for TUG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Reviews in Oncology Haematology</td>
<td>Aged ≥68 N= 20</td>
<td>Follow-up for outcomes adequate?</td>
<td>√</td>
<td>months 2b. ≥1 fall since cancer diagnosis</td>
<td>0.74</td>
<td>Max ROC for Simmonds Performance Test Battery measures: 0.72 for sit-stand</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------------</td>
<td>----------------------------------</td>
<td>---</td>
<td>------------------------------------------</td>
<td>-----</td>
<td>-------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>

NHMRC Australian National Health and Medical Research Council

HR Hazard ratio
OR Odds ratio
ECOG European cooperative oncology group
COPD Chronic obstructive pulmonary disease
ESAS Edmonton symptom assessment scale
IADL Instrumental activities of daily living scale
ADL Activities of daily living scale
GDS Geriatric depression scale
VES-13 Vulnerable elders survey-13
ROC Receiver operating curve
TUG Timed ‘up and go’

√ = Yes, X = No
Table 4. Excluded studies

<table>
<thead>
<tr>
<th>Excluded studies</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anon/Fennimore</td>
<td>Information contained in summary of conference proceedings, unable to obtain further details</td>
</tr>
<tr>
<td>O'Connell et al</td>
<td>Results of analysis of oncology subgroup not presented</td>
</tr>
<tr>
<td>Chen et al</td>
<td>Analysis of risk factors for falls not presented</td>
</tr>
<tr>
<td>Spoelstra et al</td>
<td>Analysis of subgroup of patients with cancer not presented</td>
</tr>
<tr>
<td>Spoelstra et al</td>
<td>Analysis of subgroup of patients with cancer not presented</td>
</tr>
<tr>
<td>Jones &amp; Stubblefield</td>
<td>Case series</td>
</tr>
<tr>
<td>Matsuo et al</td>
<td>Measure of risk reduction not provided</td>
</tr>
<tr>
<td>Miller &amp; Limbaugh</td>
<td>Measure of risk reduction not provided</td>
</tr>
<tr>
<td>Crannell &amp; Stone</td>
<td>Measure of risk reduction not provided</td>
</tr>
<tr>
<td>Schilsmann</td>
<td>Results of analysis of hospice subgroup not presented</td>
</tr>
<tr>
<td>Kuchinski et al</td>
<td>Effect of interventions on falls risk not presented</td>
</tr>
<tr>
<td>Twiss et al</td>
<td>Cohort includes women who do not currently have cancer</td>
</tr>
<tr>
<td>Winters-Stone et al</td>
<td>Cohort includes women who do not currently have cancer</td>
</tr>
</tbody>
</table>
Table 5. Table to show incidence of falls as reported by included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Setting</th>
<th>Cohort</th>
<th>Source of data on falls</th>
<th>Rate of falls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearse et al 2004</td>
<td>Palliative care Inpatient Units</td>
<td>Adults aged ≥18 ? cancer, non-cancer diagnosis</td>
<td>Incident forms from 2001</td>
<td>15.6 falls per 1000 patient days</td>
</tr>
<tr>
<td>Goodridge &amp; Marr 2002</td>
<td>Palliative care Inpatient Unit</td>
<td>Adults aged ≥18 Cancer (97.5%) &amp; non-cancer diagnosis</td>
<td>Incident forms from 1999</td>
<td>16.9 falls per 1000 patient days</td>
</tr>
<tr>
<td>Pautex et al 2008</td>
<td>Hospital Inpatient Palliative Care Unit</td>
<td>Adults aged ≥18 Cancer diagnosis</td>
<td>Incident forms from 2005</td>
<td>6.89 falls per 1000 patient days</td>
</tr>
<tr>
<td>O'Connell et al 2005</td>
<td>Hospital Palliative care &amp; Oncology Inpatient wards</td>
<td>Adults aged ≥18 Cancer ? +/- non –cancer diagnosis</td>
<td>Patient reporting occurrence of ≥1 fall in previous 12 months</td>
<td>84/227 (37%) reported having at least one fall in 12 months</td>
</tr>
<tr>
<td>Overcash 2007</td>
<td>Oncology Centre Inpatient wards</td>
<td>Aged ≥70 Cancer diagnosis</td>
<td>Patient reporting occurrence of ≥1 fall in previous 12 months</td>
<td>37/165 (22.4%) reported having at least one fall in 12 months</td>
</tr>
<tr>
<td>Overcash &amp; Beckstead 2008</td>
<td>Oncology Outpatient clinics</td>
<td>Age ≥70 Cancer diagnosis</td>
<td>Patient reporting occurrence of ≥1 fall in previous 12 months</td>
<td>81/297 (27%) reported having at least one fall in 12 months</td>
</tr>
<tr>
<td>Bylow et al 2008</td>
<td>Urology Outpatient Clinics</td>
<td>Aged ≥70. Prostate cancer with biochemical recurrence/ asymptomatic metastatic disease, receiving androgen deprivation therapy.</td>
<td>Patient reporting occurrence of ≥1 fall in previous 3 months</td>
<td>11/50 (22%) reported having at least one fall in 3 months</td>
</tr>
</tbody>
</table>
DISCUSSION

This literature search identified seven studies which aimed to investigate the risk factors for falls in patients with cancer. Upon critical appraisal all were found to have significant methodological limitations, precluding the generation of a new synthesis from this review, but highlighting important design and statistical issues pertinent to epidemiological studies in this area and the need for further research. Limitations of this review include incomplete searching of the grey literature, limited hand searching for articles and inadequate definition of cohorts in individual studies, particularly regarding stage of disease.

Evaluation of the cross-sectional studies of community dwelling persons highlights the inherent unsuitability of cross-sectional study design to answer this particular research question, due to the impossibility of determining whether observed impairments in functioning or physical or psychological health have predisposed to falling or resulted from it.

Going forward, researchers aiming to identify the risk factors for falling in this patient population should employ validated tools to measure exposure variables, reliable methods to ascertain the occurrence of falls and attend to the temporal relationship between the two. Additional plausible exposure variables such as measures of sarcopenia, fluid deficit and vitamin D deficiency should be included.
Studies of risk factors that do not control for strong confounders are of restricted value due to the potential for spurious results. However, in areas where there is limited knowledge of risk factors and hence confounders, preliminary investigations which utilise univariate analyses can usefully highlight variables to be included and controlled for in analysis, in subsequent studies. From the studies in inpatient settings, the following variables were not exposed to significant misclassification bias and were found to be associated with falls in univariate analysis; age (Pearse 2004, O'Connell 2005, Goodridge 2002), low blood pressure, visual impairment, cognitive impairment (Pearse 2004), performance status, fatigue (O'Connell 2005) and male gender, longer stay and low total ESAS score (Goodridge 2002). Establishing the relationship between medications and falls is particularly challenging due to the potential for confounding by indication, whereby the condition for which the medication is prescribed is itself associated with increased falls risk e.g. neuroleptic medication and delirium. Alternatively, confounding by contraindication may result in erroneous observations as highlighted by Pearse et al; in univariate analysis of their data, use of opioid medication was associated with lower risk of falling. They speculate that this may have resulted from clinicians preferentially using alternative analgesia in cognitively impaired patients for fear of exacerbating confusion. Agostini and Tinetti caution that careful consideration should be given to baseline medical characteristics which may influence medication choice and indications for medications, which should be adjusted for in multivariate analyses.
Future research must employ suitable statistical methods to adjust for confounding variables; in studies where duration of follow-up varies, survival analysis models using ‘time to fall’ as the outcome measure are appropriate. Alternatively, models which facilitate analysis of recurrent falls and accommodate variable follow-up, such as negative binomial regression or the Andersen-Gill model may be used; in trials of falls prevention interventions methods for analysing recurrent events are preferable to time to first event analysis. The effect of incident illnesses, whether or not risk factor profile differs between older and younger people with advanced cancer, and the physical and psychological sequelae of falls in this population are also worthy of investigation.

Ten studies of interventions to reduce falls risk in patients with cancer or cancer survivors were retrieved, but none met inclusion criteria. The described interventions included strategies to reduce falls rates in inpatient oncology settings by raising staff awareness of falls risk factors, attending to environmental hazards and procedural initiatives such as increased frequency of nurse rounds. The effectiveness of such initiatives, targeted at health care professionals, merits further careful evaluation.

In summary, findings from the small number of studies suggest that patients with cancer have a high risk of falling. Further research is required to determine the principal risk factors for falls in patients with advanced cancer. This will facilitate identification of patients at risk, subsequent development of strategies to reduce risk and informed decision-making regarding use of any
medications shown to increase falls risk. The challenge is to determine the
interventions which reduce the risk of falling and augment rather than
compromise quality of living for patients with advanced cancer.
Chapter 2: Pilot phase of study of the risk factors for falls in adults with advanced cancer.

Background

The challenges of conducting research with patients accessing palliative care services and their impact on study completion and external validity of research findings are well documented. Patients may be referred to palliative care services late in the course of their disease or alternatively have busy schedules, attending for radiological investigations, treatment and outpatient consultations. Symptom burden, fatigue and cognitive impairment may limit initial participation in palliative care research and patient attrition due to progressive disease or death can undermine achievement of research objectives.

We estimated that 228 participants would be required for the study of risk factor for falls, and aimed to recruit 300 subjects to allow for dropouts or missing data. This estimation was informed by the findings of a systematic review of falls risk factors in older persons, whereby the relative risk/odds ratios ranged from 1.9 for postural hypotension to 4.9 for weakness, and the assumption that our study would be able to detect the lowest of these associations at a significance level of 5% and power of 80% for the principal outcomes this study.

Based on rates of exclusion of hospice inpatient admissions to a study in which the fellow was an investigator, due to being too unwell to participate
(33%), refusal (6%) or having communication difficulties (4%). It was initially estimated that 303 patients could be enrolled in the study per year from the inpatient and day hospice services; 247 (57%) inpatients and 156 (90%) of Day Hospice patients. However, in view of the variances between the two studies regarding the nature of study participation and inclusion and exclusion criteria (see Table 1) we elected to conduct an initial pilot phase with 30 patients to (1). Measure rate of recruitment and (2). Assess the feasibility of conducting the baseline research assessment with patients with advanced cancer.

Pilot outcomes; recruitment
The proportion of patients who met the exclusion criteria exceeded estimations. During the pilot phase, whereby only 30 patients were recruited over a period of four months, 66% of patients admitted to the inpatient unit were ineligible for inclusion, including three patients who were initially eligible and willing to participate, but deteriorated prior to the scheduled baseline assessment.

Pilot outcomes; feasibility of baseline assessment
The method of assessing functional quadriceps strength, as per the initial protocol, proved impractical and of limited utility; the single leg-sit-to-stand utilises the patient's own body weight as resistance during quadriceps strength testing. The test is performed with the participant sitting in a standard chair and the examiner standing facing the patient, who is asked to rise from
the seated position using only one leg, whilst holding the examiner’s hands for balance. However, only 4/30 participants were able to complete this.

With the exception of patients with dysphasia and those requiring continuous oxygen therapy, the protocol was otherwise found to be workable and manageable for study participants. The average duration of the assessment was 50-60 minutes.

**Post-pilot changes**

1) The range of services from which patients were recruited was expanded to include the home care service, Advanced Nurse Practitioner clinic and medical outpatient clinic. This required the assistance of colleagues to independently ascertain patient eligibility, introduce the research briefly and give the patient the information and consent form.

2) Knee-extensor strength was measured by hand-held dynamometry.

3) The exclusion criteria were extended to patients with dysphasia or requiring continuous oxygen therapy.

Other strategies employed, which were associated with positive feedback from participants and may thus have improved recruitment by reducing potential gate-keeping, were use of hospice volunteer drivers, rather than taxis, for transport of outpatients and the research doctor and nurse bringing outpatient participants for refreshments in the hospice cafeteria following the research assessment. Regular presentations of the research protocol and
interim findings were provided to all staff and updates and acknowledgements posted in the hospice staff newsletter.

