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Research Article

The Impact of Geriatric Assessment on Patient Outcomes in Radiation Oncology: A Pilot Study

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ABSTRACT

Introduction: The objective of this pilot study was to obtain preliminary data on the efficacy and feasibility of incorporating geriatric assessment (GA) into radiation oncology (RO) with regard to patient outcomes and treatment decisions.

Materials and Methods: Feasibility was assessed via the percentage of patients able to complete certain aspects of the assessment on their own, or with the assistance of a carer before appointments, was recorded. Consultation times and referrals were also documented. All participants (n=30) underwent GA at baseline, before randomisation to the intervention/control arm and commencement of radiotherapy treatment planning procedures. The results of GA were relayed to the Radiation Oncologist (RO) for the intervention arm only. GA was repeated for each participant three months after the completion of radiotherapy.

Results: There was some evidence of increasing dependence, at three month follow-up, in ADLs and IADLs, less mobility (TUG score), higher GDS scores and increased vulnerability. However, these were not statistically significant. All patients underwent their predefined radiotherapy treatment plan, without modification. A number of deficits on GA were identified that may be considered significant for older patients.

Conclusion: The impact on decision making may reflect a lack of experience and familiarity with GA and how to interpret it, as well as an obvious gap in the literature as to how it affects radiotherapy patient outcomes.

Introduction

In Ireland, there will be a 50% increase in the number of cancer cases by 2025, with 60% of these in patients aged 65 and older [1]. Approximately 50% of these patients will require radiotherapy as part of their disease management [2]. This presents the radiation oncology community with unique challenges, especially in the face of unclear guidelines and limited research on the optimal approach in terms of caring for older patients. The daily nature of external beam radiotherapy over the course of a few weeks, depending on treatment site, is a significant undertaking for older patients in particular. However, as radiotherapy is a localised treatment, its toxic effects are unique to the treatment site and modality employed and are usually more tolerable than systemic treatment [3].

Depending on the area being treated, site-specific toxicity may be more evident in the older adult, which can impact quality of life, the need for treatment interruptions, and the need for additional supportive care or hospitalisations. For example, there have been concerns for the older patient when employing whole brain irradiation due to the risk of neurologic sequelae, including dementia [4, 5]. Also, there is an

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increased risk of mucositis in older patients, especially evident when treating cancers of the head and neck region [6]. This can lead to symptoms such as pain and local discomfort, with feeding difficulties and nausea, with the consequential risk of nutritional impairment. Older adults can also experience significant fatigue over the course of radiotherapy treatment [7] . Overall, radiotherapy appears to be well tolerated in older adults, however Geriatric assessment (GA) has the potential to influence treatment decisions in older patients with cancer with varying degrees of influence reported in the published literature to date, ranging from 21% to 49% of treatment approaches, either by decreasing or increasing treatment intensity [8-15]. However, while a GA could greatly enhance the preliminary assessment of older patients and distinguish for whom curative-intent treatment is appropriate or not, it is widely recognised as resource-intensive and is not integrated into the model of care in Irish oncology institutions at the current time.

The current literature on the role of GA in radiation oncology treatment is particularly limited [16]. A total of twelve non-randomised studies were included in the aforementioned systematic review by Szumacher *et al.* Four studies used a screening tool only, while the remaining studies used a combined approach of initial screening, followed by GA. Two studies demonstrated a significant association between abnormal screening and mortality, while only one study showed that GA influenced treatment decision making. Half of the studies included did not find an association between screening or GA, and treatment tolerance. It was highlighted that the majority of these studies included small sample sizes.

Also, by comparison to medical oncology, the role of GA in influencing treatment decisions, and in driving interventions for older adults with cancer, is unclear [16]. The number of studies (RCTs) investigating GA-driven interventions in oncology generally, is small (n=9), with only one study of radiation oncology by Lapid *et al.* from 2007 [17, 18]. The latter small study (n=33) of newly diagnosed patients with advanced cancer, planned to undergo radiation therapy, investigated a quality of life (QoL) intervention with patients randomised to either the intervention group or standard care. The intervention consisted of eight sessions, devised to address five QoL/CGA domains, i.e. cognitive, physical, emotional, spiritual, and social functioning, and found a significant improvement in QoL scores. Identification of previously unknown deficits is one of the major advantages of frailty screening and accompanying GA, allowing some intervention in order to optimise patient care and potentially to reverse frailty.

A limited number of other, non-randomised studies exist in radiation oncology. Goineau *et al.*, in a study of 100 localised prostate cancer patients, aged 75 and older, undergoing radiotherapy treatment, found no association between CGA and quality of life [19]. However, they found Instrumental Activities of Daily Living (IADL) impairments at baseline in approximately half of all patients enrolled in the study, as well as ADL impairments in 16% of patients. One fifth of patients presented with cognitive decline (defined as MMSE<27), 31% with depressive symptoms and more than two-thirds with significant co-morbidities, especially cardiovascular comorbidities, which may affect ADT tolerance. Malnutrition was virtually absent, suggesting that nutrition-based screening tools, such as the G8, would be of little relevance in this particular patient cohort [20]. Spyropoulou *et al*., in a radiotherapy patient population (n=230) found that patients >75 years with higher Vulnerable Elders Survey-13 (VES-13) scores were less likely to complete radiotherapy, independent of other factors that might affect radiotherapy completion [21, 22]. VES-13 is largely based on functional status, an integral part of CGA. Keenan *et al*. did not find any correlation between the Edmonton frailty score and radiotherapy toxicity. Neve *et al.*, in a small study of older head and neck cancer patients, also undergoing radiotherapy, found that patients identified as vulnerable at baseline, were less likely to complete radiotherapy [23-25].
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A further study investigated whether an objective measure of physical function, the Timed Up and Go (TUG) test, as well as the G8, had an association with acute toxicity and ability to comply with treatment. This showed no relationship between the two tests and treatment tolerance. The other was a prospective cohort study focusing on patients with head and neck cancer, in which those who reported pre-radiotherapy functional limitations were more likely to show both reduced health-related QoL during treatment, as well as a longer recovery afterwards [31]. These studies signal some of the potentially useful interventions for patients receiving radiation therapy, albeit not directly investigated or mentioned in most of the aforementioned studies which have focussed exclusively on assessment, often without mention of follow-up care. This area has been one of the gaps in the current literature in oncology generally, but more so in radiation oncology.

Some of the ways in which GA might alter treatment decisions in radiation oncology include omission of concomitant chemotherapy for example, which contributes considerable toxicity for the patient. Another adaptation is altering the type and modality of radiation treatment offered to patients. Although radiation therapy is usually well tolerated in older patients, hypofractionated radiotherapy could be considered in older patients with poor supports, lack of mobility, lack of transportation, in active caregiver roles or with social frailty, for example [8]. This would limit the burden of travel for such patients, especially those not living adjacent to regional cancer centres. This is one area where the radiotherapy service can facilitate the patient and afford greater convenience.

One example of this is in the treatment of Glioblastoma Multiforme (GBM). For patients identified as elderly/frail, 25Gy in 5 fractions has been shown to be non-inferior to 40Gy in 15, the previous standard of care for such patients [26, 27]. Alternatively, the CGA may help to identify frail patients who are not candidates for conventional, daily radiotherapy but may benefit from other (curative) modalities, such as stereotactic body radiotherapy, with fewer hospital visits and potentially less toxicity [28]. Accelerated Partial Breast Irradiation (APBI) is another option to simultaneously limit toxicity and afford greater convenience for the patient [29]. APBI uses larger radiation doses to the localised tumour bed (as opposed to the entire breast) over a shorter period of time.

Guidelines on best practice from the International Society of Geriatric Oncology (SIOG), the National Comprehensive Cancer Network (NCCN) and European Organisation for Research and Treatment of Cancer (EORTC) have recommended GA be integrated into the care of older adults with cancer, for optimal patient management [30-32]. However, there remain many unanswered questions as to its efficacy and

predictive power, sufficient to translate to incorporation of geriatric medicine principles in many centres [33, 34]. The current lack of high level evidence may be due to the complexities with regard to the conduct and interpretation of trials in older patients, where there may be multiple underlying factors to consider that may affect response to treatment, as well as biological factors that change with age [35-37]. Many authors have advocated for more focussed research efforts and older-specific trial endpoints in order to "geriatricise" trial design [38, 39].