Table 1. Table to show inclusion and exclusion criteria for study of the risk factors for falls in patients with advanced cancer.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cancer diagnosis</td>
<td>• Non-cancer diagnosis</td>
</tr>
<tr>
<td>• Aged 18 or over</td>
<td>• Unable to stand or mobilise unassisted</td>
</tr>
<tr>
<td></td>
<td>• Actively dying or considered too unwell by admitting and research team</td>
</tr>
<tr>
<td></td>
<td>• Registered Blind</td>
</tr>
<tr>
<td></td>
<td>• Unable to converse in English</td>
</tr>
</tbody>
</table>
ABSTRACT

BACKGROUND

The association between ageing and falls risk and the morbidity and mortality resulting from falls in older persons is well documented. Results from a small number of studies of patients with cancer in inpatient settings suggest that patients with advanced cancer may be at high risk of falling. We present interim results, pertaining to the incidence of falls in adults with advanced cancer, from a study of risk factors for falls in this population. In addition we test the hypothesis that patients with advanced cancer aged ≥65 years are at greater risk of falling than those aged <65 years.

METHODS.

Ambulant patients with cancer admitted to palliative care services were recruited. Demographic details were ascertained by patient interview and routine record review. Participants were followed-up by weekly telephone call for up to 6 months.

RESULTS

Follow-up has been completed for 119 patients; mean age was 66.91(±12.86) years, 53.8% male. Sixty-two participants (52.1%) fell during follow-up, median time to fall for participants aged <65 years and ≥65 years was 85 days.
and 80 days (44.07-115.93) respectively ($\chi^2=0.034$, $p=0.85$). The incidence density of falls was 2,770 per 1,000 person years.

CONCLUSIONS

One in two patients with advanced cancer fell during follow-up of up to 6 months, regardless of age. There is a need to investigate the sequelae of falls in patients with cancer, to ascertain the risk factors, and in particular the modifiable risk factors in this population.
INTRODUCTION

The association between aging and falls risk in older persons has long been recognised by specialists and generalists alike. As a result of research conducted over the past three decades, it is recognised that approximately 30% of community-dwelling older persons fall per annum, due to a complex interaction of intrinsic and extrinsic risk factors. Approximately 10% of falls result in fracture, head injury or serious soft tissue injury. Even non-injurious falls have significant negative consequences for the individual with up to 40% of those who fall subsequently experiencing a fear of falling. Fear of falling is associated with self-imposed activity restriction, leading to decline in physical performance independent of baseline function, and to development of gait and balance problems. The evidence supports the theory of a functional downwards spiral, whereby the negative sequelae of falling predispose to further falls: a history of falling in the past year is associated with a relative risk of further falls of 3.7. The financial cost of falling in older persons is not insignificant. In Ireland, during 2004, direct costs of falls and fractures in persons aged 65 years and over accounted for 1.6% of total public health expenditure.

Prevention of falls in older persons is a principal strategic objective for health and social policy makers in developed countries. Initiatives include screening all older persons annually for a history of falls, conducting a comprehensive fall evaluation in those presenting with a fall and increasing awareness in the general population of interventions that may improve balance and falls risk.
Evidence of effective interventions for reducing falls risk, in selected or unselected populations of older persons, is steadily emerging. Multicomponent interventions that target multiple risk factors, targeted exercise interventions, home hazard modification, reducing psychotropic medication and correction of vitamin D depletion have all been shown to be effective interventions for community-dwelling older persons.5 6

In comparison, very little is known of the epidemiology of falls in people with cancer. The literature published to date is limited to a small number of studies of incidence of and risk factors for falls in inpatient settings and retrospective case finding in cohorts of older persons with cancer attending outpatient services.9 21-27 Based on analysis of incident forms in Inpatient Palliative Care Units, where 97.5-100% admissions had malignant disease, researchers in the United Kingdom, Canada and Switzerland reported fall rates of 15.6, 16.9 & 6.9 falls per 1,000 patient bed days respectively; in comparison, the average rate of falling in acute hospitals in the UK in 2005-2006 was 4.8 falls per 1,000 bed days, suggesting that a diagnosis of advanced cancer confers a greater risk of falling than other illnesses.9 22 23 10

The existing research on falls in community-dwelling patients with cancer seems to refute this: the proportion of patients aged ≥70 years with cancer at any stage, reporting at least one fall in the preceding 12 months in the studies conducted by Overcash and colleagues were 22.4% (37/165) and 27% (81/297). Bylow et al reported that only 22% (11/50) of men aged ≥70 years with prostate cancer, with either biochemical recurrence or asymptomatic
metastatic disease, reported at least one fall in the preceding 3 months. However, all of the studies employed convenience sampling of patients and used retrospective reporting of falls. The latter is particularly susceptible to recall bias, as elucidated by Overcash and Riviera in a later study of 20 cancer patients aged ≥70 years, whereby 13 patients reported having fallen in the past year but 15 reported having fallen in the past 3 months.

In this paper we present preliminary findings, pertaining to the incidence of falls and details of falls, in consecutive recruits to an ongoing prospective study designed to evaluate the risk factors for falls in patients with advanced cancer. We hypothesised that patients with advanced cancer have a high incidence of falls and that patients with advanced cancer aged ≥65 years have a greater risk of falling than those aged <65 years.

METHODS

Setting and Participants
Consecutive admissions to the palliative care services provided by Our Lady’s Hospice and Care Services from 24/11/2008 until present (15/06/2010) were invited to participate. The palliative care services consist of inpatient care provided in a 36-beded inpatient unit (IPU), a Day Hospice service and a Home Care Service. The IPU offers admission to patients for symptom control, terminal care, rehabilitation and respite; in 2009, there were a total of 427 admission episodes and 250 deaths. The activity of Day Hospice follows
the model of Therapeutic Rehabilitation whereby patients attend a 6-week individualized program designed to assist return to their prior level of functioning.

Patients aged 18 years or older with a diagnosis of metastatic or loco-regionally advanced cancer were eligible for inclusion. Exclusion criteria were as follows: being unable to stand and mobilise unassisted, actively dying or considered too unwell by the admitting and research team, registered blind, using continuous oxygen, being aphasic or unable to converse in English. Eligible patients received written information on the study at the time of admission to services. Enrolment of patients with impaired cognition (Short Orientation-Memory test greater than 11) required the assent of the patient in addition to consent from their proxy. All other participants provided informed consent. The study was approved by St Vincent’s University Health Group Ethics Committee.

Data collection and patient follow-up

Demographic data was collected by transcription of data routinely recorded on the admission proforma and verified by patient interview at the time of risk factor assessment. Performance status was measured using the Palliative Performance Scale. Patients were contacted weekly from the date of baseline assessment, by telephone or in person, in order to determine if they had fallen during the preceding seven days and to record details of the fall if this had occurred. A fall was defined as an event whereby an individual inadvertently comes to rest on the ground or lower level with or without loss of
consciousness. Follow-up continued until 6 months from the time of baseline assessment, or until the occurrence of a fall, or death if these occurred prior to 6 months. Information regarding survival of patients who completed the study was obtained from an electronic palliative care patient administration database system, used by Our Lady’s Hospice & Care Services and the hospitals within its catchment area.

Statistical Analysis
Descriptive analyses of number and details of falls were conducted. Incidence density of falls was calculated as the total number of falls per the sum of patient days of follow-up, expressed as number of falls per 1000 patient years. Time to first fall was examined using survival analysis methods, including the log rank test. A term for age <65 and ≥65 years was included and 95% confidence intervals presented for median survival estimates. Demographic characteristics of participants and those who declined participation were compared using Pearson’s Chi-square test and the two-sample t-test. Statistical analysis was performed using SPSS (v16) statistical software.

RESULTS
Between 24/11/08 and 16/06/10 there were 1076 admission episodes, involving a total of 761 patients, to the services from which patients were being recruited; 457 were ineligible and 169 declined. One hundred and thirty-five patients have been recruited, of whom 119 have completed follow-up and
16 remain under follow-up. Of the participants for whom follow-up is complete, 55.5% were recruited from outpatient services and the remainder from the IPU, the mean age was 66.91 years (±12.86) and 53.8% were male. The most frequent cancer diagnoses were bronchial, breast and lower gastrointestinal cancers. There were no significant demographic differences between patients who declined and those who participated (see Table 1).

Sixty-two participants (52.1%) sustained a fall during follow-up; 24/46 (52%) participants aged <65 years and 38/73 (52.2%) aged ≥65 years fell. The median time to fall for participants aged <65 years and ≥65 years was 85 days (CI 51.54-118.46) and 80 days (44.07-115.93) respectively ($\chi^2 = 0.034$, df 1, p=0.85); see Figure 1. There was no difference in gender composition, performance status or median survival from time of recruitment, between the two age groups. The incidence density of falls was 2,770 per 1,000 person years.

Of the 62 patients who fell, including 20 who are alive at time of writing and hence have a 'censored' survival date, the median survival post-fall was 73 (CI: 52.9-93) days. Fifty-five percent of falls occurred in the community (38.7% at home, 11.3% outside, 4.8% other indoors) and the remaining 45% in hospital or hospice inpatient settings. Of the 62 participants who fell, 28 sustained soft-tissue injuries, two sustained fractures and one patient sustained a dislocation.
Table 1. Table to show demographic details of participants and patients who declined to participate.

<table>
<thead>
<tr>
<th></th>
<th>Study Participants (n=119)</th>
<th>Patients who declined (n=169)</th>
<th>Results of analysis of differences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency (%)</td>
<td>64 (53.8)</td>
<td>83 (49.1)</td>
<td>$\chi^2 = 0.609$ 1df, p = 0.44</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>66.9 (±12.9)</td>
<td>67.5 (±12.8)</td>
<td>t = 0.372, p = 0.71</td>
</tr>
<tr>
<td><strong>Cancer Diagnosis (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial</td>
<td>20 (16.8)</td>
<td>43 (25.4)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>18 (15.1)</td>
<td>21 (12.4)</td>
<td></td>
</tr>
<tr>
<td>Lower Gastrointestinal</td>
<td>14 (11.8)</td>
<td>23 (13.6)</td>
<td>$\chi^2 = 11.75$ 9df, p = 0.23</td>
</tr>
<tr>
<td>Upper Gastrointestinal</td>
<td>15 (12.6)</td>
<td>19 (11.2)</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>11 (9.2)</td>
<td>11 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Gynaecological</td>
<td>10 (8.4)</td>
<td>11 (6.5)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic &amp; hepatobiliary</td>
<td>9 (7.6)</td>
<td>15 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Urological not prostate</td>
<td>5 (4.2)</td>
<td>10 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>5 (4.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>12 (10.2)</td>
<td>16 (9.5)</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

One in two adults with metastatic or loco-regionally advanced cancer fell at least once, during follow-up of up to 6 months, regardless of age. Fifty-five percent of falls occurred outside the hospital/hospice setting and approximately half resulted in physical injury. The estimated median survival of patients at the time of fall was 73 days - an underestimation as one third of patients who fell were alive at the time of analysis.
Our findings suggest that falls are more common in adults with advanced cancer than in community-dwelling older persons: the incidence density of falls was 2,770 per 1,000 person years, more than double the rates reported for healthy older persons. These results are unprecedented; prior studies of patients with cancer reported that 22.4-27% patients experienced at least one fall per annum. Possible explanations for the divergence are that the previous studies may have included patients with earlier stage disease, that case ascertainment was based on occurrence of falls in an earlier time period or that falls were under reported due to recall bias.

It is a limitation of our study that over 50% of eligible patients declined participation. However, the demographic profiles of participants and non-participants were similar and resemble that of the total population of persons in Ireland living with advanced cancer. Whilst our results may be subject to selection bias according to characteristics that make patients more likely to be referred to palliative care services, this may be offset to a certain extent by the breadth of palliative care services provided and our strategy of recruiting from all facets of these services. Increasing age does not appear to be an independent risk factor for falls in patients with advanced cancer, suggesting that the high prevalence of falls is related to factors other than the demographic profile of cancer.

We have identified that falls are an extremely common experience in advanced cancer, and yet have raised more questions than answers: what psychological impact do falls have in the context of cancer, and does this
differ between younger and older age groups? Do falls cause a decline in physical performance independent of baseline functional ability, as in older persons? Are the risk factors, and in particular the modifiable risk factors, for falls in patients with cancer the same as in older persons? In the face of increasing numbers of people living with advanced cancer, due to population aging and effectiveness of novel treatment modalities, we contend that there is an urgent need to address these issues. Knowledge of the risk factors for falls in patients with cancer will facilitate identification of patients who are most at risk and inform decision-making by clinicians and patients regarding balancing the risk-benefit ratio of any treatments shown to increase falls risk. It will also provide the foundation for falls prevention interventions tailored to the needs of patients with advanced cancer.
Chapter 4: The prevalence of vitamin D deficiency in inpatients with advanced cancer

ABSTRACT

BACKGROUND
Vitamin D deficiency, defined as serum concentrations of < 50nmol/L is common in healthy populations; the mean vitamin D of 33,000 healthy subjects worldwide, included in a meta-analysis was 54nmol/L. In addition to its role in bone health, vitamin D is important for muscle strength and function; serum concentrations of 90-100nmol/L are associated with optimal lower limb function. We describe the prevalence of vitamin D deficiency in patients recruited consecutively to a study of the risk factors for falls in patients with advanced cancer.

METHODS
Patients admitted consecutively to a palliative care inpatient unit who were independently mobile and participated in a prospective study of the risk factors for falls in advanced cancer had blood taken for vitamin D assay.

RESULTS
Serum vitamin D levels were determined for 41 patients, 21 were male, mean age 69.8 (±12.2) years. Mean serum vitamin D was 28.3 (±18) nmol/L (range 0-71nmol/L), 36/41 (88%) had vitamin D deficiency.
CONCLUSIONS

The majority of participants had vitamin D deficiency and all had serum concentrations below that required for optimal muscle functioning. Further research is required, to identify the prevalence of vitamin D deficiency in well defined cohorts of patients with cancer, to identify protocols for safe and effective repletion of vitamin D in patients with cancer and to assess the clinical impact of repletion on muscle function, pain and falls.
Evidence has been emerging from laboratory-based and epidemiological studies, over the past two decades, to suggest that vitamin D has a much bigger role than previously thought; most tissues and cells in the body have vitamin D receptors and many others, in addition to the kidneys, have the capacity to hydroxylate 25-Hydroxyvitamin D to the active 1,25-hydroxyvitamin D. Data from observational population-based and preclinical studies implicate vitamin D deficiency in the pathogenesis of cancers, autoimmune and other common diseases.56-58

Humans largely source vitamin D from exposure of the skin to sunlight; few foods, with the exception of oily fish contain it naturally. Vitamin D deficiency is generally defined as serum concentration <50nmol/L, and based on observations of the normal physiological response, whereby parathyroid hormone levels reach their nadir at serum vitamin D concentrations of 75-100nmol/L, concentrations of 50nmol/L to 74nmol/L are defined as vitamin D insufficiency. Using this definition, it has been shown in several studies that vitamin D deficiency is prevalent both in older people living in the USA and Europe (40-100%) and in younger adults (42-52%).56

There has been much debate recently in the general medical literature, regarding the optimal approach to management of vitamin D deficiency in healthy populations; the likelihood that a ‘one size fits all’ approach will be effective is slight, as it appears that ability to produce 1,25-(OH)2D from exposure to sunlight and dietary sources is significantly affected by genetic variation in addition to age, skin pigmentation, climate, time spent outdoors
The controversy has deepened following the recent publication of revised recommended daily allowances (RDA) for vitamin D, by the Institute of Medicine (IOM). Although the RDA has been revised upwards to 600IU for children and adults up to age 70 years and 800IU for those aged over 70 years, many experts believe that the IOM have not gone far enough in raising the RDA. Furthermore, the recommendations do not address initial management of depletion; the previously recommended adequate intake for adults aged from 51 to 70 years (400IU), has been shown to be ineffective when used to treat persons with vitamin D deficiency.

The vitamin D debate is being closely observed by Gerontologists. Not only is vitamin D important for bone health; in older persons, vitamin D deficiency is associated with increased risk of falls and correction of depletion with reduced incidence of falls. A meta-analysis of 8 randomised controlled trials of vitamin D supplementation in older people found that achievement of 25OHD levels >60nmol/L was associated with a 23% reduction in falls risk. It is postulated that vitamin D binds to a specific nuclear receptor in muscle tissue leading to de novo protein synthesis, muscle cell growth and improved muscle function. A randomised controlled trial of Vitamin D therapy in stroke survivors showed that treatment with 1000IU cholecalciferol daily resulted in increased mean type II muscle fibre diameter and percentage of type II fibres. Severity of fatty degeneration and atrophy of thigh muscles, as assessed by MRI, in patients aged ≥65 years is negatively correlated with serum vitamin D concentrations (r= 0.5, p<0.05) and performance in
functional tests of lower limb muscle strength in older persons positively related to serum concentrations of vitamin D in analyses controlled for participants’ level of activity: the optimal levels of serum 25-hydroxyvitamin D for lower limb muscle function are 90-100 nmol/L.\textsuperscript{66,68,69}

The prevalence of vitamin D deficiency in patients with cancer is unknown. Studies of patients with breast cancer in North America have yielded disparate results: a study of 103 premenopausal women with breast cancer, receiving adjuvant chemotherapy, found 74% to have vitamin D <50nmol/L, whereas in a large study of 1,026 women with newly diagnosed breast cancer only 33% had vitamin D <50nmol/L.\textsuperscript{65} With regards to the prevalence of vitamin D deficiency in patients with advanced cancer, Brown \textit{et al} reported a median vitamin D concentration of 21nmol/L (range 6-128) in a cohort of 50 patients with advanced lung and gastrointestinal cancer in Scotland.\textsuperscript{70} Our research group measured serum vitamin D in a subgroup of patients recruited to a prospective study of the risk factors for falls in adults with advanced cancer, receiving palliative care. Patients with a diagnosis of metastatic or loco-regionally advanced cancer who were able to stand and mobilise unassisted were eligible for inclusion. Patients who were actively dying or considered too unwell to participate by the admitting and research team were excluded. Blood was taken for analysis of Vitamin D from patients recruited in the inpatient setting, processed within 2 hours of collection and stored at \(-20^\circ\) C until analysis. Serum vitamin D was assayed using an automated chemiluminescent assay (Liaison, Diasorin S.p.A, Italy). This immunoassay measures total vitamin D (vitamin D3 + vitamin D2). All assays were
performed in the same laboratory and by the same laboratory staff. Analytical
sensitivity was < 2.5 nmol/l and functional sensitivity was < 10.0 nmol/l.

Serum vitamin D and corrected calcium levels were determined for 41
inpatients, of whom 21 were male, mean age was 69.8 (±12.2) years and the
most common malignant diagnoses were bronchial (n=9) and breast cancer
(n=7). All were Caucasian. The mean serum vitamin D was 28.3 (±18) nmol/L
(range 0-71nmol/L), 36/41 had levels below 50nmol/L, including 3 of 4
patients taking vitamin D supplements (see Figure 1). Mean serum corrected
calcium was 2.45(±0.21) mmol/L (laboratory reference range 2.2-2.6 mmol/L).

By definition, the majority of participants (88%) had vitamin D deficiency and
all had vitamin D insufficiency and serum concentrations below that required
for optimal lower limb muscle function. Although our sample size is too small
to establish the prevalence of vitamin D insufficiency with confidence, it is
plausible that our results approximate the true prevalence of vitamin D
insufficiency in patients with advanced cancer; vitamin D deficiency is
common in healthy populations and patients with cancer may have additional
risk of deficiency due to a combination of less time spent outdoors, reduced
oral intake and gastrointestinal malabsorption.

From the evidence of the effects of vitamin D deficiency in older persons we
can theorise that vitamin D insufficiency may add to burden of the cancer
experience; as an additional risk factor for osteoporosis and suboptimal
muscle function it may have a detrimental effect on pain control, functioning
and quality of life. Severe vitamin D deficiency can be associated with musculoskeletal pain.\textsuperscript{71}

It is not yet clear whether vitamin D deficiency plays as significant a role in mediating falls risk in patients with advanced cancer as it does in older people, or how cancer-related sarcopenia, muscle fatigue and vitamin D deficiency interact in mediating cancer-related muscle dysfunction. Research is required to confirm our observation that vitamin D deficiency is highly prevalent in patients with advanced cancer. Studies of experimental design will facilitate assessment of the impact of vitamin D repletion on muscle function, pain and falls in patients with advanced cancer. The addition of vitamin D repletion, as an experimental arm, to randomised controlled trials (RCT's) of interventions for treatment of anorexia-cachexia will enable examination of the interaction between anorexia-cachexia and vitamin D deficiency. Design of such RCT's must be informed by phase I trials to identify protocols for effective and safe repletion of vitamin D in patients with cancer.

61
Figure 1. Serum vitamin D levels of study participants (n=41)

Vitamin D deficiency (88% participants)

Vitamin D insufficiency (100% participants)

Mean = 28.2659
Std. Dev. = 17.97111
N = 41
Chapter 5: Autonomic dysfunction in patients with advanced cancer; prevalence, clinical correlates and challenges in assessment.

ABSTRACT

BACKGROUND

The results of a small number of studies of autonomic function in patients with advanced cancer suggest that autonomic dysfunction (AD) is common. In other disease-specific groups this is associated with decreased survival, falls and symptoms such as postural hypotension, nausea, early satiety and fatigue. The contribution of AD to symptoms in advanced cancer is unknown.

METHODS

We conducted a prospective cohort study designed to identify the risk factors for falls in patients with advanced cancer. Ambulant adult patients admitted consecutively to palliative care services were invited to participate. Participants underwent an assessment at baseline which included standard clinical tests of autonomic function, assessment of symptom severity, muscle strength, anthropometric measurements, walking speed, medication use, comorbidities and demographics. Information regarding survival was recorded ten months following cessation of recruitment. The clinical correlates of AD, defined as definite or severe dysfunction using Ewing’s classification, were examined by univariate and multivariate logistic regression analysis. Survival analysis was conducted using Kaplan-Meier plots and the log rank test.
RESULTS

Of 185 patients recruited, 45% were unable to complete all of the clinical tests of autonomic function. Non-completion was associated with scoring high on clinical indicators of frailty. It was possible to accurately classify 138/185 (74.6%) of participants as having either definite or severe versus normal, early or atypical AD: 110 (80%) had definite/severe AD. In logistic regression analysis, age (OR=1.07 [95% CI; 1.03-1.1] P= 0.001) and increased severity of fatigue (OR=1.26 [95% CI; 1.05-1.5] p=0.016) were associated with having definite/severe AD. In analysis adjusted for age, median survival of participants with definite/severe AD was shorter than in those with normal/early/atypical classification (χ²= 4.3, p=0.038).

CONCLUSIONS

Autonomic dysfunction is highly prevalent in patients with advanced cancer and is associated with increased severity of fatigue and reduced survival. Due to frailty, up to 45% of participants were unable to complete standard clinical tests of autonomic function. In order to further investigate the impact of AD and the therapeutic potential of treatment of AD in patients with advanced cancer, the validity of alternative novel methods of assessing autonomic function must be appraised.
INTRODUCTION

The autonomic nervous system innervates blood vessels, the airways, intestines and urogenital organs and is largely under involuntary control. It regulates and coordinates bodily functions by effecting secretory activity of glands and contraction and relaxation of smooth and cardiac muscle. Autonomic neuropathy may be idiopathic or occur as a complication of other conditions or as result of drugs. It is recognised as a common complication of diabetes mellitus; for many it remains subclinical, with only a minority experiencing symptoms such as postural hypotension, nausea, vomiting and early satiety related to gastroparesis, nocturnal diarrhoea, bladder-emptying problems and male erectile dysfunction. Autonomic dysfunction (AD) has also been shown to be a negative prognostic indicator following acute myocardial infarction and stroke. The underlying mechanism is thought to be an increased risk of cardiac arrhythmias as a result of decreased vagal tone.

Autonomic dysfunction has been described in patients with advanced cancer, in whom a high prevalence of AD is identified. Postulated causes include decreased physical activity, treatment with vinca alkaloids or other medications, or paraneoplastic processes. The precise contribution of AD to clinical findings and prognosis in advanced cancer is unclear. Only one study has demonstrated a relationship between AD and symptoms in patients with advanced cancer; Bruera et al. found that patients with advanced breast cancer in whom all tests of cardiovascular autonomic function were abnormal were more likely to report symptoms of postural hypotension and chronic unexplained nausea. More recent research on AD in advanced cancer...
has focussed on its prognostic significance; a small number of studies have identified a relationship between AD and shorter survival in advanced cancer.\textsuperscript{82-84}

Cardiovascular autonomic neuropathy has been shown to be a risk factor for falls in older adults with dementia.\textsuperscript{55} We conducted a prospective study of the risk factors for falls in patients with advanced cancer. In view of the reported high prevalence of AD in patients with advanced cancer we elected to include tests of cardiovascular autonomic function in our research assessment. Autonomic function is most commonly measured by the application of a group of clinical tests, which aim to measure sympathetic and parasympathetic activity, by measuring end-organ responses to physiological perturbations.\textsuperscript{85} Ewing \textit{et al} devised a battery of four tests which generate three outcome measures of parasympathetic activity and two of sympathetic activity, the results of which can be used to grade the severity of autonomic dysfunction.\textsuperscript{86} In this chapter we specifically report our findings in relation to the frequency and clinical correlates of AD, highlight and evaluate the difficulties experienced in measuring autonomic function in patients with advanced cancer, and make recommendations regarding the direction of future research in this area.