Medical Research Council (MRC) guidelines on complex intervention evaluation, advise a phased approach to the implementation of complex interventions in medicine [40]. This includes feasibility studies (whether the study can be carried out effectively) and pilot trials (a scaled down version of the trial), with the aim of optimising aspects of study design for consideration during a larger scale implementation of in the future. This ensures both internal validity in one's own institution and aids external validity also as some of the issues are common to both. Due to the complex nature of GA, and its implications for older patients, which involves multiple patient/healthcare contacts and clinical judgement as to its relevance, it was considered appropriate to pilot the current proposed geriatric oncology programme, before progression to a larger trial.

Another difficulty in the published literature in relation to GA, lies with the lack of standardisation of assessment approaches to date [41]. In order to address the current lack of consensus as to the optimal method of GA to be undertaken, a national consultation process and Delphi study were carried out seeking consensus from Irish radiation and medical oncologists and geriatricians, as well as a team of international experts in the field of geriatric oncology research [42]. This provides the basis and rationale for the current study, which aims to establish its clinical feasibility and significance. Studies to date have largely focussed on treatment decisions in surgical/medical oncology, with fewer studies attempting to relate GA assessment and outcomes to radiotherapy related endpoints, although some smaller studies have been carried out [24, 43]. In relation to the study itself, it was hypothesized that implementation of GA has the potential to affect patient outcomes and radiotherapy treatment decisions for older patients. The aims and results are thus presented in two sections. Part 1 will focus on feasibility, while Part 2 will focus on patient outcomes.

Part 1

The primary aim of this feasibility study and two-arm, randomised pilot trial was to assess the feasibility of conducting an RCT on the effectiveness of conducting GA in older patients undergoing radiotherapy.

Part 2

The secondary aim was to obtain preliminary data on the prevalence of geriatric impairments in an older patient population undergoing radiotherapy treatment and the efficacy of GA-driven interventions on patient outcomes (acute radiation-induced toxicity and treatment compliance).

Materials and Methods

A two-arm, randomised, controlled trial was chosen. The two treatment arms were as follows:

I Arm 1

Usual care. Primary Oncologist was only notified with abnormal cognitive or depression screening results that ethically could not be withheld. The ability to provide informed consent for the study would be reassessed at this stage, if appropriate. Usual care does not typically include GA domains.

II Arm 2

Usual care plus GA results and recommendations. These were conveyed to the primary oncologist in written form within 2 days of assessment completion.

Potential participants were recruited from a single institution oncology outpatient clinic of participating radiation oncologists (ROs) before a radiotherapy treatment decision had been finalised. This study took place at a Dublin radiotherapy centre (St. James's Hospital), which forms part of a wider network of radiotherapy departments as part of Saint Luke's Radiation Oncology Network. The centre treated approximately 1,400 patients each year during that period, of which 32% were aged 70 and older. The majority of cases were outpatients, however there are some inpatient facilities also. There was no dedicated geriatrician provided for oncology, however referral pathways exist if required, and were defined as part of the preparatory work for this study.

Participants were deemed eligible for the study if they met the following criteria at pre-screening: age >70 years old, diagnosis of solid tumour malignancy or lymphoma, initially planned to undergo radiotherapy treatment of at least 3 weeks duration (with or without chemotherapy), life expectancy with treatment of 6 months or greater (as judged by their RO), receiving follow-up care in St. James's Hospital and able to provide written informed consent for the study. Exclusion criteria were patients who were currently under the continuous care of a geriatrician or who had moderate/severe dementia, symptomatic brain metastases, or pre-existing major neurological or psychiatric disorders (impacting ability to consent). Recruitment occurred, on a part-time basis, between August 2014 and September 2015.

All participants underwent GA at baseline, before randomisation to the intervention/control arm and before commencement of radiotherapy treatment planning procedures. Randomisation procedures are an important aspect of any pilot study, to determine any issues going forward to full trial. This is in keeping with the published literature [44, 45]. All face-to-face assessments were completed by the same individual, who was a radiation therapist with specific training in the methods of GA used. The results of GA were relayed to the Radiation Oncologist (RO) for the intervention arm only, unless significant psychiatric/cognitive/other issues were identified. The results of this assessment and impact on radiotherapeutic decision making were then noted for the intervention arm, including any unknown issues identified and additional referrals for follow-up/remedial care.

A summary of GA findings was sent within two working days both in writing and verbally to the patient's RO. The findings on the individual domains were summarised, and recommendations made regarding further referrals and supportive care. Based on the GA, predefined evidence-based interventions deemed necessary were recommended and discussed with the clinician at the time of presentation of the findings. These were based on the previous Delphi study and a corresponding US version [46]. The patient's consultant reviewed the summary of the findings and the interventions that were recommended, and agreements were made on the necessary referrals. GA was repeated for each participant, by the study investigator, approximately three months after the completion of radiotherapy. Again, every effort was made to coincide with other scheduled appointments, in order to reduce the burden of travel for patients.

In keeping with pilot and feasibility study methodology, no formal sample size calculation was performed, as the objectives related to recruitment, retention, feasibility and acceptability of the trial [45, 47]. Also, there were no previous completed trials of this intervention in this population and investigations of changes in key trial parameters relating to patient outcomes and impact on decision making were exploratory only. The total number of participants recruited was small (n = 30), but consistent with recommendations for feasibility studies in the published literature, with recommendations of at least 12 participants per arm [47, 48].

In order to reduce the risk of bias in randomised controlled trials, a double blind design is recommended, whereby neither the participant nor the researcher are aware of the allocation arm [49]. This may eliminate both performance and detection bias when analysing the outcomes measured. However, blinding isn't always feasible, as was the case in the current study, which involved interaction between the researcher and the patient, as well as interventions for the non-control arm.

As described previously, the methodological basis for the current pilot study was based on the results of a prior consensus process, please see Table 1 for a brief summary. Eight domains were selected as part of the GA, including functional status and mobility, nutrition, mood, comorbidity, cognition, number of medications, and social support status.

Sociodemographic information, including patient age, race and ethnicity, highest level of education achieved, and marital status were abstracted from the medical record. The tumour stage, previous surgery, radiation therapy dose and schedule (intended and received), chemotherapy type, dose and schedule (intended and received) were also collected. Please see (Table 2) below for a full list of assessments used, including threshold values signifying impairment.

Table 1: Summary of GA.

DOMAIN	ASSESSMENT TOOL	DOMAIN	ASSESSMENT TOOL
Functional status	ECOG ADL* IADL* Falls history*	Social support	Patient history/caregiver interview*
Objective physical performance	TUG	Polypharmacy	Number of total medications*
Comorbidity	Charlson Comorbidity Index (age-adjusted)	Psychological status	GDS* Patient history/interview
Nutrition	MNA-SF	Cognition	MMSE
Screening tool	G8	Additional Frailty Measures	Balducci criteria Clinical Frailty Scale

ECOG PS indicates European Cooperative Oncology Group Performance Status; ADL, Activities of daily living; IADL, Instrumental Activities of Daily Living; .TUG, Timed Up and Go test; MMSE, Mini Mental State Examination; MNA SF, Mini Nutritional Assessment Short Form; GDS, Geriatric Depression Scale; G8, Geriatric 8.
*Indicates eligible for self-completion

III Outcome Measures

i Feasibility

For self-administered items, feasibility was assessed via the percentage of patients able to complete certain aspects of the assessment on their own, or with the assistance of a carer before appointments, was recorded. Consultation times and referrals were also documented.

ii Treatment Tolerance and Compliance

Treatment tolerance and compliance were defined as follows:
Rate of (one or more fractions) unplanned radiotherapy interruptions or radiotherapy incompletion (one or more fraction less than the prescribed radiation dose).
Radiotherapy/chemotherapy dose reduction during a course of treatment
Chemotherapy withdrawal
Hospital admission (not elective) rate

IV Assessment of Factors Determining the Treatment Plan

A summary of GA findings was sent within two working days both in writing and verbally to the patient's RO. Recommendations were made based on previous research, which represents consensus on best supportive care for each GA deficit, as well as the patient's own unique circumstances [42, 46]. Any changes to the treatment plan were noted, as well as any unidentified issues that the RO had previously been unaware of, and additional referrals made. ROs were asked if GA results influenced their decision-making in order to identify factors that influenced the patient's subsequent treatment (i.e. age, stage of disease, performance status, GA measures used). Clinicians ranked each factor, on a ten point Likert scale to determine which were the most influential in their decision making process. ROs also noted any additional interventions/referrals made as a result of GA recommendations. This

was completed for each individual patient in the treatment arm (n=15). In total, four ROs participated in this study.

Table 2: Assessments used in the pilot study and scores signifying impairment.

DOMAIN	TOOL	**SCORE SIGNIFYING IMPAIRMENT**
Physical function	ADL IADL Falls history	Any ADL or IADL impairment Any history of falls
Objective physical performance	TUG	<10s Freely mobile <20s Mostly independent 20-29s Variable mobility >20s Impaired mobility 13.5s threshold for increased falls risk
Comorbidity	Charlson Comorbidity Index	Evaluated on a case-by-case basis
Nutrition	MNA-SF	Normal nutritional status 12-14 At risk of malnutrition (8-11 points) Malnourished (0-7 points)
Social support	Patient history/caregiver interview	Any deficit noted
Polypharmacy	Number of total medications	≥5 medications
Psychological Status	GDS Patient history/interview	10-19 mildly depressed 20-30 severely depressed
Cognition	MMSE	24-30=normal
Screening	G8	≤ 14

V Toxicity

Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, as this was the toxicity grading system employed in the participating radiotherapy department [50].

VI Statistical Analysis

In this pilot study, patient outcomes were analysed on the entire cohort of enrolled patients rather than according to the two treatment groups. This was deemed appropriate due to the negligible influence on treatment decisions (reported below) and minimal intervention beyond routine care in the control arm. Also, as it was a pilot study, it was not sufficiently powered to determine the relative benefit of GA between arms. Descriptive statistics for patient characteristics, health and functional status measurements, and outcome characteristics were calculated. Normally distributed data were summarised using means and SD; non-normally distributed data were summarised using medians and ranges. Normality tests were conducted using the Shapiro-Wilk test, recommended for small sample sizes [51]. The student's t test (metric data) was used to analyse differences between baseline and follow-up assessments, or Wilcoxon signed rank test (non-parametric data). Data were analysed using IBM Statistical Package for Social Sciences Version 22 (SPSS Inc., Chicago, IL, USA). All p values presented are two-sided using an alpha of 0.05.

VII Ethical Considerations

This study was conducted in accordance with the ethical principles derived from the Declaration of Helsinki [52]. The study was approved by the Saint Luke's Radiation Oncology Network (SLRON) and Faculty of Health Sciences, Trinity College Dublin (TCD), Faculty of Health Sciences Research Ethics Committees. Written and verbal informed consent were obtained from all patients before inclusion.

Results

I Part 1 Results Feasibility

i Patient Participation and Characteristics

Among 58 eligible inpatients, 30 (52%) agreed to participate and were randomised, 15 to the intervention group and 15 to usual care (control) group. Baseline characteristics are presented in Table 3. The median age (range) was 73 (70-89) and the majority (77%) were male and had a diagnosis of prostate cancer (63%).

ii Feasibility

Self-completion was possible (for items identified with an asterix on (Table 1) for the majority (n=26/30, 87%) of participants. The average length of time taken for the study co-ordinator to complete (face-to-face) assessments was 31.2 minutes. When calculating the cost of this per department, overheads and level of expertise of the person conducting the assessment need to be taken into account, as well as the cost of referral to geriatric medicine and supportive care services (as judged on an individual patient basis). These cost calculations are therefore complex, and dependent on the level of frailty identified, considered beyond the scope of the study.

Recruitment rates were lower than anticipated. The mean rate of recruitment per month at the study site was 2.5. This may have resulted from an underestimate of the number of eligible patients at the start of the study. Of the 58 patients approached to take part, 28 were unwilling at the outset to be contacted by the study team. Of those whose eligibility was confirmed, reasons provided for non-participation were mainly related to the timing of recruitment at the initial appointment with the RO, with many patients reporting feeling overwhelmed and anxious. There were also some competing larger studies that were prioritised within the centre. Better representation of clinical trial staff at the study

centre may have avoided some of the issues encountered with recruitment, as this study was undertaken on a part-time basis.

As patients were recruited at a point when they may have been very anxious about their upcoming treatment, this might have affected their motivation to agree to being recruited to a clinical trial. This was less of an issue for patients with prostate cancer, who generally had a number of pre-treatment visits to their RO, especially if undergoing ADT. There was an indication that participants who entered the study were relatively young in terms of the target patient group that was initially aimed for (median age 73) i.e. the majority of patients were in the "young old" category. Once participants were randomised, follow-up was generally good, in terms of completion of questionnaires, suggesting that this part of the methodology would be transferrable to a larger trial. Attendance at follow-up appointments was poorer however, with 4/30 patients unable to attend due to distance to the oncology centre and inconvenience. Acceptability was not assessed directly but adherence to study procedures gives an indication, as does the initial rate of willingness to participate. One participant refused cognitive assessment, due to a previous negative experience. However, all other patients reported no issues with the assessment itself.

Table 3: Patient characteristics.

Characteristics	Control arm	Intervention arm	Total (n=30) n(%)
Age: median(range)	72(70-79)	75(71-89)	73(70-89)
Gender: Male	14(46.67)	9(30)	23(76.67)
Female	1(3.33)	6(20)	7(23.33)
Marital Status: Married	12(40)	9(30)	21(70)
Single	0(0)	1(3.33)	1(3.33)
Widowed	3(10)	5(16.67)	8(26.67)
Highest Educational Attainment: Primary	8(26.67)	11(36.67)	19(63.33)
Secondary	5(16.67)	4(13.33)	9(30)
Third Level	2(6.67)	0(0)	2(6.67)
Type of Cancer (Primary Site):	13(43.33)	6 (20)	19 (63.33)
Prostate	1(3.33)	2(6.67)	3(10)
Rectum	0(0)	1(3.33)	1(3.33)
Endometrium	0(0)	2(6.67)	2(6.67)
Cervix	1(3.33)	2(6.67)	3(10)
NHL	0(0)	1(3.33)	1(3.33)
Vulva	0(0)	1(3.33)	1(3.33)
Bladder			
Type of Treatment:	2(6.67)	4(13.33)	6(20)
Radiotherapy alone	0(0)	4(13.33)	4(13.33)
Concurrent chemo-radiation (CRT)	1(3.33)	1(3.33)	2(6.67)
Neo-adjuvant CRT	12(40)	6(20)	18(60)
Radiotherapy and Androgen Deprivation Therapy (ADT)			

Note: Listed as proportions n(%), apart from age

The majority of participants were educated to primary level (63%) only and in receipt of radiotherapy alone, or in combination with ADT (Androgen Deprivation Therapy - 80% in total). Six patients were commenced on chemoradiation, two of these in the neo-adjuvant setting.

II Part 2: Patient Outcomes and Treatment Decision Making

All randomised patients completed the baseline GA assessment. The impact of decision making was recorded for the intervention arm only, after presentation and discussion of GA results with the referring consultant. See (Figure 1) below for study schema.

GA: Patient Outcomes

I Baseline GA

Most patients (n=29; 97%) had an ECOG status of 0–1. One patient had an ECOG status of 2 and none had a score of 3. GA outcomes are presented in (Table 4 (a)) below. All patients were independent for ADLs at baseline and 83% for IADLs. The mean TUG score was 10.64 (SD=2.3) and 7% (n=2) of patients had experienced two falls in the previous six months. The median MMSE score was 27 (range 20-30; normal range >24). One patient reported symptoms suggestive of mild depression (Geriatric Depression Scale >4/15), with the majority of patients reporting no significant signs. The mean number of medications taken per patient was 3.76 (2.63), with 37% (n=11) taking >5 medications i.e. polypharmacy. The majority of patients had good nutritional status at baseline (83%, n=25), four patients were identified as being at risk of malnutrition, and one malnourished. The majority of patients had an age-adjusted Charlson score of 4-7 (n=29, 97%).