**METHODS**

**Setting and Participants**

Eligible patients who were admitted consecutively to the palliative care services provided by Our Lady’s Hospice and Care Services (November 24,
2008 – Dec 24, 2010) were invited to participate. The palliative care services consist of inpatient care provided in a 36-bed inpatient unit (IPU), a day hospice service and a home care service. Patients aged 18 years or older with a diagnosis of metastatic or loco-regionally advanced cancer were eligible for inclusion. Exclusion criteria were as follows: being unable to stand and mobilize unassisted, actively dying or considered too unwell by the admitting and research teams, registered blind, using continuous oxygen, and being aphasic or unable to converse in English. Eligible patients received written information on the study at the time of admission to services. Enrollment of patients with impaired cognition (Short Orientation-Memory Concentration Test (SOMCT) score greater than 11) required the assent of the patient in addition to consent from their proxy. The SOMCT error score ranges from 0-28; the normal score range is 0-6. All other participants provided informed consent. The study was approved by St. Vincent’s University Health Group Ethics Committee.

**Data Collection**

Demographic details, comorbidities and medications were transcribed from admission notes and verified at patient interview. The following were considered to be cardioactive medications; beta blockers, tricyclic antidepressants, nitrates, rate-limiting calcium antagonists, anticholinergics and other antiarrhythmics.

All assessments were conducted between 0900hrs and 1300hrs. All participants were asked to refrain from smoking and caffeine ingestion on the
morning of assessment, but were not asked to stop any of their usual medications or fast. A physician and research nurse performed the tests of autonomic function in a quiet room at ambient temperature (21–23°C). Autonomic function tests were carried out using a modified Ewing’s battery. Heart rate was measured by ECG using standard limb leads; heart rate (HR) tests were excluded if invalidated by arrhythmia, excessive ectopic activity or movement artefact. Blood pressure (BP) was monitored using the Finometer Pro device (Finapres Medical Systems BV, Amsterdam, the Netherlands) which enables noninvasive beat-to-beat BP measurement from finger arterial BP. The BP recordings are derived from the circumferential pressure generated by a finger cuff, which is varied to maintain a constant digital arterial size, as measured by a photoplethysmograph. Under such conditions the external cuff pressure equals the internal digital arterial pressure. Participants rested in the supine position for at least ten minutes before testing. During this time they were covered with a blanket and wore a thermal mitten with glove liner in order to improve BP signal pick-up. Blood pressure tests were excluded if the trace was obscured by movement artefact or artefact due to external pressure on the finger-cuff.

Parasympathetic tests
1. Deep breathing

Whilst supine, participants were requested to ‘take slow deep breaths, so that each breath in lasts five seconds and each breath out lasts 5 seconds, for a total of six consecutive breaths’. This was rehearsed prior to testing and the tester guided the timing of the breaths for the participant by verbally counting
through each of the six breaths/cycles. The maximum and minimum HR during each breathing cycle was calculated from the corresponding shortest and longest R-R interval, and the response recorded as the mean of the differences during three successive breathing cycles.

2. Active stand

Participants were requested to stand up from the supine position as quickly as possible and to remain standing, in silence, for three minutes, with the monitored arm resting by their side. Assistance with rising was provided when this could not be achieved independently. Heart rate response was measured as the ratio of the maximum R-R interval at or around the 30\textsuperscript{th} beat after starting to stand, to the minimum R-R interval at or around the 15\textsuperscript{th} beat.

3. Valsalva manoeuvre

The Valsalva manoeuvre was achieved by forced expiration, against an open glottis. Participants were requested to achieve a constant pressure of 40mmHg for 15 seconds. The procedure was rehearsed prior to testing and the tester guided the participant by counting aloud through the fifteen seconds. The test was performed three times and the best response used for analysis. A minimum of one test achieving 30mmHg for 12 seconds was required for inclusion. Heart rate response was taken as the ratio of the maximum R-R interval shortly after the manoeuvre to the minimum R-R interval during the procedure.

Sympathetic test

1. Active stand
The change in BP was measured as the difference between the baseline BP whilst supine and the lowest BP after standing.

Results for the Valsalva manoeuvre were graded as normal or abnormal, and all other tests as normal, borderline or abnormal using the values recommended by Ewing et al. Overall autonomic function was described using Ewing's classification system:

- Normal: all tests normal or one borderline
- Early dysfunction: one of the three HR tests abnormal or two borderline
- Definite dysfunction: two or more HR tests abnormal
- Severe dysfunction: two or more HR tests abnormal plus one BP test abnormal or both borderline
- Atypical pattern: any other combination of abnormal tests.

Severity of tiredness, nausea, loss of appetite and shortness of breath were measured using the Edmonton Symptom Assessment Scale; an 11 point numerical rating scale from 0-10, whereby larger numbers represent increased symptom severity. Information regarding survival of study participants was obtained from an electronic palliative care patient administration database system, used by Our Lady's Hospice & Care Services and the hospitals within its catchment area. Survival in days was measured from the day of assessment. The analysis of survival times was conducted on Sept 24, 2011.
BMI was calculated from participants' height and weight as measured on the day of assessment, and weight loss by subtracting current weight from reported weight prior to cancer diagnosis. Walking speed was measured using the timed 'Up and Go' (TUG) whereby the participant is asked to rise from a seated position, walk to a marked spot three metres away, turn around and return to their seat. The participant is instructed to walk at their normal pace and may use any gait aid normally used. Timing is started when the participant is instructed to 'go' and stopped when they are seated in the chair again. Grip strength was measured three times in each hand using a hydraulic hand dynamometer (Jamar, Samons Preston Rolyan, Bolingbrook, IL). The result used was the best result of the six measurements.

**Statistical methods**

Demographic details and clinical variables were summarised using descriptive statistics. Comparisons of groups of categorical variables were conducted using the Chi-square test, of normally distributed continuous variables using the 2-sample t-test and of non-parametric variables using the Mann-Whitney U test. Variables shown to be associated with AD in univariate analyses, with p<0.1, were entered into logistic regression models, using forwards and backwards stepwise variable entry. Only variables that were significant at p<0.05 were retained in the model. The relationship between AD and survival was examined using survival analysis methods, including the log rank test.

**RESULTS**

During the study period, there were 1,607 admission episodes involving 1,117 individuals, of whom 693 (62%) were ineligible, 239 (21.4%) declined and 185
(16.6%) were recruited. There were no significant demographic differences between participants and those who declined (see Table 1).

**Completion of individual components of Ewing's battery**

**HR response to deep breathing.**

The HR data of 14/185 (7.6%) participants were invalidated by arrhythmia. A further nine participants were unable to complete three consecutive breaths according to the study protocol, due to inattention and/or difficulty understanding and retaining information. The median SOMCT error score in those who completed the test was 2 compared with 6.5 (p=0.015) in those who did not complete it.

**HR response to active stand.**

The HR data of 14/185 (7.6%) participants were invalidated by arrhythmia and one by excessive artefact at the time of standing.

**BP response to active stand.**

The BP data of 42/185 (22.7%) participants was invalidated due to failure to obtain a good quality trace or due to artefact; most commonly due to external pressure on the finger cuff at the time of the stand.

**HR response to Valsalva manoeuvre.**

Eighty-three (45%) participants were unable to complete the Valsalva manoeuvre. We conducted analyses to explore our *post-hoc* hypothesis that the high prevalence of non-completion of the Valsalva manoeuvre was due to the phenotypic characteristics of our study population. We observed that
patients who had features consistent with the geriatric syndrome of frailty were less likely to be able to complete the Valsalva manoeuvre. See Table 2 for results. In view of the high prevalence of dyspnoea in advanced cancer we included the ESAS item on severity of shortness of breath in our analysis, but found that this was not associated with ability to complete the Valsalva manoeuvre.

Table 1. Demographic details of participants and those who declined participation.

<table>
<thead>
<tr>
<th></th>
<th>Participants (n=185)</th>
<th>Declined (n=239)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male (%)</td>
<td>52.4</td>
<td>50.2</td>
<td>$\chi^2=0.2, 1\text{df}$ $p=0.65$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68±12.6</td>
<td>68.3±13.1</td>
<td>t=0.12, $p=0.9$</td>
</tr>
<tr>
<td>Cancer diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial</td>
<td>18.4</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>14.1</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Lower Gl</td>
<td>14.1</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>Upper Gl</td>
<td>11.4</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>9.7</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Gynaecological</td>
<td>7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Pancreatic/hepatobiliary</td>
<td>6.5</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Urological not prostate</td>
<td>5.4</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>2.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10.8</td>
<td>12.1</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Features of participants according to whether they were able to complete the Valsalva manoeuvre.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean/median (Valsalva completed)</th>
<th>Mean/median (Valsalva not completed)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss (Kg)</td>
<td>4.3</td>
<td>7.8</td>
<td>0.09 (t=-1.7)</td>
</tr>
<tr>
<td>BMI</td>
<td>26</td>
<td>22.6</td>
<td>&lt;0.0001 (t=4.9)</td>
</tr>
<tr>
<td>TUG (secs)</td>
<td>14.06*</td>
<td>18.7*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grip strength (kg)</td>
<td>24.5*</td>
<td>18.0*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Tiredness (ESAS)</td>
<td>3*</td>
<td>4*</td>
<td>0.2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.4</td>
<td>71.5</td>
<td>0.001 (t=-3.3)</td>
</tr>
</tbody>
</table>

*Median value

Prevalence of autonomic dysfunction and associated factors

Due to the high levels of missing data pertaining to the HR response to Valsalva manoeuvre and BP response to active stand, it was only possible to accurately define autonomic function, using Ewing's classification (normal, definite, severe or atypical), for 91/185 (49.2%) participants (see Figure 1). By collapsing the Ewing's classification into a binary classification of definite/severe versus other, it was possible to accurately classify 138/185 (74.6%) participants as having either normal, early or atypical, (other category) versus definite or severe AD. Of 138 patients 110 (80%) had definite or severe AD. Having definite/severe AD was associated with increasing age; see Table 3 for contingency table of binary AFT classification according to age groups defined by quartiles ($\chi^2$ for trend =7.6, p=0.006). In univariate analysis, gender, taking cardioactive medication and having a
diagnosis of diabetes mellitus were not associated with binary AFT classification \( (\chi^2 = 0.17, \ p=0.7, \chi^2 = 0.89, \ p=0.4 \text{ and } \chi^2 = 0.4, \ p=0.5 \) respectively), whereas having at least one cardiovascular comorbidity was associated with having definite/severe AD \( (\chi^2 = 3.79, \ p=0.05) \). Having definite/severe AD was associated with severity of tiredness as measured using the ESAS (median 4/10 versus 2/10, \( p=0.006 \)), but not with severity of appetite loss (median 3/10 versus 1/10, \( p=0.07 \)) or nausea (median 0/10 versus 0/10, \( p=0.9 \)). Age, taking cardioactive medications, severity of tiredness (ESAS) and severity of appetite loss (ESAS) were entered into the logistic regression models. However, only age \( (\text{OR} = 1.07 \ [95\% \text{ CI}; 1.03-1.1]\ P=0.001) \) and severity of tiredness \( (\text{OR}=1.26 \ [95\% \text{ CI}; 1.05-1.5] \ p=0.016) \) were shown to be significantly associated with a diagnosis of definite or severe autonomic dysfunction.

The median survival for participants with definite/severe AD was 106 days \( (95\% \text{ CI}; 78.6-133.4) \) compared with 135 days \( (95\% \text{ CI}; 24.8-245.2) \) in those with normal/early/atypical classification \( (\chi^2 = 4.8, \ p=0.028) \) (see Figure 2). The relationship between AD and survival persisted in analysis adjusted for age, defined by quartiles as above \( (\chi^2 = 4.3, \ p=0.038) \).