Patients were classified by their G8 scores (Table 4 (b)) as fit (G8 > 14, n = 23, 77%) or vulnerable (G8 ≤ 14, n = 7, 23%). The majority of patients (n=21, 70%) were considered fit by Balducci criteria, and only 24% (n=7) as vulnerable or frail on the CFS [53].

II Three Month Follow-up GA

GA outcomes at three month follow-up were not significantly different from baseline, as seen in (Table 4). There was some evidence of increasing dependence in ADLs and IADLS, slower walking speed (TUG score), higher GDS scores and increased vulnerability. However, these were not statistically significant.

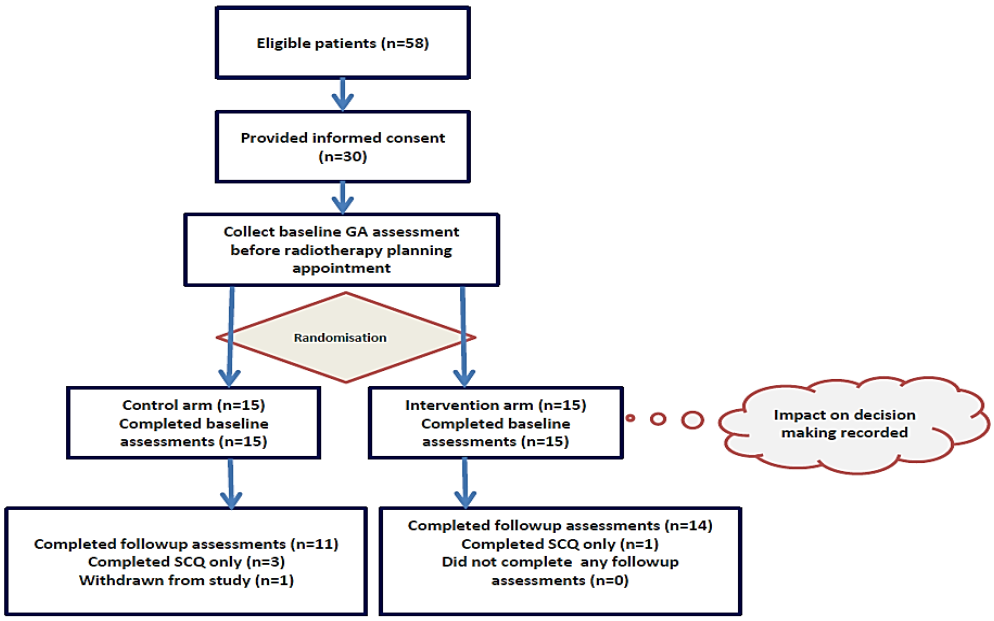

Figure 1: Study schema.

Table 4: GA outcomes at baseline and follow up **(a)** GA domains **(b)** screening tools and frailty criteria.

(a)

Domain	Baseline (n=30)		3m Follow-up (n=29 SCQ, 25 All)		Difference Between Baseline and 3mFollowup (p values)
	n	%	n	%	
Functional Status					
Independent in both ADLs/IADLs	25	83	21	72	
Dependent in >1 ADL	0	0	1	3	0.32
Dependent in >1 IADL	5	17	8	28	0.08
Objective Physical Performance					
Timed Up and Go (TUG)					0.871
Mean TUG score in seconds (SD)	10.64	2.3	11.24	3.76	
>13.5s High falls risk	3	10	4	16	
Number of falls in the previous 6 months					
0	24	80	27	93	
1	4	13	2	7	
> 2	2	7	0	0	
Co-morbidities					0.317
Charlson score 0-3	0	0	0	0	
Charlson score 4-7	29	97	27	93	
Charlson score 8-11	1	3	2	7	
Cognitive Status					
Median MMSE score (out of 30: >24=normal cognition)(range)	27	(20-30)	27	(20-30)	0.432
Psychological Status					0.075
GDS 0-4 (normal)	29	97	24	83	
GDS 5-8 (mild depression)	1	3	4	14	
GDS 9-11 (moderate depression)	0	0	1	3	
GDS 12-15 (severe depression)	0	0	0	0	
Number of Medications					
Mean number per patient (SD)	3.76	2.63	3.48	2.5	0.073
Polypharmacy (>5 medications)	11	37	10	34	
Nutritional Status (MNA)					0.98
12-14 points: Normal nutritional status	25	83	21	84	
8-11 points: At risk of malnutrition	4	13	3	12	
0-7 points: Malnourished	1	3	1	4	

(b)

Domain	Baseline (n=30)		3m Follow-up (n=29 SCQ, 25 All)		Difference Between Baseline and 3m Follow-up (p values)
	n	%	n	%	
Screening (G8 Score)					0.434
Score indicating impairment G8 ≤ 14	7	23	6	24	
Score not indicating impairment G8 > 14	23	77	19	76	
Mean (SD)	14.83	2.26	15.06	1.95	
Balducci Frailty					
Fit	21	70	19	73	
Vulnerable	7	23	4	15	
Frail	2	7	3	12	
Clinical Frailty Scale					
1. very fit	4	13	2	8	
2. well	12	40	11	42	
3. managing well	6	20	6	24	
4. vulnerable	2	7	1	4	
5. mildly frail	5	17	5	20	
6. moderately frail	0	0	1	4	
7. severely frail	0	0	0	0	
8. very severely frail	0	0	0	0	
9.terminally ill	0	0	0	0	

III Treatment Compliance

Of those enrolled, 100% completed baseline measures and 83% completed the full post-intervention assessment. One patient with prostate cancer only completed 6 out of 37 planned radiotherapy treatments due to concerns regarding loops of small bowel in the treatment area observed on daily imaging and was therefore withdrawn from the study at this stage as it was considered more appropriate to continue the patient on ADT alone. Another patient had their chemoradiation treatment terminated after 25 (out of 28) treatments due to development of a subdural haematoma necessitating surgery. A female patient undergoing chemo-radiotherapy for endometrial cancer had a dose reduction of taxol based chemotherapy due to the development of peripheral neuropathy. One patient missed one day of treatment due to illness (non-treatment related). A further patient with prostate cancer experienced a delay commencing radiotherapy due to his wife's bereavement. Another patient with prostate cancer, who had been on ADT, had their Casodex terminated due to concerns re: Liver Function Test (LFT) results. One female patient experienced a significant fall (tibia fracture) between CT planning and the start of radiotherapy, however this did not incur any delay in starting RT.

IV Acute Toxicity

Acute toxicity was evaluated weekly in all patients. Maximum toxicity recorded was grade 2 (8/30 patients, 27%). The majority of patients experience mild (grade 1) toxicity.

RO Outcomes

I Modifications to Radiotherapy Treatment Plan

All patients underwent their predefined radiotherapy treatment plan, without modification. Any changes with respect to chemotherapy were unrelated to GA results, as these were only communicated to participating ROs.

II Factors Influencing Treatment Decision

For the treatment arm, ROs were asked if GA results influenced their decision-making in order to identify factors that impacted the patient's subsequent treatment (i.e. age, stage of disease, performance status, GA measures used). Clinicians ranked each factor, on a ten point Likert scale, to determine which were the most influential in the decision making process. Overall, ROs ranked stage of disease, PS and chronological age as the most influential factors in determining patient's treatment (see Table 5).

III Additional Information Revealed by GA

A summary of the GA findings was sent within two working days both in writing and verbally to the patient's RO. Results of GA revealed new information, previously not known to the referring RO, in 7/15 (47%) patients (intervention arm) assessed at baseline. This included multiple GA deficits (functional status, history of falls, cognition and nutritional status), a history of falls for two patients, poor cognition for two patients

(one of whom had been lost to follow-up with the dementia services), mild depression and falls risk for a patient with poor mobility related to the onset of peripheral neuropathy while on chemotherapy.

Table 5: Factors affecting treatment decisions.

Factors Affecting Decision Making (in order of influence)	Mean Rank (SD)
1. Disease stage	8.8 (2.33)
2. ECOG PS	8.33 (2.16)
3. Chronological Age	6.33 (2.82)
4. Functional Status (ADL/IADL)	5.33 (3.33)
5. Comorbidities	5.07 (2.99)
6. Cognition	4.8 (2.88)
7. Psychological Status	4.73 (3.06)
8. Objective physical performance	4.27 (2.4)
9. Social support status	4.13 (2.83)
10. Nutritional status	3.93 (2.81)
11. Polypharmacy	3.53 (2.61)

IV Patient Referrals and Interventions

As a result of GA outcomes, one patient underwent extensive rehabilitation in the geriatric medicine department, including detailed assessment in the Falls and Blackout unit. A diagnosis of dementia was also made for the latter patient. Another patient, who had been lost to follow-up with the dementia services, was reinstated under their care. One patient who had a history of falls was referred to her GP for vision correction. Psycho-oncology services were consulted for the patient with queried depression. For the patient identified as being at risk of falling, the local General Practitioner and community nurse were contacted in order to provide support and assistance in the home.

Discussion

To our knowledge, this is the first study to attempt to systematically investigate the feasibility and acceptability of a randomised controlled trial regarding the implementation of GA in radiation oncology. RCTs are considered the gold standard in clinical trial design, yet there has been a relative lack of such trials in geriatric oncology until recent times. This may reflect methodological issues, such as those highlighted in this feasibility study. The aim of this pilot study was to obtain preliminary data on the efficacy of a novel GA intervention on patient outcomes and treatment decisions in radiation oncology. Studies to date have focussed predominantly on medical and surgical oncology, and little is known about the impact of GA on the radiotherapy decision making process and patient outcomes [9, 10, 12, 16].

It is a significant problem for evidence-based oncology care, that older adults are under-represented in oncology clinical trials, despite the incidence of cancer in this age group, estimated to be 60% of all cancer cases [54-57]. A greater focus on phased introduction of trials, in keeping with MRC guidelines and appreciation of institutional issues may help to increase the success of future trials. Selection of more appropriate endpoints is also important in "geriatricising" trial design [39, 58-60]. This has recently been highlighted by Nipp *et al*., who described the need for "pragmatic" clinical trials for older adults with cancer [61]. There is a large unmet need to investigate older patients' outcomes under more realistic conditions i.e. varying degrees of fitness and frailty. Inclusion criteria need to be broader to facilitate this and have been used in other studies [62].

This trial provided important data to inform a definitive trial. The sample size was purposely small owing to the focus of the trial objectives. Despite some aspects of the study proving quite effective (for example, randomisation, intervention costs and adherence to baseline study requirements), data revealed the existence of a number of feasibility issues to consider going forward to a full trial. With regard to patient related factors in trial recruitment, Hempenius *et al.*, in a randomised controlled trial of a geriatric liaison intervention also found under-recruitment of frail older adults to be related to the burden of additional hospital visits for patients, as well as insufficient awareness of the study by medical personnel [63]. While the majority of patients in our pilot study were fit, rather than frail, the same issues were found. Hempenius *et al.* adapted their design to facilitate home visits in order to overcome this. To enhance awareness, promotional material with the study logo was used and the study protocol was continuously presented to new staff. While these measures were effective, they incurred additional resource investment in terms of time, budget and staffing, which may not be feasible in every centre.

It must be acknowledged there was suboptimal conversion to consent amongst eligible patients in the current study. Reasons offered for non-participation were generally related to the timing of information provision, which is an important consideration. Another possibility is that the study information was not provided by the study investigator, as the first point of contact. Also, other studies were ongoing in the department at the time, which may have taken priority. Acceptability of trial procedures did not seem to be a factor for patients. In a similar (Irish) patient population, little difference between younger and older patients was found with regard to willingness to participate in clinical trials [64]. Furthermore, a similarly designed Phase II study, by Puts *et al*. has demonstrated the ability to recruit 60 patients over a one-year period, for a similar trial protocol [65]. However, the infrastructure and experience with recruitment in geriatric oncology are much greater in that particular centre. There is also some evidence to suggest that older patients are less likely to be offered a clinical trial by their clinician [66, 67].

Traditionally, trials in geriatric oncology tend to include mixed patient populations. Given the difficulties in data interpretation and the multiple confounding factors that may present themselves, there is a great need to develop site specific guidelines for patient care and a greater body of research on how age-related differences manifest and interact with (radiotherapy) treatment. In our study, there was a preponderance of patients with prostate cancer, which highlights the suitability of focussing on this patient group in our institution for the more definitive trial. Minimisation by age is an additional measure that aids equal distribution of patients between the control and intervention arms of randomised controlled trials [31, 68].

In this study, GA had no effect on radiotherapy decision making in this small sample of radiotherapy patients from a mixed patient population, the majority of whom were prostate cancer patients. The study sample included predominantly fit and relatively young patients, which undoubtedly impacted these results. There were no significant differences between the study groups in terms of baseline and follow-up GA results, however there was a trend towards greater dependence and increased vulnerability. The inability to impact treatment decisions may be attributed in part to a lack of experience with GA, as well as a known lack of education on geriatrics in medical curricula. Many oncology professionals therefore feel ill-equipped to interpret the findings of a GA. Despite the fact that the majority of patients with cancer are older, most oncologists receive little training in the specialised care of older patients [69]. When an older patient presents to oncology, they are often segregated from their co-existing geriatric care, as the oncology and geriatric medicine disciplines often work in isolation, with little collaboration about patients. There were no issues identified in the current study with regard to radiotherapy treatment compliance or toxicity. A similar study (n=30) of radiotherapy patients, concluded that vitamin D deficiency and decreased gait speed correlated to radiotherapy toxicity in older patients with cancer, however given the study sample, these results require further investigation in specific populations [43].

GA has been shown to impact treatment decisions in cancer care, with variations in the literature extending from 20% to 49% impact [70]. Commonly, less aggressive treatments are offered, especially with regard to systemic treatments, and this is independent of who conducts the GA. In larger trials by Kenis *et al.* and Decoster *et al.* modifications were mainly chemotherapy related and where no GA was carried out, radiotherapy decisions were only altered in 0.4% of cases [9, 10]. Caillet *et al.* also reported similar results, with the most common change in treatment decision being a switch from chemotherapy to supportive care [11]. Studies similarly suggest that the impact of GA may be limited to patients undergoing more toxic treatments, such as chemotherapy and targeted therapy [9, 71].

Neve *et al*., in a small study of head and neck cancer patients undergoing radiotherapy, found that patients identified as vulnerable by G8, were less likely to complete radiotherapy [24]. On a larger scale, Pignon *et al*. reported that there should be "no age limit for radical radiotherapy in head and neck tumours" in a pivotal meta-analysis, in 1996, collating data from 1,589 patients (26% of whom were over the age of 65 years) enrolled in five EORTC trials [72]. No differences were observed in overall survival, locoregional control, acute objective mucosal reactions, weight loss, and late effects. However, mucositis was much more pronounced in older adults, as well as other acute toxicities requiring timely and efficacious supportive care, including GA. It could be argued that this meta-analysis is now somewhat outdated, but subsequent studies have testified to the significance of toxicity in older head and neck cancer patients [73]. We did not ascertain the predictive power of the G8 screening tool in the current study, however as stated previously, our patient population was predominantly fit to begin with and did not include head and neck cancer patients, who could potentially benefit more from GA, as demonstrated in other studies [74, 75].

Spyropoulou *et al*., in a general radiotherapy patient population (n=230) found that patients >75 years with higher VES-13 scores were less likely to complete radiotherapy, independent of other factors that might affect radiotherapy completion [21]. VES-13 is largely based on functional status, which correlates somewhat with the results of the current study, that demonstrated greater functional dependence over time. Context is also important in terms of integrating GA into oncology. It would be ideal if every department had regular access to a geriatrician. This may afford greater credibility and influence in the treatment decision making process. Unfortunately, the current worldwide shortage of geriatricians means that most centres must attempt to integrate GA, using existing resources and expertise [76]. Timing is also important. Horgan *et al.* found that when the treatment plan was decided before GA, it altered the decision in only one patient, whereas when the treatment plan was undecided at the time of referral, the GA impacted the final treatment decision in 83% of cases [12]. The ideal time for intervention is before discussion of the patient case at the multidisciplinary meeting, before the patient is referred for radiotherapy/chemotherapy or other modality.