Eighty-four of the 143 participants (58.7\%) who had valid active stand BP data had a systolic BP drop of at least 30mmHg on standing.
Figure 1. Pie chart to show prevalence of autonomic dysfunction in patients with advanced cancer (n=91)

Ewing's classification of autonomic dysfunction:
- Normal
- Early
- Definite
- Severe
- Atypical

Figure 2. Kaplan-Meier plot to show relationship between survival and autonomic function (n=138)

AFT classification:
- Normal/early/atypical
- Definite/severe
- Censored
Table 3. Binary AFT classification according to age (quartiles)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;58 yrs</th>
<th>58-67yrs</th>
<th>68-76yrs</th>
<th>≥77yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal/early/atypical AFT classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>14</td>
<td>5</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Expected count</td>
<td>6.3</td>
<td>7.3</td>
<td>7.1</td>
<td>7.3</td>
</tr>
<tr>
<td><strong>Definite/severe AFT classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Count</td>
<td>17</td>
<td>31</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Expected count</td>
<td>24.7</td>
<td>28.7</td>
<td>27.9</td>
<td>28.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>31</td>
<td>36</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Expected count</td>
<td>31</td>
<td>36</td>
<td>35</td>
<td>36</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Using Ewing’s classification it was possible to diagnose the presence or absence of definite or severe AD in 138/185 (74.6%) participants, of whom 80% had definite/severe AD. This finding is consistent with the prevalence of moderate/severe AD measured in patients with advanced cancer (n=50), as reported by Walsh and Nelson, and in men with advanced cancer (n=48), as reported by Strasser et al of 82% and 81%, respectively. In our study, severity of fatigue was greater in patients with definite/severe AD, and although ESAS scores for loss of appetite were greater in those with definite/severe AD, this did not reach statistical significance. Median ESAS scores for nausea were zero in both groups, which most likely reflects the
availability of effective treatment for this symptom. Having definite/severe AD was associated with shorter survival. Although this confirms the findings of previous studies of AD in patients with advanced cancer, it has yet to be clarified whether AD causes shorter survival or if factors associated with shorter survival, such as increased time spent in bed, contribute to severity of AD.

A striking finding of our study was the poor feasibility of conducting autonomic function testing, using Ewing’s battery, in patients with advanced cancer. Forty-five percent of patients were unable to complete the Valsalva manoeuvre, despite our having adopted a lower threshold for the duration, pressure and number of tests completed, than is standard. The results of the post hoc analyses supported our observation that more frail patients were less likely to be able to complete the Valsalva manoeuvre. Prior to the active stand, participants were requested not to grip anything with their right hand during the process of rising or during the three minute stand: most participants did receive the assistance of one of the testers to rise from the supine to seated position. Despite this many participants experienced difficulty with getting up quickly. Additionally, we took steps to ensure a good digital BP recording by keeping the participant warm prior to testing. Despite these measures, BP data from 23% of participants were invalid, mainly due to artefact from external pressure on the finger cuff at the time of standing or due to a poor quality trace.
Walsh and Nelson reported that participants in their study also had difficulty with rising from a supine position to standing, and that they found the Valsalva manoeuvre stressful, but despite this 48/50 (96%) patients managed to complete it.\textsuperscript{77} Bruera \textit{et al} reported that 8/43 (18.6%) participants had missing HR and BP data for the active stand as they were unable to stand up readily. It is likely that our use of beat-to-beat BP measurement from finger arterial BP; though now the standard in clinical and research autonomic function laboratories, resulted in our relatively high rate of failure in obtaining active stand BP data in this patient population. All other studies in patients with advanced cancer measured BP at the brachial artery with a sphygmomanometer, which has the drawback of not providing continuous monitoring, but is less susceptible to artefact resulting from external pressure and peripheral vasoconstriction.

Our use of a modified version of the Ewing's battery of tests was a notable study limitation: we omitted a second test of sympathetic function, the BP response to isometric exercise, whereby the patient is instructed to grasp a dynamometer and sustain a fixed, isometric contraction for 3 minutes at 30% maximum effort. We omitted this test for pragmatic reasons: an accurate diagnosis of definite AD according to Ewing's classification can be made based on 3 HR tests; this test had the lowest rate of completion in Walsh and Nelson's earlier study, as participants found it difficult. Furthermore, this test has been shown to have low sensitivity and specificity, due to problems standardising muscular effort and variability in muscle afferent activity when tested in trained versus untrained muscles.\textsuperscript{77,85}
The ranges for normal values for each test were derived by Ewing from tests in healthy subjects aged 16-69 years. However, HR responses to deep breathing, active stand and the Valsalva manoeuvre decline with age. Our use of Ewing's normal values, rather than determining age-specific normal values from testing age-matched controls, may have resulted in false negative test results in younger patients and also means that we cannot isolate the effect of a diagnosis of advanced cancer from the effect of normal aging on AD. Despite this, 54.8% of those aged less than 58 years were classified as having definite/severe AD. Unlike previous studies, we did not exclude patients who had other medical conditions known to be associated with AD or those taking medications which may affect autonomic reflexes. However, we found that in the context of advanced cancer, these conditions do not significantly increase the risk of AD.

Autonomic dysfunction is common in patients with advanced cancer. The findings of Bruera et al suggest that AD may be associated with symptoms of postural hypotension and unexplained nausea. In view of the high prevalence of orthostatic hypotension (OH) in this study, we recommend routine enquiry for symptoms suggestive of OH and measurement of lying and standing BP in patients with advanced cancer. Management of OH includes discontinuation of antihypertensive medication, adoption of physical counter-manoeuvres, and use of mineralocorticoid (e.g. fludrocortisone) and/or adrenergic agonist (e.g. midodrine) medications.
In this study, patients with definite or severe AD had higher scores for severity of tiredness, as measured by the ESAS. Fatigue has been shown to be associated with AD in patients with Multiple Sclerosis and Primary Biliary Cirrhosis. Impaired autonomic function has also been described in patients with Chronic Fatigue Syndrome (CFS) and patients with vasovagal syncope (VVS) have been shown to have higher levels of fatigue than age-matched controls. A postulated explanation for these associations is that fatigue occurs as a result of impaired organ perfusion related to hypotension. Alternative explanations, in the case of CFS, are that AD develops as a result of reduced physical activity, or that both the fatigue and AD have a common aetiology. However, early studies in patients with CFS and VVS suggest that severity of fatigue may improve with treatment of AD related postural hypotension. In a cross-sectional study of patients with VVS diagnosed and treated by a single Falls and Syncope Service (n=91), patients whose syncopal symptoms had responded to conventional treatment (conservative advice, followed three months later in the event of persistent symptoms, by commencement of either fludrocortisone, midodrine or a selective serotonin reuptake inhibitor) reported less severe fatigue and daytime sleepiness than those with persistent syncopal symptoms. In a pilot study of 10 patients with CFS shown to have abnormal cardiovascular responses to a head-up tilt test, for 6 patients, treatment with midodrine resulted in normalisation of cardiovascular responses at three months, followed by an improvement in fatigue scores 4-8 weeks later. Exploration of the relationship between autonomic dysfunction and fatigue, the potential for reversibility of AD with pharmacological intervention, and the impact of this on
fatigue and survival in patients with advanced cancer, are all worthy of further investigation.

However, in view of our findings relating to the feasibility of conducting standard clinical tests of autonomic function in a large cohort of patients with advanced cancer, we recommend that the reliability and validity of novel methods of assessment of autonomic function are investigated further. The findings of Fadul et al suggest that measurement of heart rate variability (HRV) may provide a useful measure of AD in this population, for both research and clinical purposes. Power spectral analysis of heart rate fluctuations, recorded by continuous electrocardiogram, provide a simple and non-invasive technique for analysing autonomic function. In their study of men with advanced cancer, Fadul et al found a strong association between the results of the Ewing’s battery and the time domain measure 'standard deviation of normal to normal beat interval' ($r=0.44$, $p=0.002$).\(^8^3\)

**CONCLUSIONS**

Autonomic dysfunction is highly prevalent in advanced cancer and is associated with severity of fatigue. Research findings in patients with VVS and CFS suggest that correction of autonomic dysfunction-related postural hypotension may result in alleviation of fatigue. Future research on the impact of AD and its treatment in patients with advanced cancer must also address the potential for novel methods of assessment of autonomic function to provide a reliable proxy for the standardised clinical tests; due to frailty, 45%
of participants in this study were unable to complete Ewing's battery of tests emphasising the need to explore alternative methods for evaluation of autonomic function in this population.
Chapter 6: Reliability testing of hand-held dynamometry when used to test knee-extensor strength in patients with advanced cancer.

ABSTRACT

BACKGROUND

Our objective was to determine the test-retest and inter-rater reliability of hand-held dynamometry when used to measure knee-extensor strength in patients with advanced cancer.

METHODS

Adults with metastatic or locally advanced cancer recruited from inpatient and outpatient palliative care services to a study of the risk factors for falls. Consecutive recruits (n=30) underwent repeat testing of right knee extensor strength using hand-held dynamometry after an interval of one hour by the same researcher in order to assess test-retest reliability. The next 15 patients underwent retesting by a second researcher. The intra-class correlation coefficient and limits of agreement were calculated.

RESULTS

Test-retest reliability; the difference between the two measurements increased with the magnitude of the measurement, mean leg strength = 113 ±43.1 N, 95% ratio limits of agreement 0.81–1.5, intra-class correlation coefficient = 0.9. The inter-rater testing mean leg strength = 128.5 ±35.1 N, 95% limits of agreement = –57.24 to 36.06 N. Intra-class correlation coefficient = 0.83.
CONCLUSIONS

Test-retesting and inter-rater testing yielded high intra-class correlation coefficients but the limits of agreement were wide. In test-retesting, the difference between tests increased as the magnitude of measurement increased. It has been widely reported that hand-held dynamometry is reliable when used to measure muscle strength in frail or elderly persons. However, our results show that, even in these populations, reliability may be compromised by inadequate tester strength.
INTRODUCTION

Loss of skeletal muscle mass is a recognised feature of aging and lower limb muscle weakness a recognised risk factor for falls in older persons. In advanced cancer, muscle strength may be adversely affected by many factors, including anorexia-cachexia-associated skeletal muscle wasting, immobilisation and proximal myopathy related to corticosteroid treatment. We conducted a prospective study of the risk factors for falls in patients with advanced cancer. Our selection of independent risk factor variables was informed by a review of the literature on falls risk factors in older persons. Hence, we wished to include an objective, responsive and reliable measure of lower limb strength as an independent variable. We also wished the method of testing be potentially transferrable to clinical settings, in the event that it was shown to be a risk factor for falls in advanced cancer.

Hand-held dynamometry (HHD) provides an objective measure of muscle strength and the equipment is generally small and portable. Although demonstratively less reliable when used by testers of below average strength to test large muscle groups (such as the knee extensors of young healthy subjects), it is widely reported to be reliable in testing muscle strength of older or infirm individuals. It has been shown to have good test-retest reliability when used to measure knee extensor strength in 10 community dwelling elderly persons, 41 community dwelling older persons with a history of falling and in 13 patients referred for domiciliary physiotherapy. Bohannon and Andrews also reported a high level of inter-rater reliability for
HHD when used to measure strength of knee extensors in mostly post-stroke patients undergoing physiotherapy.\textsuperscript{105}

Based on our expectation that knee extensor strength and hence reliability of HHD would be similar in our patient cohort to that of older or frail persons, we elected to measure knee extensor strength using HHD. The testing protocol, including the positioning of transducer and subject, were informed by trials with healthy subjects. Here we report the results of reliability testing, the aim of which was to establish inter-rater and test-re-test reliability of measurements taken by the two testers involved in the research project.

**METHODS**

Patients aged over 18 years with a diagnosis of cancer that is metastatic or locally advanced, admitted consecutively to home care, day care and inpatient palliative care services, were screened for eligibility for inclusion in the study of the risk factors for falls. Exclusion criteria included being unable to sit-to-stand and mobilise six metres independently, or being considered too unwell to participate, or actively dying by the admitting physician and research team. The study was approved by St Vincent’s University Health Group Ethics Committee.

During the validation phase of the project, consecutive patients underwent repeat testing of right (R) leg strength. The testing protocol was as follows: the subject was seated, hips and knees at 90°, hands resting on the top of their thighs. Following verbal explanation, the dynamometer was placed 10cm
distal to the tibial tuberosity and the subject asked to 'straighten your leg as strongly as you can, stronger, stronger, release (4 seconds). The MicroFET 2 (Hoggan Health Industries) was used (see Figure 4). The maximal force was noted and the best of three was recorded as the result. Both tester and subject were blinded to the result. The test was repeated one hour later, by the same tester for the first 30 subjects and by the second tester for the next 15 subjects; the testers alternated who tested first.