The most significant finding in the current study, was the number of previously unknown issues that were identified by GA that clinicians may not have detected by routine assessment. These were identified and relayed to the medical team in 7 out of 15 patients in the intervention arm. Previous studies looking at the impact of GA on treatment decisions, reported intervention rates in the region of approximately 70% [70]. Social support and management of polypharmacy were the most commonly reported concerns, followed by nutritional deficits and finally psychological/ cognitive/mobility/falls risk/comorbidities in the remaining 20% of cases. Adequate social support is important for a range of physical and mental health outcomes, including cancer survival and is closely related to quality of life [77-81]. Social support is also important for those who are required to attend oncology treatments e.g. attending daily radiotherapy treatments. Many may already be in a caregiving role or may require caregivers themselves at some point in the future, as a result of cancer, or its treatment.

Polypharmacy is most likely linked to the treatment of both cancer and other comorbidities and should be assessed to ensure the appropriateness of all medications [82]. It is widely recognised that polypharmacy is common in patients with cancer, and more attention should be paid to assessing and optimising polypharmacy which could potentially lead to improvements in adverse drug reactions, medical costs, and quality of life [83-85]. Polypharmacy is also linked to increased risk of falls, which is another outcome that has significant implications for older patients [86]. Most oncology departments do not employ routine screening for falls risk. Screening for falls is recommended for all older adults with cancer, as research suggests that falls have a negative impact on quality of life, due to traumatic injury, subsequent fear of falling, and increased dependence [87]. Screening for and correcting reversible risk factors, in combination with falls prevention education, are considered essential in reducing falls.

A further important findings in the current pilot study was in relation to cognitive status. One patient with an MMSE score of 20 had been lost to follow-up with the dementia services. Another patient (aged 89) who was referred to geriatric medicine for numerous deficits, was diagnosed with dementia. While these findings did not impact on the radiotherapeutic approach, they are important. A basic assumption of informed consent for treatment is that patients have capacity.

Undiagnosed dementia is very prevalent in the published literature in the acute hospital setting, ranging from 20% to 50%, and is expected to increase in the coming decades [88-90]. Early diagnosis of cognitive impairment is important in order to implement earlier treatment and effective management [91]. However, oncologists often feel unable to manage or diagnose cognitive impairment. Therefore, baseline measurement of cognition should be included for all older patients at a minimum.

Strengths and Limitations

This first pilot geriatric oncology programme highlighted a number of unknown limitations in relation to GA for patients undergoing radiotherapy treatment. It also highlighted the feasibility of implementing GA in radiation oncology. The results of this small heterogeneous sample of radiotherapy patients need to be interpreted with caution, however. The impact on decision making may reflect a lack of experience and familiarity with GA and how to interpret it, as well as an obvious gap in the literature as to how it affects radiotherapy patient outcomes. Due to the nature of the pilot study, full blinding was not possible. In addition, as this study included a variety of cancer sites, it is possible that numerous confounding factors existed, limiting interpretation of results. A further limitation of this study is the small sample size and low recruitment rate. Primary tumour type and radiotherapy doses employed were not directly comparable by virtue of the heterogeneous nature of our sample. The general performance status of all patients was good, and the majority would be considered fit by CGA. There was an indication that participants who entered the study were relatively young in terms of the target patient group that was initially aimed for (median age 73) i.e. the majority of patients were in the "young old" category.

Conclusion

GA had no effect on radiotherapy decision making in this small sample of radiotherapy patients from a mixed patient population, the majority of whom were prostate cancer patients. The study sample included predominantly fit and relatively young patients, which undoubtedly impacted these results. There were no significant differences between the study groups in terms of baseline and follow-up GA results, however there was a trend towards greater dependence and increased vulnerability. There were no issues identified with regard to radiotherapy treatment compliance or toxicity. The most significant finding in the current study, was the number of previously unknown issues that were identified by GA, that clinicians may not have detected by routine assessment.

Based on these preliminary results, recommendations for future research include investigation of: 1) longitudinal changes in GA domains and whether there is evidence of decline after radiotherapy completion and 2) identification of the prognostic factors indicative of poor outcome for selected and more defined patient groups undergoing radiotherapy, incorporating previous recommendations on consideration of optimal trial design in an older patient population.

References

1. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C et al. (2013) Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 14: 877-882. [Crossref]
2. Slotman BJ, Cottier B, Bentzen SM, Heeren G, Lievens Y et al. (2005) Overview of national guidelines for infrastructure and staffing of radiotherapy. ESTRO-QUARTS: Work package 1. *Radiother Oncol* 75: 349-356. [Crossref]
3. Perez CA (2004) Principles and practice of radiation oncology. 4th ed. / Carlos Perez ... [et al.] ed. Philadelphia, Pa. ; London: Lippincott Williams & Wilkins.
4. Son Y, Yang M, Wang H, Moon C (2015) Hippocampal dysfunctions caused by cranial irradiation: A review of the experimental evidence. *Brain Behav Immun* 45: 287-296. [Crossref]
5. Laack NN, PD Brown (2004) Cognitive sequelae of brain radiation in adults. in Seminars in Oncology. *Semin Oncol* 31:702-713. [Crossref]
6. de Castro Jr G. and R S Guindalini (2010) Supportive care in head and neck oncology. *Curr Opi Oncol* 22: 221-225. [Crossref]
7. Muszalik M, Kołucka-Pluta M, Kędziora-Kornatowska K, Robaczewska J (2016) Quality of life of women with breast cancer undergoing radiotherapy using the Functional Assessment of Chronic Illness Therapy-Fatigue questionnaire. *Clin Interv Aging* 11: 1489-1494. [Crossref]
8. Mohile SG, Heckler C, Fan L, Mustian K, Jean-Pierre P et al. (2011) Age-related differences in symptoms and their interference with quality of life in 903 cancer patients undergoing radiation therapy. *J Geriatric Oncol* 2: 225-232. [Crossref]
9. Decoster L, Kenis C, Van Puyvelde K, Flamaing J, Conings G et al. (2013) The influence of clinical assessment (including age) and geriatric assessment on treatment decisions in older patients with cancer. *J Geriatr Oncol* 4: 235-241. [Crossref]
10. Kenis C, Bron D, Libert Y, Decoster L, Van Puyvelde K et al. (2013) Relevance of a systematic geriatric screening and assessment in older patients with cancer: results of a prospective multicentric study. *Ann Oncol* 24: 1306-1312. [Crossref]
11. Caillet P, Canoui-Poitrine F, Vouriot J, Berle M, Reinald N et al. (2011) Comprehensive Geriatric Assessment in the Decision-Making Process in Elderly Patients With Cancer: ELCAPA Study. *J Clin Oncol* 29: 3636-3642. [Crossref]
12. Horgan AM, Leighl NB, Coate L, Liu G, Palepu P et al. (2012) Impact and feasibility of a comprehensive geriatric assessment in the oncology setting: a pilot study. *Am J Clin Oncol* 35: 322-328. [Crossref]
13. Girre V, Falcou MC, Gisselbrecht M, Gridel G, Mosseri V, Bouleuc C et al. (2008) Does a Geriatric Oncology Consultation Modify the Cancer Treatment Plan for Elderly Patients? *J Gerontol Ser A Biol Sci Med Sci* 63: 724-730. [Crossref]
14. Chaibi P, Magné N, Breton S, Chebib A, Watson S et al. (2011) Influence of geriatric consultation with comprehensive geriatric assessment on final therapeutic decision in elderly cancer patients. *Crit Rev Oncol Hematol* 79: 302-307. [Crossref]
15. Barthelemy P, Heitz D, Mathelin C, Polesi H, Asmane I et al. (2011) Adjuvant chemotherapy in elderly patients with early breast cancer. Impact of age and comprehensive geriatric assessment on tumor board proposals. *Crit Rev Oncol Hematol* 79: 196-204. [Crossref]

16. Szumacher E, Sattar S, Neve M, Do K, Ayala AP et al. (2018) Use of Comprehensive Geriatric Assessment and Geriatric Screening for Older Adults in the Radiation Oncology Setting: A Systematic Review. *Clin Oncol (R Coll Radiol)* 30: 578-588. [Crossref]
17. Soubeyran P, Terret C, Bellera C, Bonnetain F, Jean OS et al. (2016) Role of geriatric intervention in the treatment of older patients with cancer: rationale and design of a phase III multicenter trial. *BMC Cancer* 16: 932. [Crossref]
18. Lapid M I, Rummans TA, Brown PD, Frost MH, Johnson ME, Huschka MM et al. (2007) Improving the quality of life of geriatric cancer patients with a structured multidisciplinary intervention: a randomized controlled trial. *Palliat Support Care* 5: 107-114. [Crossref]
19. Goineau A, Campion L, d'Aillières B, Vié B, Ghesquière A et al. (2018) Comprehensive Geriatric Assessment and quality of life after localized prostate cancer radiotherapy in elderly patients. *PLoS ONE* 13: e0194173. [Crossref]
20. Bellera CA, Rainfray M, Mathoulin-Pélissier S, Mertens C, Delva F et al. (2012) Screening older cancer patients: first evaluation of the G-8 geriatric screening tool. *Ann Oncol* 23: 2166-2172. [Crossref]
21. Spyropoulou D, Pallis AG, Leotsinidis M, Kardamakis D (2014) Completion of radiotherapy is associated with the Vulnerable Elders Survey-13 score in elderly patients with cancer. *J Geriatric Oncol* 5: 20-25. [Crossref]
22. Saliba D Orlando M, Wenger NS, Hays RD, Rubenstein LZ (2000) Identifying a short functional disability screen for older persons. *J Gerontol Series A, Biol Sci Medi Sci* 55: M750-M756. [Crossref]
23. Keenan LG, O'Brien M, Ryan T, Dunne M, McArdle O (2017) Assessment of older patients with cancer: Edmonton Frail Scale (EFS) as a predictor of adverse outcomes in older patients undergoing radiotherapy. *J Geriatric Oncol* 8: 206-210. [Crossref]
24. Neve M, Jameson MB2, Govender S3, Hartopeanu C (2016) Impact of geriatric assessment on the management of older adults with head and neck cancer: A pilot study. *J Geriatric Oncol* 7: 457-462. [Crossref]
25. Middelburg JG, Mast ME, de Kroon M, Jobsen JJ, Rozema T et al. (2017) Timed get up and go test and geriatric 8 scores and the association with (chemo-) radiation therapy noncompliance and acute toxicity in elderly cancer patients. *Int J Rad Oncol Biol Phy* 98: 843-849. [Crossref]
26. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J et al. (2015) International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme. *J Clin Oncol* 33: 4145-4150. [Crossref]
27. Roa, W, Brasher PM, Bauman G, Anthes M, Bruera E et al. (2004) Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 22: 1583-1588. [Crossref]
28. Palma D, Visser O, Lagerwaard FJ, Belderbos J, Slotman BJ et al. (2010) Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non–small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 28: 5153-5159. [Crossref]
29. Kuerer HM, Thomas B. Julian, Eric A. Strom, H Kim Lyerly, Armando E. Giuliano et al. (2004) Accelerated partial breast irradiation after conservative surgery for breast cancer. *Ann Sur* 239: 338-351. [Crossref]
30. Wildiers H, Heeren P, Puts M, Topinkova E, Janssen-Heijnen ML et al. (2014) International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol* 32: 2595-2603. [Crossref]
31. Hurria A, Wildes T, Blair SL, Browner IS, Cohen HJ et al. (2014) Senior adult oncology, version 2.2014: clinical practice guidelines in oncology. *J Nat Comprehens Cancer Net* 12: 82-126. [Crossref]
32. Pallis AG, Fortpied C, Wedding U, Van Nes MC, Penninckx B et al. (2010) EORTC elderly task force position paper: Approach to the older cancer patient. *Eur J Cancer* 46: 1502-1513. [Crossref]
33. Moy B, Flaig TW, Muss HB, Clark B, Tse W et al. (2014) Geriatric Oncology for the 21st Century: A Call for Action. *J Oncol Pract* 10: 241-243. [Crossref]
34. Tremblay D, Charlebois K, Terret C, Joannette S, Latreille J (2012) Integrated oncogeriatric approach: a systematic review of the literature using concept analysis. *BMJ Open* 2: e001483. [Crossref]
35. Taghipour S, Banjevic D, Fernandes J, Miller AB, Montgomery N (2012) Predictors of competing mortality to invasive breast cancer incidence in the Canadian National Breast Screening study. *BMC Cancer* 12: 299. [Crossref]
36. Rose BS Jeong JH, Nath SK, Lu SM, Mell LK (2011) Population-Based Study of Competing Mortality in Head and Neck Cancer. *J Clin Oncol* 29: 3503-3509. [Crossref]
37. Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B et al. (2005) The origins of age-related proinflammatory state. *Blood* 105: 2294-2299. [Crossref]
38. Dale W, Mohile SG, Eldadah BA, Trimble EL, Schilsky RL et al. (2012) Biological, Clinical, and Psychosocial Correlates at the Interface of Cancer and Aging Research. *J Nat Cancer Inst* 104: 581-589. [Crossref]
39. Lichtman SM (2012) Clinical trial design in older adults with cancer—The need for new paradigms. *J Geriatric Oncol* 3: 368-375.
40. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I et al. (2008) Developing and evaluating complex interventions: the new Medical Research Council guidance. *Brit Med J* 337: a1655. [Crossref]
41. Puts MT, Hardt J, Monette J, Girre V, Springall E et al. (2012) Use of Geriatric Assessment for Older Adults in the Oncology Setting: A Systematic Review. *J Natl Cancer Inst* 104: 1133-1163. [Crossref]
42. O'Donovan A, MS Leech M, Mohile SG (2015) Expert consensus panel guidelines on geriatric assessment in oncology. *Eur J Cancer Care* 24: 574-589. [Crossref]
43. Ulger S, KM Kilic MK, Kilic D, Cetin BE, Ulger Z et al. (2015) Estimating Radiation Therapy Toxicity and Tolerability with Comprehensive Assessment Parameters in Geriatric Cancer Patients. *Asian Pac J Cancer Prev* 16: 1965-1969. [Crossref]
44. Thabane L, Ma J, Chu R, Cheng J, Ismaila A et al. (2010) A tutorial on pilot studies: the what, why and how. *BMC Medical Res Methodol* 10: 1. [Crossref]
45. Shanyinde M, RM Pickering, M Weatherall (2011) Questions asked and answered in pilot and feasibity randomised controlled trials. *BMC Med Res Methodol* 11: 117. [Crossref]
46. Mohile S G, Velarde C, Hurria A, Magnuson A, Lowenstein L et al. (2015) Geriatric Assessment-Guided Care Processes for Older Adults: A Delphi Consensus of Geriatric Oncology Experts. *J Nat Comprehensive Cancer Net* 13: 1120-1130. [Crossref]
47. Moore CG, Carter RE, Nietert PJ, Stewart PW (2011) Recommendations for planning pilot studies in clinical and translational research. *Clin Transl Sci* 4: 332-337. [Crossref]