**Statistical analysis**

Agreement between two measurements was examined by calculation of the limits of agreement from the mean difference/bias (D) and the standard deviation of the differences (SD). The interpretation is that for a new individual from the studied population, there is 95% probability that the difference between any two measurements should lie within the limits of agreement.\textsuperscript{106-108} The data was first checked for heteroscedasticity (whether the differences between measurements depend on the magnitude of the measurement) by examination of mean-versus-differences plots and calculation of the corresponding Kendall's correlation coefficient. In the event that heteroscedasticity was present the data underwent logarithmic transformation and reassessment for resolution of the relationship between log difference and log mean and the geometric standard deviation was calculated. In this case, the 95% ratio limits of agreement were calculated by division and multiplication of the mean difference by the square of the geometric standard deviation (GSD), the interpretation being slightly different as described below.\textsuperscript{108,109} Intra-class correlation coefficients (ICC) were calculated.\textsuperscript{110}
RESULTS

Test-retest reliability

The mean age of participants was 60 ± 12.5 years, 18/30 were male. Mean right leg strength was 113 ± 43.1N (11.5kg). Figure 1 shows the mean-vs-absolute differences plot: Kendall's tau = 0.33, p = 0.01. Figure 2 shows the mean-vs-absolute differences plot for transformed data: Kendall's tau = 0.03, p = 0.84. Mean difference = 1.1, GSD² = 1.36, ratio limits of agreement are 0.81–1.5 (1.1 ±/× 1.36). ICC = 0.9.

Inter-rater reliability

Mean age of participants was 69±9.6 years, 7/15 were male. The mean right leg strength was 128.5 ±35.1N (13.1kg). See mean-vs-absolute differences plot (Figure 3): Kendall's tau = 0.18, p = 0.35. D = -10.59 ±23.8N, 95% limits = -10.59 ±46.65N = -57.24 to 36.06N. ICC = 0.83.
Fig. 1. Test-retest reliability; mean-vs-differences plot (n=30)

Fig. 2. Test-retest reliability; mean-vs-differences plot after log transformation (n=30)
DISCUSSION

Analysis of test-retest data and inter-rater data yielded ICC's of 0.9 and 0.83 respectively. The ICC provides an estimate of the proportion of the total variance that is accounted for by the variation between subjects, the remaining variance being attributable to the variation between repeated measurements within subjects. The ICC alone provides useful, but
incomplete information regarding reliability, as it gives no sense of the actual magnitude of within-subject differences. An additional drawback is that its value is influenced by the variance in the sample population.

The second statistical method that we used produces an absolute measure of reliability; the limits of agreement provide an estimate of the 95% confidence intervals for the mean difference or bias between two measurements, assuming that the difference is constant and does not vary with the size of the measurement. If logarithmic transformation is required in order to satisfy this assumption, 95% ratio limits of agreement are generated.

The statistical measures, used by Schaubert et al and Bohannon to express absolute reliability, were the coefficient of variation (CV), and the technical error of the measurement (TEM). The former equates to $100 \times \frac{\text{within-subject SD}}{\text{sample mean}}$ and the latter approximates the within-subject standard deviation. Atkinson and Nevill argue that reliability measures based on one standard deviation are inadequately useful and that instead, in the case of CV, the sample SD should be multiplied first by 1.96 before being expressed as the CV in order to cover 95% rather than 68% of the repeated measures. For the Schaubert et al and Bohannon data this would yield CV’s of approximately 22.8% and up to 25% respectively, from which one may draw less confident conclusions regarding the test-retest reliability of HHD to measure leg strength in older or frail persons.
The 95% ratio limits of agreement for the test-retest data were 0.81-1.5; hence, for any individual within the population, there is 95% probability that any two tests will differ due to measurement error by no more than 19% in a negative direction or 50% in a positive direction. Analysis of the inter-rater reliability data shows that tester one’s measurements were on average 10.59 N less than those of tester two and that for measurements taken on a new subject within the target population, there is 95% probability that the difference between the two testers would be between -57.24 and 36.06N.

To summarise, test-retesting and inter-rater testing of HHD for measurement of knee extensor strength in patients with advanced cancer yielded high ICC’s but the limits of agreement were wide, relative to the mean measurement. Inspection and analysis of the test-retest data revealed increasing difference between tests as the magnitude of measurement increased, suggesting that our less than satisfactory results were at least in part due to stronger subjects’ ability to overcome tester strength. Whilst it has been widely written that HHD is reliable when used to test muscle strength in frail or elderly populations, it is clear that tester strength is as important a determinant of reliability as the characteristics of the sample being tested. The mean knee extensor strength of community-dwelling elderly fallers tested by Wang et al, using very similar methods, was comparable to that of our own sample. In contrast to our results however, test-retesting of the right leg yielded an ICC of 0.99 and limits of agreement of ±14.8 N (standard error of the mean × 1.96 × √2). In order to investigate the effect of tester strength on test-retest and inter-rater reliability, Wilholm and Bohannon used three testers with measurably different strengths.
to measure strength in three muscle groups in 27 healthy adults. They found HHD testing for muscle groups with a mean force of up to 120N to be reliable regardless of tester strength. This is equivalent to the mean strength of knee extensor measurements in our sample, but despite our having taken the step of placing the transducer more proximal to the knee than typically described, in order to maximise the lever arm to give best mechanical advantage to the tester, we were unable to demonstrate adequate test-retest or inter-rater reliability. Patient characteristics may also have negatively impacted on our results: in advanced cancer, fatigue characterised by reduced endurance and abnormal muscle metabolism is common and may have impacted upon participants' ability to make a consistent maximal effort. Alternatively, the consistency of effort may have been negatively affected by discomfort at the site of transducer placement, mentioned by some of the participants in this study and also noted by Kelln et al.

In conclusion, published results of reliability testing of hand-held dynamometry to measure muscle strength in frail or older populations are not generalisable, as reliability is significantly influenced by the strength of the tester. In addition, some authors have employed inadequate statistical measures to describe reliability, leading to overly conservative estimates of measurement error. Ideally, medical rehabilitation practitioners or researchers considering using HHD to measure baseline or post-intervention muscle strength, should personally trial the device before purchasing, to assess its reliability when used by them to test a sample of their target population. Alternatives, which waive the issue of tester strength, include attachment of the dynamometer to
a fixed stable structure or construction of a resistance-enhanced
dynamometer. Although neither have the appeal of HHD alone in terms of
simplicity and portability and the latter would require specialist skills, both
have been shown to have better test-retest and inter-rater reliability than
conventional HHD.113 114
ABSTRACT

PURPOSE

A small number of retrospective studies of inpatients with advanced cancer suggest that a cancer diagnosis confers a high risk of falls. In adults with advanced cancer we aimed to prospectively document the incidence of falls, identify the risk factors for falls, and determine if falls in this population occur predominantly in older patients.

PATIENTS AND METHODS

Consecutive admissions to community and inpatient palliative care services with metastatic or loco-regionally advanced cancer who were able to mobilize unassisted were recruited. Risk factor assessment and questionnaire were conducted on initial encounter. Patients were followed-up by weekly telephone contact for 6 months or until time of fall or death. The relationship between covariates and time to fall was examined using hazard ratios (HR) derived from univariate and multivariate Cox proportional hazards models.

RESULTS

Of 185 participants (52.4% male, age 68±12.6yrs), 93 (50.3%) fell; 35/66 (53%) of participants aged <65 years and 58/119 (48.7%) aged ≥65 years fell; 42% falls resulted in injury. Having a primary brain tumor or brain metastasis (HR 2.5 p=0.002), number of falls in the preceding three months (HR=1.27
p=0.005), severity of depression (HR=1.12 p=0.012), daily benzodiazepine
dose (HR=1.05 p=0.004) and having cancer-related pain (HR=1.96 p=0.024)
were independently associated with time to fall in multivariate analysis.

CONCLUSIONS

Fifty percent of adults with advanced cancer will experience a fall, associated
with high risk of physical injury. There is a compelling need to incorporate
assessment and management of modifiable falls risk factors into
comprehensive cancer care.
INTRODUCTION

Prevention of falls in older persons is a recognized healthcare priority: each year one in three community-dwelling persons aged 65 years or more experiences a fall; 40-60% of falls result in injury and 6% in fractures; fall related accidents are implicated in 40% of admissions to long-term care; and 40% of those who fall subsequently experience fear of falling, which can result in self-imposed activity restriction, leading to decline in physical performance independent of baseline function.\(^3\)\(^{115}\) Hence falls in older persons can have a significantly negative impact on the individual, but also incur considerable financial health and social care costs.

In contrast, there are very limited oncology and palliative care data on falls. Systematic assessment, modification of falls risk factors and patient education are not prioritized in oncology and palliative care services as in aged care settings.\(^{116}\) However, reported inpatient fall rates in oncology and palliative settings far exceed those of acute and community hospitals.\(^{10}\) Arguably, this higher incidence of falls could simply reflect the demographic profile of cancer; approximately 75% cancer deaths occur in those aged \(\geq 65\) years,\(^{117}\) and the results of a large cross-sectional survey of Medicare beneficiaries suggests that a cancer diagnosis in older persons is associated with increased risk of falling.\(^{118}\) However, it is unknown if falls in patients with cancer occur predominantly in older patients, or if the predictors in this population differ from those identified in older populations.

Previous studies of risk factors for falls in patients with cancer were selectively conducted in inpatient settings, had limited length of follow-up (mean duration
of stay 11-46 days) and none employed methods of statistical analysis to accommodate variable lengths of follow-up. Analyses to adjust for confounding variables were conducted in two of the four studies. One study found that low lying systolic blood pressure and impaired cognition were independently associated with inpatient falls. In a retrospective study, delirium was retained in a predictive model of falls risk, albeit with borderline statistical significance, whereas a comorbid diagnosis of COPD had a significant independent association.

Although the studies conducted to date have demonstrated a high incidence of falls in inpatients with cancer, their capacity to identify independent predictors of falls was limited. The generalizability of these study findings is further compromised due to the relatively short duration of follow-up, high levels of missing data and retrospective study designs. Here we report on a prospective study in patients with advanced cancer designed to address the following objectives: (1) to determine the incidence of falls over a maximum follow-up time period of six months; (2) to determine whether falls in this population occur predominantly in older persons; and (3) to identify the modifiable and non-modifiable risk factors for falls in this population.

METHODS

Participants.

Eligible patients admitted consecutively to the palliative care services provided by Our Lady's Hospice and Care Services (24/11/08–24/12/10) were
invited to participate. Services include inpatient care, day hospice, and home care. Adults with a diagnosis of metastatic or loco-regionally advanced cancer were eligible for inclusion. Exclusion criteria were: inability to stand and mobilize unassisted, actively dying or considered too unwell by the admitting and research teams, registered blind, using continuous oxygen, aphasia or inability to speak English. Informed consent was obtained. Enrollment of patients with impaired cognition [Short Orientation-Memory-Concentration Test (SOMCT) score >11] required patient assent and proxy consent. The study was approved by St. Vincent’s University Health Group Ethics Committee.

**Data Collection.**

A standardized baseline assessment, based on recently published guidelines on comprehensive falls risk assessment, included a clinical examination, verification of data routinely collected upon service admission and additional questionnaires. The clinical examination included autonomic function tests, assessments of sarcopenia, cachexia, functional mobility and sensory modalities. All assessments were conducted between 0900hrs and 1300hrs.

**Autonomic Function**

Autonomic function was assessed using standard bedside clinical tests as described by Ewing *et al*; parasympathetic activity by measurement of the heart rate response to deep breathing, standing up from a supine position, and the Valsalva manoeuvre. Sympathetic activity was assessed by
measurement of the blood pressure (BP) response to standing.\textsuperscript{86} Heart rate was measured by surface electrocardiogram. Heart rate tests were excluded if invalidated by arrhythmia, excessive ectopic activity or movement artefact. Blood pressure was monitored by noninvasive beat-to-beat measurement from finger arterial BP. Autonomic function was described, using Ewing's classification system, for participants who had complied with sufficient tests for the classification scheme to be applied. Full details of the protocol for autonomic assessment have been described in Chapter 5. Orthostatic hypotension was defined as a drop $\geq$20mmHg in systolic BP within 3 minutes of standing.\textsuperscript{120}

**Physical characteristics and functional mobility.**

Sarcopenia, defined as the combination of low muscle mass and strength\textsuperscript{121} was determined by measurement of the mean arm muscle circumference (MAMC) and hand-grip strength, respectively. The MAMC was calculated from the mid-arm circumference and triceps skinfold thickness measured on the right arm. The triceps skinfold thickness was measured using a Harpenden skinfold caliper and the result recorded as the mean of 3 measurements. Hand-grip strength was measured 3 times in each hand using a hydraulic hand dynamometer and the maximum of the six measurements used as the result.