48. Julious SA (2005) Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Stat* 4: 287-291.
49. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D et al. (2011) The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 343: d5928. [Crossref]
50. US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.03. 2010. USA: National Institutes of Health, National Cancer Institute, 2016.
51. Peat J and B Barton Index, in Medical Statistics. (2008) Blackwell Publishing Inc. p. 317-324.
52. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. Bulletin of the World Health Organization, World Medical Association. 2001. 79: 373.
53. Balducci L and M Extermann (2000) Management of cancer in the older person: a practical approach. *Oncologist* 5: 224-237. [Crossref]
54. Hutchins LF et al. (1999) Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *New Engl J Med* 341: 2061-2067. [Crossref]
55. Murthy VH, HM Krumholz, CP Gross (2004) Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA* 291: 2720-2726. [Crossref]
56. Sateren, WB, Trimble EL, Abrams J, Brawley O, Breen N et al. (2002) How Sociodemographics, Presence of Oncology Specialists, and Hospital Cancer Programs Affect Accrual to Cancer Treatment Trials. *J Clin Oncol* 20: 2109-2117. [Crossref]
57. Greenlee RT, Murray T, Bolden S, Wingo PA (2000) Cancer statistics, 2000. *CA: A Cancer J Clinicians* 50: 7-33. [Crossref]
58. Senn B et al. (2013) Developing and evaluating complex interventions: the new Medical Research Council guidance. *Studies* 59: 587-92.
59. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG et al. (2013) End Points and Trial Design in Geriatric Oncology Research: A Joint European Organisation for Research and Treatment of Cancer–Alliance for Clinical Trials in Oncology–International Society of Geriatric Oncology Position Article. *J Clin Oncol* 31: 3711-3718. [Crossref]
60. Hurria A, Dale W, Mooney M, Rowland JH, Ballman KV et al.(2014) Designing Therapeutic Clinical Trials for Older and Frail Adults With Cancer: U13 Conference Recommendations. *J Clin Oncol* 32: 2587-2594. [Crossref]
61. Nipp RD, Yao NA, Lowenstein LM, Buckner JC, Parker IR et al. (2016) Pragmatic study designs for older adults with cancer: Report from the U13 conference. *J Geriatric Oncol* 7: 234-241. [Crossref]
62. Rousseau F, Retornaz F, Joly F, Esterni B, Abadie-Lacourtoisie S et al. (2010) Impact of an all-oral capecitabine and vinorelbine combination regimen on functional status of elderly patients with advanced solid tumours: A multicentre pilot study of the French geriatric oncology group (GERICO). *Critical Rev Oncol/Hematol* 76: 71-78. [Crossref]
63. Hempenius L, Slaets JP, Boelens MA, van Asselt DZ, de Bock GH et al. (2013) Inclusion of frail elderly patients in clinical trials: Solutions to the problems. *J Geriatric Oncol* 4: 26-31. [Crossref]
64. Ayodele O, Akhtar M, Konenko A, Keegan N, Calacsan et al. (2016) Comparing attitudes of younger and older patients towards cancer clinical trials. *J Geriatric Oncol* 7: 162-168. [Crossref]
65. Puts MT, Sattar S, Kulik M, MacDonald ME, McWatters K et al. (2018) A randomized phase II trial of geriatric assessment and management for older cancer patients. *Supportive Care in Cancer* 26: 109-117. [Crossref]
66. Kemeny MM, Peterson BL, Kornblith AB, Muss HB, Wheeler J et al. (2003) Barriers to Clinical Trial Participation by Older Women With Breast Cancer. *J Clin Oncol* 21: 2268-2275. [Crossref]
67. Townsley CA, Chan KK, Pond GR, Marquez C, Siu LL et al. (2006) Understanding the attitudes of the elderly towards enrolment into cancer clinical trials. *BMC Cancer* 6: 34. [Crossref]
68. Scott NW, McPherson GC, Ramsay CR, Campbell MK et al. (2002) The method of minimization for allocation to clinical trials: a review. *Controlled Clinical Trials* 23: 662-674. [Crossref]
69. Morris L, Thiruthaneeswaran N, Lehman M, Hasselburg G, Turner S (2017) Are Future Radiation Oncologists Equipped With the Knowledge to Manage Elderly Patients With Cancer? *Int J Radiation Oncol Biol Phys* 98: 743-747. [Crossref]
70. Hamaker ME, Schiphorst AH, ten Bokkel Huinink D, Schaar C, van Munster BC (2014) The effect of a geriatric evaluation on treatment decisions for older cancer patients – a systematic review. *Acta Oncologica* 53: 289-296. [Crossref]
71. Extermann, M, Boler I, Reich RR, Lyman GH, Brown RH et al. (2012) Predicting the risk of chemotherapy toxicity in older patients: The Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) score. *Cancer* 118: 3377-3386. [Crossref]
72. Pignon T, Horiot JC, Van den Bogaert W, Van Glabbeke M, Scalliet P (1996) No age limit for radical radiotherapy in head and neck tumours. *Eur J Cancer* 32: 2075-2081. [Crossref]
73. Lusinchi A et al. (1990) Radiation therapy for head and neck cancers in the elderly. *Int J Rad Oncol Biol Phys* 18: 819-823.
74. Pottel L, Lycke M, Boterberg T, Pottel H, Goethals L et al. (2014) Serial comprehensive geriatric assessment in elderly head and neck cancer patients undergoing curative radiotherapy identifies evolution of multidimensional health problems and is indicative of quality of life. *Eur J Cancer Care* 23: 401-412. [Crossref]
75. Pottel L, et al. (2012) Determination of an adequate screening tool for identification of vulnerable elderly head and neck cancer patients treated with radio(chemo)therapy. *J Geriatric Oncol* 3: 24-32.
76. Golden AG, MA Silverman, SB Issenberg (2015) Addressing the Shortage of Geriatricians: What Medical Educators Can Learn From the Nurse Practitioner Training Model. *Acad Med* 90: 1236-1240. [Crossref]
77. Glass TA, De Leon CF, Bassuk SS, Berkman LF (2006) Social engagement and depressive symptoms in late life: longitudinal findings. *J Aging Health* 18: 604-628. [Crossref]
78. Barth J, S Schneider, R Von Känel (2010) Lack of social support in the etiology and the prognosis of coronary heart disease: a systematic review and meta-analysis. *Psychosomatic Med* 72: 229-238. [Crossref]
79. Beasley JM, Newcomb PA, Trentham-Dietz A, Hampton JM, Ceballos RM et al. (2010) Social networks and survival after breast cancer diagnosis. *J Cancer Survivorship* 4: 372-380. [Crossref]
80. Michael YL, Berkman LF, Colditz GA, Holmes MD, Kawachi I (2002) Social networks and health-related quality of life in breast cancer survivors: a prospective study. *J Psychosomatic Res* 52: 285-293. [Crossref]
81. Jackson JM, Rolnick SJ, Coughlin SS, Neslund-Dudas C, Hornbrook MC et al. (2007) Social support among women who died of ovarian cancer. *Supportive Care in Cancer* 15: 547-556. [Crossref]
82. Maggiore RJ, Dale W, Gross CP, Feng T, Tew WP et al. Polypharmacy and Potentially Inappropriate Medication Use in Older Adults with Cancer Undergoing Chemotherapy: Effect on Chemotherapy-Related

Toxicity and Hospitalization During Treatment. *J Am Geriatrics Society* 62: 1505-1512. [Crossref]

83. Puts MT, Costa-Lima B, Monette J, Girre V, Wolfson C et al. (2009) Medication problems in older, newly diagnosed cancer patients in Canada: how common are they? *Drugs & Aging* 26: 519-536. [Crossref]
84. Sokol K, J Knudsen, and M Li (2007) Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management 1. *J Clin Pharmacy and Ther* 32: 169-175. [Crossref]
85. Lees J, A Chan (2011) Polypharmacy in elderly patients with cancer: clinical implications and management. *Lancet Oncol* 12: 1249-1257. [Crossref]
86. Kongkaew C, PR Noyce, DM Ashcroft (2008) Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 42: 1017-1025. [Crossref]
87. Wildes TM, Depp B, Colditz G, Stark S (2016) Fall-risk prediction in older adults with cancer: an unmet need. *Supportive Care in Cancer* 24: 3681-3684. [Crossref]
88. Sampson EL et al. (2009) Dementia in the acute hospital: prospective cohort study of prevalence and mortality. B*rit J Psychiatry* 195: 61-66. [Crossref]
89. Travers C, Byrne G, Pachana N, Klein K, Gray L (2013) Prospective observational study of dementia and delirium in the acute hospital setting. *Internal Med J* 43: 262-269. [Crossref]
90. Pierce M, S Cahill, E O'Shea Prevalence and Projections of Dementia in Ireland, 2011 Report prepared for Genio Ltd. Available from: https://www.genio.ie/system/files/publications/Dementia_Prevalence_2011_2046.pdf Accessed January 2020. 2014.
91. Nagy B, Brennan A, Brandtmüller A, Thomas SK, Sullivan SD et al. (2011) Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE-and ADL-based models. *Int J Geriatric Psychiatry* 26: 483-494. [Crossref]