Low muscle mass was defined as MAMC below the 5th percentile for adults of the same gender and nationality aged 65 years.\textsuperscript{122} Low muscle strength was classified as hand-grip strength less than 30kg for males and 20kg for females.\textsuperscript{123} Cachexia was defined as more than 10% weight loss since the
onset of the cancer illness. Functional mobility was assessed using the ‘timed up and go’ test whereby the participant is timed in walking to a marked spot three metres away, turning around and returning to their seat.

Sensory modalities.

Visual acuity was measured using a Snellen chart. The participant was requested to wear corrective lenses, if normally worn, and the result recorded as the last full line read by the worst eye. Vibration sense was measured at the interphalangeal joint of the left hallux using a 64 Hz tuning fork. The tuning fork was set in motion by compressing the tynes together, applied over the bony surface and the participant asked to indicate when vibration was no longer detected. The result was recorded as the intensity of vibration at this point, read as the number adjacent to the intersection of the triangles on the damper (range 0-8; as vibration diminishes, number increases). Prior to testing at the hallux, the procedure was demonstrated by placing the vibrating tuning fork over the participant’s distal radius.

Tactile sensitivity was measured at the left lateral malleolus using a Semmes-Weinstein Aesthesiometer which contains 6 nylon filaments of equal length, but varying in diameter. The force required to bend each filament is calibrated and ranges from 0.07-300g. Following demonstration of the procedure at the wrist, the participant was requested to close their eyes whilst filaments of increasing diameter were applied to the skin, to the point that the filament bowed.
Other assessments

Demographic details and routine clinical assessment data were extracted from the standard admission proforma. Where possible, medication use was expressed as dose consumed; otherwise medication class use was defined as a binary variable. Daily opioid dose was expressed as parenteral morphine equivalent received in the previous 24 hours (the Mean Equivalent Daily Dose/MEDD). Daily benzodiazepine dose was expressed as the oral diazepam equivalent dose.\textsuperscript{127} Corticosteroid use was recorded as the cumulative oral dexamethasone dose consumed during the 28 days prior to assessment. Performance status was measured using the Palliative Performance Scale (PPSv2)\textsuperscript{128} and cancer pain classified using the Edmonton Classification System for Cancer Pain (ECS-CP).\textsuperscript{129} Symptom severity was assessed using the Edmonton Symptom Assessment System (ESAS).\textsuperscript{88} Quantity and quality of nocturnal sleep was assessed using items 1-4 of the seven item Insomnia Severity Index (ISI).\textsuperscript{130} Cognition was assessed using the SOMCT (score range 0-28; normal score $\leq 6$).\textsuperscript{52} Severity of urinary continence was measured using the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF).\textsuperscript{131} History of falling during the preceding three months was recorded as reported by the participant. A fall was defined as an event whereby an individual inadvertently comes to rest on the ground or another level with or without loss of consciousness.\textsuperscript{54}

Outcome ascertainment.

Patients were interviewed weekly from the date of baseline assessment, by telephone or in person, to determine if they had fallen during the preceding
seven days and to record details of any reported events. Systematic follow-up was maintained for six months, or until the occurrence of a fall, or death, if these occurred prior to six months.

**Statistical analysis.**

Demographic differences between participants and those who declined participation were tested using chi-square and two-sample t-tests. Descriptive analyses of the number and details of falls were conducted and incidence density of falls calculated as the total number of falls per the sum of patient days of follow-up, expressed as number of falls per 1,000 patient years. Median time to first fall and 95% confidence intervals were calculated and time to fall was summarized graphically by Kaplan-Meier curve.

The relationship between independent variables and time to first fall was examined using a Cox proportional hazards model, censored at the date of death or the end of follow-up. A final multivariate model was fitted by stepwise selection, using $p < 0.05$ and $p > 0.1$ as limits for variable entry and removal, respectively. The proportional hazards assumption was tested for each variable in the final model by examination of Schonfield residuals and log-cumulative hazard plots.

For variables not associated with time to fall in univariate analysis, but for which more than 25% of participants had missing data, the relationship between having missing data and time to fall was tested using the log-rank test. Statistical analysis was performed using SPSS (v16) and Stata 12.0.
RESULTS

During the study period, there were 1,607 admission episodes involving 1,117 individuals, of whom 693 (62%) were ineligible, 239 (21.4%) declined and 185 (16.6%) were recruited. There were no significant demographic differences between participants and those who declined (see Table 1).

Of the 185 participants, 93 (50.3%) experienced a fall during follow-up; 35/66 (53%) of participants aged <65 years and 58/119 (48.7%) of participants aged ≥65 years. Of those who did not fall, 56/92 (60.9%) died prior to completion of follow-up and 36/92 (39.1%) completed the six month follow-up period.

Median time to fall was 96 days (CI: 64.66-127.34); see Figure 1. The incidence density of falls was 2,291.2 falls per 1,000 patient years. Most falls (61.3%) occurred in the community (43% at home, 14% outside, 4.3% other indoors) and the remaining 38.7% in hospital or hospice inpatient settings. Of the fallers, 35 (37.6%) sustained soft-tissue injuries, three (3.2%) sustained fractures and one patient sustained a dislocation. Most falls (60%) occurred between 0800-2000 hours.

Time to fall had a significant univariate association with having a primary brain tumor or brain metastasis, number of medications, antidepressant use, daily benzodiazepine dose, cumulative corticosteroid dose, having cancer-related pain, tiredness, depression, anxiety, and drowsiness as measured by the ESAS, ISI score, cognition and number of falls in the preceding three months (see Table 2).
Table 1. Demographic details of participants and those who declined participation.

<table>
<thead>
<tr>
<th></th>
<th>Participants (n=185)</th>
<th>Declined (n=239)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male (%)</td>
<td>52.4</td>
<td>50.2</td>
<td>$\chi^2=0.2$, 1df</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$p=0.65$</td>
</tr>
<tr>
<td>Age (years)</td>
<td>68±12.6</td>
<td>68.3±13.1</td>
<td>$t=0.12$, 9df</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$p=0.9$</td>
</tr>
<tr>
<td>Cancer diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchial</td>
<td>18.4</td>
<td>23.4</td>
<td>$\chi^2=5.7$, 9df</td>
</tr>
<tr>
<td>Breast</td>
<td>14.1</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Lower Gl</td>
<td>14.1</td>
<td>13.8</td>
<td>$p=0.8$</td>
</tr>
<tr>
<td>Upper Gl</td>
<td>11.4</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>9.7</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Gynaecological</td>
<td>7</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Pancreatic/hepatobiliary</td>
<td>6.5</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Urological not prostate</td>
<td>5.4</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>2.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10.8</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>Site of recruitment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient services (home care, day hospice and clinic)</td>
<td>61.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inpatient unit</td>
<td>38.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Autonomic function and orthostatic hypotension (OH) were the only explanatory variables with more than 4% missing data. We previously reported the challenges of conducting bedside clinical tests of autonomic function and participant characteristics associated with non-completion (see Chapter 5). Median time to fall in those with complete and missing data for either autonomic function classification (log-rank test: $\chi^2 = 0.34$, $p=0.56$) or OH ($\chi^2=0$, $p=0.99$) was similar.

Variables significantly associated with time to fall in univariate analysis were entered into a multivariate model. The effect of having a primary brain tumor or brain metastasis was attenuated in the preliminary full multivariate model.
(OR=1.9, p=0.12). Diazepam was the only medication with an independent effect. Cancer pain remained strongly significant, as did number of falls in the past 3 months. The effects of tiredness, depression and anxiety were all reduced in the multivariate analysis, possibly due to their colinearity.

Finally, a backwards stepwise selection process including all the variables entered into the full multivariate model yielded the final model shown in Table 3. The presence of a primary brain tumor or brain metastasis, number of falls in the preceding three months, severity of depression, daily benzodiazepine dose and having cancer-related pain were independently associated with time to fall.

Four of the five variables included in the final model met the proportional hazards assumption. Cancer-related pain as defined by the ECS-CP did not meet this assumption (p=0.03). Further investigation revealed no effect of pain in the first 50 days after baseline, but a strong effect between 50 days and the end of follow-up, caused by a very small number of falls in the ‘no pain’ group. To test the sensitivity of the remaining parameter estimates in the multivariate model to this departure from the proportional hazards assumption, a model was estimated including all other variables in the multivariate model, but stratified on the pain variable. The co-efficients under this model were not substantially different to that under the primary model.
Table 2. Results of univariate and multivariate analyses.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency</th>
<th>Mean (SD)</th>
<th>Univariate Analyses</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td>Demographic and disease characteristics</td>
<td></td>
<td>Hazard ratio</td>
<td>P value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>68/185</td>
<td>68.12 (±12.6)</td>
<td>1 (0.99-1.02)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>88/185</td>
<td>0.87 (0.58-1.3)</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Brain metastases/ primary</td>
<td>24/185</td>
<td>2.40 (1.39-4.13)</td>
<td>0.004</td>
<td>1.9 (0.84-4.43)</td>
</tr>
<tr>
<td>Vascular comorbidities* (number)</td>
<td>0.75 (±1.03)</td>
<td>0.99 (0.8-1.22)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Comorbidities (number)*</td>
<td>0.23 (±0.44)</td>
<td>0.87 (0.55-1.37)</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Performance status (PPSv2)</td>
<td>70 (mode)</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td>Hazard ratio</td>
<td>P value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>Taking antidepressant</td>
<td>46/185</td>
<td>1.60 (1.04-2.46)</td>
<td>0.04</td>
<td>1.19 (0.68-2.08)</td>
</tr>
<tr>
<td>Taking anticonvulsant</td>
<td>57/185</td>
<td>1.20 (0.79-1.87)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Taking antipsychotic</td>
<td>15/185</td>
<td>1.60 (0.82-3.26)</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>Daily diazepam dose equivalent (mg)*</td>
<td>4.23 (±5.9)</td>
<td>1.07 (1.03-1.10)</td>
<td>&lt;0.0001</td>
<td>1.05 (1.01-1.09)</td>
</tr>
<tr>
<td>Cumulative corticosteroid dose (mg)*</td>
<td>31.2 (±53.5)</td>
<td>1.00(1.00-1.01)</td>
<td>0.08</td>
<td>1.00 (1.00-1.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------</td>
<td>-------</td>
<td>------------------</td>
<td>-------</td>
<td>------------------</td>
</tr>
<tr>
<td>Morphine Equivalent Daily Dose (mg)*</td>
<td>45.3</td>
<td>(±106.9)</td>
<td>1.00</td>
<td>(1.00-1.00)</td>
</tr>
<tr>
<td>Total number medications*</td>
<td>8.7</td>
<td>(±3.9)</td>
<td>1.06</td>
<td>(1.01-1.11)</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer pain (ECS-CP nociceptive or neuropathic)</td>
<td>138/185</td>
<td>1.75 (1.03-2.97)</td>
<td>0.03</td>
<td>1.87 (1.03-3.4)</td>
</tr>
<tr>
<td>Incident pain (ECS-CP)</td>
<td>64/184</td>
<td>1.2 (0.79-1.83)</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Pain severity (ESAS)*</td>
<td>1.43</td>
<td>(±2.1)</td>
<td>1.07</td>
<td>(0.97-1.17)</td>
</tr>
<tr>
<td>Tiredness severity (ESAS)*</td>
<td>3.29</td>
<td>(±2.8)</td>
<td>1.10</td>
<td>(1.02-1.19)</td>
</tr>
<tr>
<td>Depression severity (ESAS)*</td>
<td>0.97</td>
<td>(±2.1)</td>
<td>1.15</td>
<td>(1.06-1.25)</td>
</tr>
<tr>
<td>Anxiety severity (ESAS)*</td>
<td>1.64</td>
<td>(±2.4)</td>
<td>1.13</td>
<td>(1.05-1.22)</td>
</tr>
<tr>
<td>Drowsiness (ESAS)*</td>
<td>1.86</td>
<td>(±2.5)</td>
<td>1.12</td>
<td>(1.03-1.21)</td>
</tr>
<tr>
<td>Insomnia Severity Index*</td>
<td>3.89</td>
<td>(±3.7)</td>
<td>1.07</td>
<td>(1.02-1.13)</td>
</tr>
<tr>
<td>ICIQ-SF*</td>
<td>2.85</td>
<td>(±4.7)</td>
<td>1.03</td>
<td>(0.98-1.07)</td>
</tr>
<tr>
<td>SOMCT*</td>
<td>4.0</td>
<td>(±4.4)</td>
<td>1.05</td>
<td>(1.01-1.1)</td>
</tr>
<tr>
<td><strong>Autonomic function, physical characteristics and sensory modalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite/severe autonomic dysfunction</td>
<td>110/138</td>
<td>1.33 (0.74-2.39)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension (SBP drop ≥ 20mmHg)</td>
<td>111/143</td>
<td>0.96 (0.56-1.66)</td>
<td>0.89</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Count</td>
<td>Hazard Ratio (95% CI)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-------</td>
<td>-----------------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Sarcopenia</td>
<td>54/185</td>
<td>1.28 (0.82-1.99)</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Hand grip strength (kg)*</td>
<td>22.39 (±8.25)</td>
<td>1 (0.97-1.02)</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Cachexia (&gt;10% weight loss)</td>
<td>75/180</td>
<td>1.22 (0.8-1.87)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>BMI (body mass index) &lt;18.5 kg/m²</td>
<td>19/185</td>
<td>1.34 (0.73-2.46)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>BMI ≥25 kg/m²</td>
<td>77/185</td>
<td>1.36 (0.9-2.04)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Timed 'Up and Go' (seconds) &lt;13 (comparator)</td>
<td>53</td>
<td>0.08</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Timed 'Up and Go' (seconds) 13-20</td>
<td>70</td>
<td>1.78 (1.07-2.9)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>Timed 'Up and Go' (seconds) &gt;20</td>
<td>62</td>
<td>1.45 (0.85-2.5)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Visual acuity*</td>
<td>6/18 (mode)</td>
<td>0.99 (0.98-1.01)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Vibration sense threshold*</td>
<td>5.39 (±2.3)</td>
<td>1.03 (0.94-1.12)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>Tactile sensitivity threshold (grams)*</td>
<td>4.3 (±0.7)</td>
<td>1.00 (0.99-1.00)</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Number of falls in preceding 3 months*</td>
<td>0.7 (±1.2)</td>
<td>1.2 (1.04-1.43)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

*continuous variables (Hazard ratio represents adjustment in risk for one unit in value of variable).

CI confidence interval
ECS-CP Edmonton Classification System for Cancer Pain
ESAS Edmonton Symptom Assessment Scale
ICIQ-SF International Consultation on Incontinence Questionnaire-Short Form.
SOMCT Short Orientation-Memory Concentration Test.
SBP Systolic blood pressure
Table 3. Variables associated with time to fall in Cox Regression Model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain primary/brain metastasis</td>
<td>2.50 (1.41-4.42)</td>
<td>0.002</td>
</tr>
<tr>
<td>Number of falls in preceding 3 months*</td>
<td>1.27 (1.08-1.50)</td>
<td>0.005</td>
</tr>
<tr>
<td>Depression severity (ESAS)*</td>
<td>1.12 (1.03-1.22)</td>
<td>0.012</td>
</tr>
<tr>
<td>Total daily diazepam dose equivalent (mg)*</td>
<td>1.05 (1.02-1.09)</td>
<td>0.004</td>
</tr>
<tr>
<td>Cancer-related pain</td>
<td>1.96 (1.09-3.53)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

*continuous variables (hazard ratio represents adjustment in risk for one unit in value of variable).

CI Confidence interval
ESAS Edmonton Symptom Assessment Scale

DISCUSSION

This study is the first to investigate the incidence and risk factors of falls in patients with advanced cancer prospectively over a six month period and across a range of settings. Falls incidence exceeded that in community-dwelling older persons. One in every two patients with advanced cancer, regardless of age, experienced a fall during study follow-up; the corresponding incidence density of falls of 2,291.2 falls per 1,000 patient
years is more than double the rate for healthy older persons. The consequences of falls are significant in this frail population; forty-two percent of falls resulted in injury and 4% in fracture or dislocation.

Patients with a primary brain neoplasm or metastases were more than twice as likely to fall as patients without cerebral involvement. Neurological deficits, cognitive dysfunction with associated reduced safety awareness, and corticosteroid-related proximal myopathy and weight gain all represent plausible explanatory biological mechanisms.

A history of falling is an independent predictor of future falls; the hazard risk of falling increases by 1.27 for each fall experienced in the preceding three months. Daily dose of benzodiazepine is an independent predictor for falling in patients with advanced cancer; for every milligram of diazepam or its equivalent, the hazard increases by 1.05; hence patients receiving the mean daily dose of benzodiazepine (4.23mg) prescribed in this study were 1.25 times more likely to fall than those not receiving this class of drug. Severity of depression, as rated by participants using the ESAS, was also shown to be an independent risk factor for falling.

The presence of a cancer-related pain syndrome was identified as an independent predictor for falling in the final model. However, this relationship violates the proportional hazards assumption and the nature of the observed change in hazard function over time, whereby the hazard of falling is unaffected by pain until day 50, lacks rational explanation. Additionally, variables likely to be correlated with cancer-related pain classification, such as
MEDD or ESAS pain score, were not associated with falling in univariate or multivariate analyses, suggesting that this may be a spurious finding.

Of the independent predictors for falls in patients with advanced cancer, past history of falls and use of psychoactive medication are recognized to be two of the strongest risk factors for falls in community-dwelling older persons, in addition to strength, gait and balance problems. Quantifying falls risk associated with use of medications is particularly challenging, due to potential confounding by the condition for which the drug is prescribed. Nonetheless, the association between falls and benzodiazepine use persisted after adjustment for severity of anxiety and insomnia. Sedation, dizziness and postural disturbances present plausible mechanisms for this association. Although we did not examine the relative risk associated with short versus long acting benzodiazepines, research in older persons suggests that benzodiazepine-related falls risk is not negated by preferential use of short-acting drugs.

Depression is associated with falls in older persons; postulated pathways include reduced physical activity, cognitive dysfunction, depression-related sleep disturbance and antidepressant use. The association between depression and falls risk observed in this study persisted when adjusted for antidepressant use. In the full multivariate analysis anxiety appears to have a stronger independent effect than depression, but in the backwards stepwise process, depression is retained as a predictor in preference to anxiety. This suggests that depression is the stronger independent predictor of falls, possibly because depression captures the residual effects of other excluded
variables including ISI, SOMCT, drowsiness and tiredness. Further studies are needed in order to fully determine these associations.

We had expected low muscle mass and strength to be risk factors for falls in this cohort. In our original research protocol, in addition to measuring grip strength to facilitate classification of sarcopenia, quadriceps extensor strength was measured using a hand-held dynamometer. However, inter-rater and test-retest reliability testing identified systematic measurement error, precluding its continued application and inclusion as an independent variable (see Chapter 6). Hand-grip strength has been shown to be a reliable measure of muscle strength, closely correlated to leg strength and a predictor for falls in older persons.\textsuperscript{139,140} Neither sarcopenia, grip strength nor cachexia was significantly associated with falls, however there was some evidence of an effect of each that may have been too small to be detected in the present study. This may be because each represents a single potential root cause yielding only a small contribution to the overall hazard relative to other variables more strongly associated with falls risk, either because they are highly correlated with other causal factors or encompass multiple physiological parameters. The TUG is an example of such a composite measure; it evaluates the interaction of a number of impairments such as muscle weakness, balance and gait characteristics.\textsuperscript{141} It is considered to be a valuable falls risk assessment tool in older persons, whereby optimal time cut-offs for prediction of falls have been identified, based on an observed linear relationship between the time taken to complete the test and falls risk.\textsuperscript{142} However, we observed a trend towards a non-linear relationship between the TUG and falls risk whereby participants who took between 13 and 20 seconds...
to complete the test were at greater risk of falls than those who took less than 13 or more than 20 seconds. Two previously conducted studies of the relationship between the TUG and functional mobility help explain this observation; both identified that completion time of less than 20 seconds reflects functional independence in tasks such as bathing, using stairs and going outdoors. Hence it is plausible that patients who take in excess of 20 seconds to complete the test have a lower risk of falls than those who take 13-20 seconds, as they are more likely to receive assistance when completing activities of daily living.

Orthostatic hypotension (OH) was highly prevalent, but not predictive of falls in this cohort. Similarly, the evidence for OH as an independent predictor for falls in older persons is limited, despite most international falls prevention guidelines citing the importance of its assessment.

We did not measure possible extrinsic risk factors for falls or acute precipitants of falls, such as inattention or delirium, and these should be explored in future studies. The mode of measurement of depression is a limitation of this study. While use of the ESAS to measure depression is appealing in terms of clinical ease, it is not a diagnostic tool for depression and hence we cannot say that a diagnosis of depression is a risk factor for falls in patients with advanced cancer. ESAS scores need to be explored with the patient, adopting an interprofessional approach encompassing nonpharmacological supportive interventions to manage distress not related to clinical depression and judicious levels of pharmacological intervention for those with clinical depression. Non-benzodiazepine hypnotics which act at the
benzodiazepine receptor, namely zolpidem and zopiclone were considered as benzodiazepines in this analysis, precluding an estimation of their relative hazard.

Falls are common in adults with advanced cancer and are associated with a high risk of physical injury. Studies in older persons suggest that falls are likely to adversely affect quality of life due to injury, fear of falling and increased dependence, and to increase health and social care costs. The utility of falls risk screening tools has been questioned recently, largely on the basis that they may provide false reassurance to staff and fail to direct falls prevention interventions effectively. Around 50% of adults with advanced cancer fall in a six month period; we contend that assessment for risk factors for falls, modification of identified risk factors and patient education regarding preventing and managing falls should become a routine component of comprehensive advanced cancer care and be offered to all patients. Based on our findings we recommend that alternative options for the management of sleep disturbance and anxiety are considered, particularly for patients with brain metastases or primary brain tumors, a history of falls or coexistent depression.
ACKNOWLEDGEMENTS

I would like to thank my supervisor Professor Rose Anne Kenny for her direction and guidance and being an enduring source of inspiration; my co-supervisor Dr Peter Lawlor, for granting me the fantastic opportunity to conduct this work and for his support, encouragement and sharing of expertise; and Ms Brid Nolan, Research Nurse for her commitment and professionalism and being a pleasure to work with.

I wish to gratefully acknowledge Dr Chie Wei Fan for sharing her expertise regarding analysis of tests of autonomic function, and Dr Roman Romero-Ortuno, Dr Lisa Cogan and Ms Clodagh Cunningham of the TRIL Clinic for providing training in conducting autonomic function tests.

I am grateful to Dr Kathleen Bennett and Dr George Savva for their advice regarding statistical analyses and Mr Tim Foran for his assistance in resolving “technical glitches”.

I would like to express my heartfelt thanks to Ms Geraldine Tracey, Ms Eleanor Fallon, all the staff of the Day Hospice, Home Care Service and Inpatient Unit at Our Lady’s Hospice and Care Services, Walter Walsh and Carolyn Roe and all the volunteer drivers and the phlebotomy team, for all their support and assistance throughout the duration of this project.

This research was funded by the Health Research Board and Irish Hospice Foundation through the Palliative Care Fellowship Award (HSR/2008/17).
Additional funding also was received from The Atlantic Philanthropies, The Irish Cancer Society, the Irish Hospice Foundation and a generous donation to Our Lady's Hospice and Care Services from Mr Michael Boyle.

Finally, this project would not have been possible without the commitment, enthusiasm and generosity of the patients who participated.
REFERENCES


15. Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Medical Research Methodology*: Biomed Central Ltd, 2009.


47. Tinetti ME, Williams TF, Mayewski R. Fall risk index for elderly patients based on number of chronic disabilities.[see comment]. *American Journal of Medicine* 1986;80(3):429-34.


64. DeLuca HF. Vitamin D. *The Linus Pauling Institute Micronutrient Information Center* 2010.


70. Brown D, Milroy R, Preston T. The relationship between an inflammation-based prognostic score (Glasgow Prognostic Score and serum biochemical variables


82. Heart rate variability for prediction of life span in hospice cancer patients. 10th Congress of the European Association for Palliative Care; 2007; Budapest, Hungary.


114. Lu T-W, Hsu H-C, Chang L-Y, Chen H-L. Enhancing the examiner's resisting force improves the reliability of manual muscle strength measurements:


