Evaluation of geriatric assessment and management on the toxic effects of cancer treatment (GAP70+): a cluster-randomised study

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Summary

Background Older adults with advanced cancer are at a high risk for treatment toxic effects. Geriatric assessment evaluates ageing-related domains and guides management. We examined whether a geriatric assessment intervention can reduce serious toxic effects in older patients with advanced cancer who are receiving high risk treatment (eg, chemotherapy).

Methods In this cluster-randomised trial, we enrolled patients aged 70 years and older with incurable solid tumours or lymphoma and at least one impaired geriatric assessment domain who were starting a new treatment regimen. 40 community oncology practice clusters across the USA were randomly assigned (1:1) to the intervention (oncologists received a tailored geriatric assessment summary and management recommendations) or usual care (no geriatric assessment summary or management recommendations were provided to oncologists) by means of a computer-generated randomisation table. The primary outcome was the proportion of patients who had any grade 3–5 toxic effect (based on National Cancer Institute Common Terminology Criteria for Adverse Events version 4) over 3 months. Practice staff prospectively captured toxic effects. Masked oncology clinicians reviewed medical records to verify. The study was registered with ClinicalTrials.gov, NCT02054741.

Findings Between July 29, 2014, and March 13, 2019, we enrolled 718 patients. Patients had a mean age of 77·2 years (SD 5·4) and 311 (43%) of 718 participants were female. The mean number of geriatric assessment domain impairments was 4·5 (SD 1·6) and was not significantly different between the study groups. More patients in intervention group compared with the usual care group were Black versus other races (40 [11%] of 349 patients *vs* 12 [3%] of 369 patients; p<0·0001) and had previous chemotherapy (104 [30%] of 349 patients *vs* 81 [22%] of 369 patients; p=0·016). A lower proportion of patients in the intervention group had grade 3–5 toxic effects (177 [51%] of 349 patients) compared with the usual care group (263 [71%] of 369 patients; relative risk [RR] 0·74 (95% CI 0·64–0·86; p=0·0001). Patients in the intervention group had fewer falls over 3 months (35 [12%] of 298 patients *vs* 68 [21%] of 329 patients; adjusted RR 0·58, 95% CI 0·40–0·84; p=0·0035) and had more medications discontinued (mean adjusted difference 0·14, 95% CI 0·03–0·25; p=0·015).

Interpretation A geriatric assessment intervention for older patients with advanced cancer reduced serious toxic effects from cancer treatment. Geriatric assessment with management should be integrated into the clinical care of older patients with advanced cancer and ageing-related conditions.

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Introduction

Communication of treatment tolerability is essential for informed and shared decision making between patients, their families, and their oncologists. Clinical trials capture clinician-reported toxicity as measured by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) to assess tolerability. Tolerability data derived from clinical trials are particularly important to guide clinical decision making when treatment is palliative, prognosis is poor, and multiple treatment options are available.

Adults aged 70 years and older with ageing-related conditions are under-represented in clinical trials that have established the standard of care for treatment of advanced cancer.[1] Ageing-related conditions (ie, disability, comorbidity, and geriatric syndromes) are highly prevalent in older patients cared for by community oncologists.[2] Older patients often state that their goals for treatment of their advanced cancers include minimising the risk of toxic effects and maximising function and quality of life.[3,4] Many older adults assert that they would forgo intensive treatments if such treatments posed a substantial risk to their independence.[5] Since therapeutic

Research in context

Evidence before this study

Adults aged 70 years and older with ageing-related conditions are under-represented in trials that have established the standard of care for treatment of advanced cancer. Ageing-related conditions (ie, disability, comorbidity, and geriatric syndromes) are highly prevalent in older patients with advanced cancer who are cared for in community oncology practices. Geriatric assessment uses patient-reported and objective measures to evaluate ageing-related domains (eg, function). Geriatric assessment can guide cancer treatment decisions and management recommendations for ageing-related conditions. To develop a multi-component geriatric assessment intervention for community oncology practices, we conducted a Delphi consensus study with geriatric oncology experts in the USA. Furthermore, the American Society of Clinical Oncology (ASCO) facilitated a systematic review of the literature. We searched PubMed, using the search terms "geriatric assessment" and "humans" and "clinical trial, phase II" or "clinical trial, phase III" or "controlled clinical trial" or "meta-analysis" from Jan 1, 2005, to Sept 30, 2017, for studies published in English. Of the 70 records identified by our search, we found 10 relevant abstracts that were reviewed by the ASCO guideline panel. Only two publications provided evidence that we included in the systematic review—both were pilot studies with small sample sizes. The published literature showed a dearth of interventions to improve tolerability outcomes of older patients with advanced cancer who were receiving treatment.

Added value of this study

Interventions are needed to guide clinical decision making for older patients with advanced cancer and ageing-related conditions who are at high risk for adverse outcomes. We hypothesised that providing a geriatric assessment summary with management recommendations (ie, a geriatric assessment intervention) to community oncologists would lower serious toxicity from high-risk cancer treatments through improved decision making. The geriatric assessment intervention reduced the risk of serious toxic effects in older patients with advanced cancer and ageing-related conditions. In the intervention group, more patients had reduced treatment intensity at cycle one (ie, primary dose reduction), indicating an effect on treatment decision making. Patients in the intervention group also had fewer falls and had more medications discontinued, reducing polypharmacy. Reduced dose intensity in the intervention group did not compromise survival, which was similar between the study groups.

Implications of all the available evidence

To our knowledge, the GAP70+ trial is the first nationwide cluster randomised trial to show that geriatric assessment and geriatric assessment-guided management, when integrated into oncology care, can reduce treatment toxicity, falls, and polypharmacy in older patients with advanced cancer who are receiving treatment. Geriatric assessment and geriatric assessment-guided management should be considered the standard of care for older patients with advanced cancer and ageing-related conditions who are starting a new treatment regimen with a high risk of toxicity.

clinical trials often do not address the endpoints most valued by older adults,[6] interventions are needed to guide clinical decision making for this vulnerable population who are at high risk for adverse outcomes.

The American Society of Clinical Oncology (ASCO), the Cancer and Aging Research Group (CARG), and the International Society of Geriatric Oncology all recommend integration of geriatric assessment into oncology clinical care.[2] Geriatric assessment uses patient-reported and objective measures to evaluate ageing-related domains (eg, function, cognition, and comorbidity). Based on studies showing that geriatric assessment can identify older adults at the highest risk of serious toxic effects from chemotherapy, an ASCO guideline recommends that all older adults receiving chemotherapy undergo geriatric assessment.[2] Nevertheless, despite studies showing feasibility,[2] enhanced communication,[3,7] and improved patient and caregiver satisfaction,[3] implementation of geriatric assessment and geriatric assessment-guided management remains uncommon,[8,9] in part because of a paucity of data showing benefits on cancer-specific outcomes.

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To our knowledge, this is the first nationwide cluster-randomised clinical trial to evaluate whether providing a geriatric assessment summary with management recommendations (ie, a geriatric assessment intervention) to community oncologists can improve clinical outcomes for older adults with advanced cancer. We hypothesised that the geriatric assessment intervention would lower serious toxic effects from high-risk cancer treatments through improved decision making.

Methods

Study design and participants

In this cluster-randomised trial—the Geriatric Assessment for Patients 70 years and older (GAP70+) trial—we recruited practices from the University of Rochester NCI Community Oncology Research Program (UR NCORP) Research Base network. NCORP is a national network in the USA that brings cancer clinical trials and care delivery studies to people in their communities. NCORP Community Affiliates (ie, networks of community oncology practices) receive NCI funding to enrol patients onto cancer clinical trials and care delivery studies coordinated by NCI-funded NCORP Research Bases. Community oncology practices in the USA are generally not physically located at an academic or medical teaching institution or hospital. The UR NCORP Research Base

developed practice clusters in collaboration with the individual community oncology practices. Practice clusters were built from community oncology practices that expressed interest in study participation. Practice clusters were comprised of NCORP-affiliated community oncology practices that had overlap between any participating study team members (figure 1). If an oncologist, coordinator, or research nurse or any other research study staff worked at multiple community practices those practices would be grouped into a cluster. Because of this crossover, multiple community oncology practices could be in one practice cluster, and practice clusters varied in size. Participating practice clusters represent a large geographical area across the USA (appendix p 2). Although the UR NCORP Research Base coordinated study activities, the University of Rochester (Rochester, NY, USA) did not enrol participants. The University of Rochester and all participating practice clusters obtained approval from their institutional review boards.

Only patients of enrolled oncologists were eligible to participate in the study.[8] Patient eligibility criteria included age 70 years or older, at least one geriatric assessment domain impairment other than polypharmacy,[2,3] an incurable advanced solid tumour or lymphoma (ie, stage III or IV), ability to provide informed consent independently or via a health-care proxy, and an understanding of English. Patients were eligible if they planned to start a new cancer treatment regimen with a high risk of toxic effects within 4 weeks. Since patients were required to have incurable cancers, treatment was to be initiated for palliative intent, with the presumed goals of prolonging survival or reducing symptoms rather than cure. Eligible regimens had to include at least one chemotherapy agent or have a more than 50% prevalence of grade 3–5 toxic effects as determined by the primary oncologist with review and approval by a clinical team masked to the study group at the Research Base.[10] Oncologists selected the specific treatment regimen, dosing, and schedules. For those regimens that did not include a chemotherapy agent, clinician investigators on the study team (SGM and MRM) who were masked to study groups verified that the regimen had a more than 50% prevalence of grade 3–5 toxic effects after review of published data and drug labels.

Patients provided written informed consent for participation in the study. The study protocol and measures are available online.

Randomisation and masking

Practice clusters were randomly assigned (1:1) to one of the two study groups (the geriatric assessment intervention or standard of care) by means of a computer-generated randomisation table. The randomisation was stratified by practice size (large vs small based on recrutment of 20 or more patients per year to UR NCORP studies). UR NCORP Research Base statisticians (CH [listed in the Acknowledgments] and EC) provided oversight for all randomisation procedures. Previous accrual records from UR NCORP studies were used to stratify practice clusters as high or low accruing sites. Because this study evaluated a model of care, participants

See **Online** for appendix

For more on the **study protocol and measures** see https://www.mycarg.org/

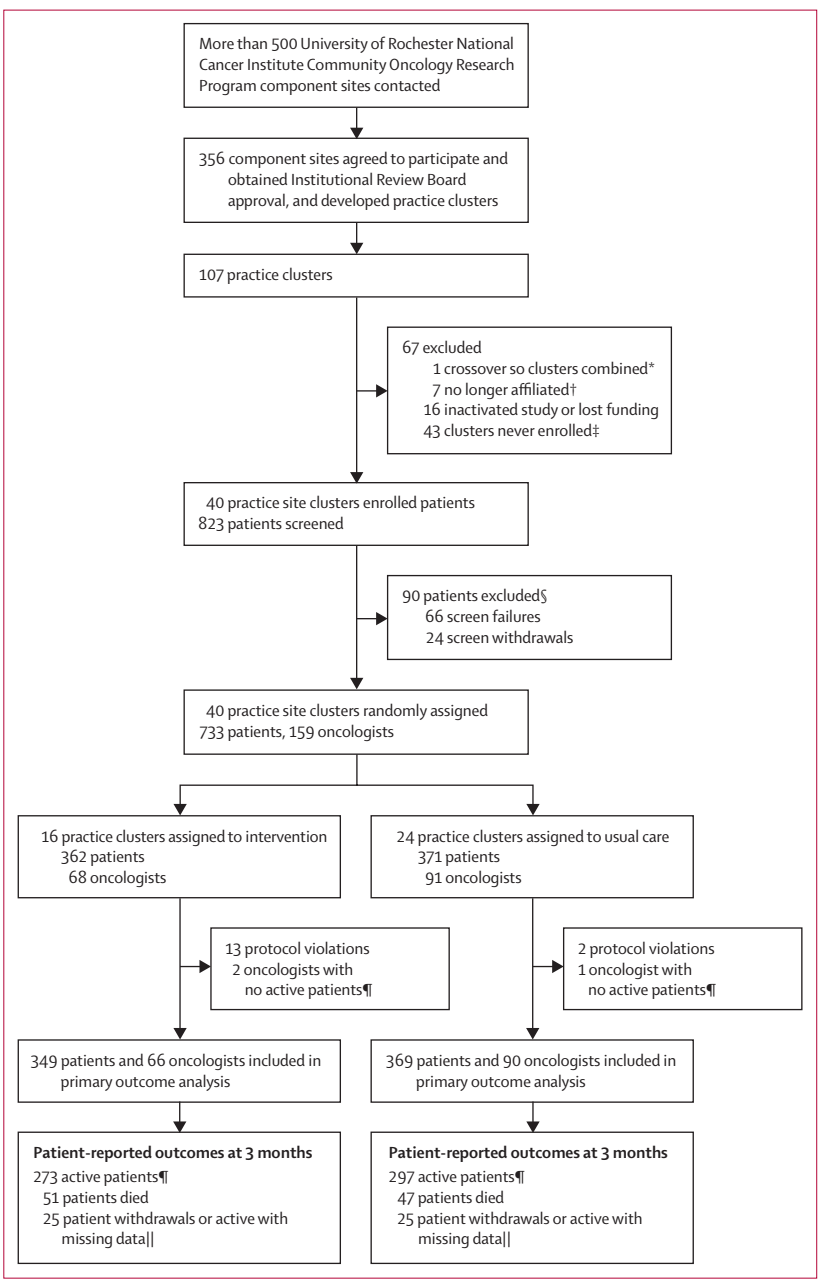

Figure 1: **CONSORT flow diagram**

*One cluster was combined with another cluster because of oncologist crossover. †Sites are no longer associated with their respective University of Rochester National Cancer Institute Community Oncology Research Program or with the University of Rochester Research Base. ‡Clusters that maintained Institutional Review Board approval but never actually enrolled any participants. §Patients who were screened but either failed screening eligibility or withdrew before completing the baseline visit. ¶A patient is considered active if they complete all or some patient-reported outcomes, including patients who have a missed visit because of illness, hospitalisation, or scheduling; 25 patient withdrawals or active with missing data. ||Includes patients who withdrew or were active with missing data (eg, entered hospice and no longer completed study procedures).

and staff at the community oncology clinics were not masked. Other than the statisticians who completed the analyses, all Research Base investigators were masked to the assignment. Furthermore, masking was preserved among the clinical team members who centrally reviewed treatment and toxic effect data.

Procedures

For the geriatric assessment intervention group, the study team developed the geriatric assessment summary and geriatric assessment-guided management recommendations for the intervention, including cancer treatment considerations (eg, dose reduction in cycle one with escalation as tolerated), through literature review, guidelines, and expert consensus.[2,11] In usual care, patients completed the geriatric assessment measures but a summary and management recommendations were not provided to the oncologists. Patients in both study groups underwent a geriatric assessment that evaluated eight domains (physical performance, functional status, comorbidity, cognition, nutrition, social support, polypharmacy, and psychological status) using patient-reported and objective measures before starting the new treatment regimen.[2,11] Patients had the option of completing the patient-reported geriatric assessment measures at home or in the medical practice. Practice staff (ie, research coordinators) reviewed the measures for completion and administered the objective cognition and physical performance tests (appendix pp 3–6). At practices randomly assigned to the intervention group, staff generated a tailored geriatric assessment summary and management recommendations using a web-based platform. At study entry, oncologists in the intervention practices received brief training about geriatric assessment and were told that they had autonomy for how they wished to use this strategy for their enrolled patients. Training provided an overview of how the geriatric assessment summary could be used to guide treatment decisions and how recommendations could be used to guide management of ageing-related conditions.[2] For usual care, oncologists received alerts for significantly impaired scores on depression and cognitive screening tests (appendix pp 3–6); a geriatric assessment summary and recommendations were not provided. Geriatric assessment outcome measures were completed at 4–6 week, 3-month, and 6-month follow-up visits. We have previously described the geriatric assessment intervention in a separate report, which showed benefits for improved communication.[3]

Outcomes

The primary outcome measure for this study was the proportion of participants who experienced grade 3–5 toxic effects within 3 months of starting a new treatment regimen.

In both study groups, study coordinators prospectively captured and assessed the frequency and severity of all grade 3–5 toxic effects using NCI CTCAE version 4 for the primary outcome for 3 months or until the treatment regimen was discontinued. The study coordinators confirmed grading of the toxic effects with the patient and treating oncologist; the oncologist also confirmed the association between the observed toxic effect and treatment decisions. The Research Base received all medical records. A Research Base team, masked to study group and led by an oncologist (MRM), reviewed toxicity grading by comparing data forms with medical records. If discrepancies were identified, practice staff reviewed and resolved them.

We examined the effects of geriatric assessment on treatment intensity and survival as secondary outcomes. At UR NCORP, two masked clinicians (MRM, MAF, or AM) reviewed each enrolled patient's medical record and treatment regimen and used guidelines and clinical trials to determine standard dosing. We evaluated the proportion of patients who received a reduced intensity regimen (eg, lower dose or omission of an agent compared with standard) at cycle one. Subsequently, we calculated the relative dose intensity (RDI;[12] ie, the ratio of the total dose actually delivered to standard dose [not planned dose]) over the first 3 months of treatment. Study coordinators captured survival up to 1 year after registration. As an exploratory outcome, we examined the effects of the intervention on geriatric assessment outcomes over 3 months.

Statistical analysis

We determined the trial sample size using data about toxic effects and intra-cluster correlation (ICC) among seven different sites from a CARG multicentre study.[13] This design provided 80% power to detect a 13% reduction in the proportion of participants who had any grade 3–5 chemotherapy toxic effect within 3 months of treatment initiation, assuming a two-sided significance level of 0·05 and an ICC of 0·10. Accounting for a drop-out rate of 10% between consent and registration, the targeted accrual was 700 participants. All eligible participants were included in analyses. We originally aimed for participation of 16 practice clusters. Since recruitment was initially slower than anticipated, we allowed more practices to participate (as specified by the protocol) but did not adjust the total sample size.

We used descriptive statistics to evaluate demographics, geriatric assessment results, clinical information, and outcome measures. Bivariate analyses were done to compare between-group differences in patient characteristics, treatments, and outcome measures using χ^2 tests for categorical variables and *t* tests for continuous variables.

For the primary outcome, we applied generalised linear mixed model (GLMM) methodology to account for the cluster-randomised study design. The proportion of patients who had any grade 3–5 toxic effect within 3 months was the response, and study group was the fixed effect. Practices were included as a random effect,

independent of residual error. Estimation was done using the residual pseudo likelihood procedure, assuming a binary distribution and log link. Using the fitted model, we provided risk ratio estimates comparing the proportion of patients who had toxic effects between the study groups. We also examined the proportion of patients in each study group who had any grade 3–5 toxic effects in stratified analyses by cancer treatment history and cancer type and calculated risk ratio estimates for these subgroups.

We determined the effect of the intervention on 6-month and 1-year survival using the Cox shared frailty model that included practices as a random effect and report adjusted hazard ratios (HRs) from the model. To evaluate the proportion of patients who underwent reduced treatment intensity in the first cycle, we used a similar GLMM approach as with the primary outcome. We analysed RDI with a linear mixed model (LMM), with RDI as the response, study group as the fixed effect, and practices as a random effect.

To assess the effect of the intervention on geriatric assessment outcomes over time, we used longitudinal LMMs. The model was adjusted for study group and baseline value as fixed effects and practices as a random effect independent of within-subject random effects, and the model was fit via restricted maximum likelihood. We used an unstructured correlation matrix for the repeated measures from the same subject. When a mixed effect model did not converge, linear or generalised linear models without practice random effects were used.

We used SAS version 9.4 for statistical analyses. The University of Rochester Wilmot Cancer Institute's Data and Safety Monitoring Committee reviewed the trial yearly. The trial is registered on ClinicalTrials.gov, NCT02054741.

Role of the funding source

Other than providing feedback on study design during reviews, the funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	All patients (n=718)	Geriatric assessment intervention group (n=349)	Usual care group (n=369)
Age, years	77·2 (5·4)	77·2 (5·7)	77·2 (5·2)
70–79	494 (69%)	244 (70%)	250 (68%)
80–89	204 (28%)	94 (27%)	110 (30%)
≥90	18 (3%)	10 (3%)	8 (2%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
Gender			
Male	405 (56%)	203 (58%)	202 (55%)
Female	311 (43%)	145 (42%)	166 (45%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
Race or ethnicity			
Non-Hispanic White	628 (87%)	281 (81%)	347 (94%)
Black	52 (7%)	40 (11%)	12 (3%)
Other	35 (5%)	26 (7%)	9 (2%)
Missing	3 (<1%)	2 (1%)	1 (<1%)
Marital status			
Single or never married	17 (2%)	11 (3%)	6 (2%)
Married or domestic partnership	449 (63%)	212 (61%)	237 (64%)
Separated, widowed, or divorced	250 (35%)	125 (36%)	125 (34%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
Education			
Less than high school	111 (15%)	58 (17%)	53 (14%)
High school graduate	244 (34%)	119 (34%)	125 (34%)
Some college or above	361 (50%)	171 (49%)	190 (51%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
Income			
≤US$50 000	371 (52%)	189 (54%)	182 (49%)
>US$50 000	190 (26%)	94 (27%)	96 (26%)
Declined to answer	155 (22%)	65 (19%)	90 (24%)
Missing	2 (<1%)	1 (<1%)	1 (<1%)
(Contiued from previous coumn)			
Cancer type			
Breast	56 (8%)	19 (5%)	37 (10%)
Gastrointestinal	246 (34%)	132 (38%)	114 (31%)
Genitourinary	109 (15%)	56 (16%)	53 (14%)
Gynaecological	43 (6%)	29 (8%)	14 (4%)
Lung	180 (25%)	64 (18%)	116 (31%)
Lymphoma	46 (6%)	23 (7%)	23 (6%)
Other	38 (5%)	26 (7%)	12 (3%)
Cancer stage			
III	77 (11%)	42 (12%)	35 (9%)
IV	628 (87%)	304 (87%)	324 (88%)
Other	13 (2%)	3 (1%)	10 (3%)
Previous chemotherapy	185 (26%)	104 (30%)	81 (22%)
Number of impaired geriatric assessment domains	4·5(1·6)	4·6(1·6)	4·4(1·5)
Impaired geriatric assessment domains*			
Physical performance	669 (93%)	314 (90%)	355 (96%)
Polypharmacy	584 (81%)	287 (82%)	297 (80%)
Comorbidity	484 (67%)	236 (68%)	248 (67%)
Functional status	412 (57%)	200 (57%)	212 (57%)
Nutrition	439 (61%)	211 (60%)	228 (62%)
Cognition	261 (36%)	140 (40%)	121 (33%)
Social support	194 (27%)	111 (32%)	83 (22%)
Psychological status	205 (29%)	107 (30%)	98 (27%)

Data are mean (SD) or n (%). Missing data for any variable were less than 5%.
*See appendix (pp 3–6) for further detail.

Table 1: **Patient baseline characteristics**

Results

Between July 29, 2014, and March 13, 2019, 40 practice clusters (16 randomly assigned to the geriatric assessment intervention and 24 assigned to usual care) enrolled participants, including 156 oncologists and 718 eligible patients (figure 1). Patients had a mean age of 77·2 years (SD 5·4) and 311 (43%) of 718 participants were female. Although most baseline characteristics were similar across study groups, more patients in the intervention group were Black or other races and less were non-Hispanic White compared with the usual care arm (table 1). More patients in the intervention group had previous chemotherapy and had gastrointestinal cancers; lung cancer was more prevalent in the usual care group (table 1). The mean number of geriatric assessment domain impairments was 4·5 (SD 1·6) and was not significantly different between the study groups. Patients in the intervention group had a lower prevalence of impaired physical performance, but a higher prevalence of impaired social support and cognitive impairment (table 1). Baseline data for oncologists[8] were previously published.

440 (61%) of 718 evaluable patients had any grade 3–5 toxic effect within 3 months of starting a new treatment regimen; of these, five (1%) had a grade 5 toxic effect (ie, death). A lower proportion of patients in the intervention group had grade 3–5 toxic effects (177 [51%] of 349 patients) compared with patients in the usual care group (263 [71%] of 369 patients). The geriatric assessment intervention reduced the risk of toxic effects (adjusted risk ratio [RR] 0·74, 95% CI 0·64–0·86; p=0·0001; clustering effect p=0·16; figure 2). The proportion of patients who had a grade 3–5 toxic effect was lower in the geriatric assessment intervention group compared with the usual care group when stratifying by history of previous chemotherapy and cancer type (appendix p 7). In additional sensitivity stratified analyses, we evaluated the robustness of the results with respect to covariates with imbalance between the study groups. We found that the direction of the treatment effect was consistent across all categories and the geriatric assessment intervention was favoured for all subgroups (appendix p 8).

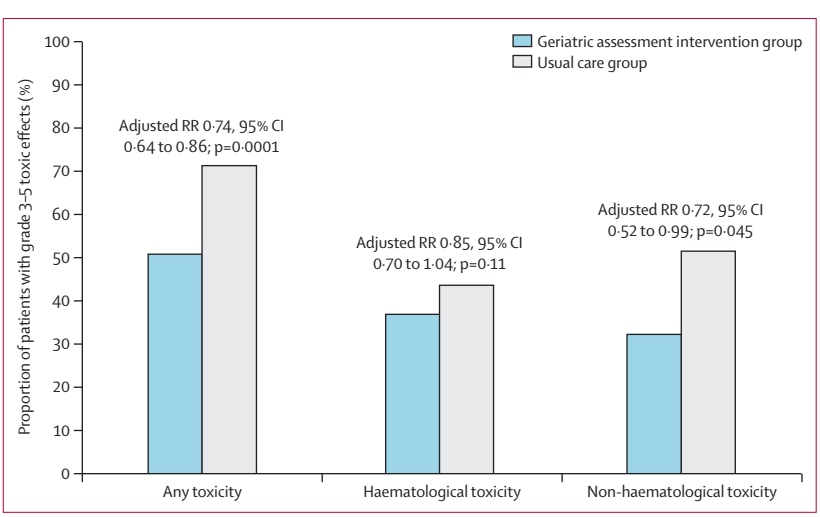

Figure 2: **Prevalence of any grade 3–5 Common Terminology Criteria for Adverse Events toxic effects over 3 months**
RR=risk ratio.

Of the 867 grade 3–5 non-haematological toxic effects, the most common were fatigue or generalised weakness (94 [11%] of 867), electrolyte imbalance (90 [10%] of 867), gastrointestinal distress (86 [10%] of 867), infection (67 [8%] of 867), and hypovolaemia or dehydration (64 [7%] of 867). The proportion of patients with any grade 3–5 non-haematological toxic effect was lower in the intervention group (111 [32%] of 349 patients) compared with the usual care group (191 [52%] of 369 patients), with a lower risk of non-haematological toxic effects for patients in the intervention group (adjusted RR 0·72, 95% CI 0·52–0·99; p=0·045; clustering effect p<0·0001; figure 2). Of the 857 grade 3–5 haematological toxicities, the most common were decreased neutrophil count (210 [25%] of 857), decreased lymphocyte count (188 [22%] of 857), and anaemia (187 [22%] of 857). Although a lower proportion of patients had grade 3–5 haematological toxic effects (128 [37%] of 349 patients) in the intervention group than in the usual care group (162 [44%] of 369 patients), we found no statistically significant reduction in haematological toxicity risk (adjusted RR 0·85, 95% CI 0·70–1·04; p=0·11; clustering effect p=0·36; figure 2).

We recorded the prevalence of the most common chemotherapy regimens (table 2). Chemotherapy regimens most commonly included taxanes or platinum agents. There were differences in chemotherapy treatment patterns between the study groups (p=0·011); a higher proportion of patients in the geriatric assessment intervention group received less intense combinations. A higher proportion of patients in the intervention group versus the usual care group received single agent chemotherapy (79 [23%] of 349 patients *vs* 68 [18%] of 369 patients), chemotherapy plus other agents (eg, monoclonal antibodies; 85 [24%] of 349 patients *vs* 66 [18%] of 369 patients), and non-chemotherapy regimens (44 [13%] of 349 patients *vs* 41 [11%] of 369 patients). A higher proportion of patients in the usual care group compared with the geriatric assessment intervention group received doublet chemotherapy (141 [40%] of 349 patients *vs* 194 [53%] of 369 patients). Planned use of granulocyte colony-stimulating factor prophylaxis was similar between the intervention and usual care groups (73 [22%] of 338 patients *vs* 73 [20%] of 363 patients; p=0·63).

A higher proportion of patients in the intervention group received treatment at a reduced dose intensity than standard at cycle one (170 [49%] of 349 patients) compared with patients in the usual care group (129 [35%] of 369 patients; figure 3). The intervention was associated

with a higher likelihood of receiving reduced intensity treatment (adjusted RR 1·38, 95% CI 1·06 to 1·78; p=0·015; clustering effect p=0·024). There were more dose reductions because of toxic effects over 3 months in the usual care group (213 [58%] of 369 patients) compared with the intervention group (149 [43%] of 349 patients), but the difference was not significant (adjusted RR 0·85, 95% CI 0·68 to 1·08; p=0·18; clustering effect p=0·0006). Patients in the intervention group had a lower RDI over 3 months than those in the usual care group (0·63 in 310 patients *vs* 0·68 in 331 patients; adjusted between-arm difference –0·05, 95% CI –0·09 to –0·01; p=0·025).

The proportion of patients alive at 6 months was similar for the intervention group compared with the usual care group (250 [72%] of 349 patients *vs* 275 [75%] of 369 patients; p=0·38). We found no survival differences between the study groups at 6 months (adjusted HR 1·13; 95% CI 0·85–1·50; p=0·39; clustering effect p=0·036) or 1 year (adjusted HR 1·05, 95% CI 0·85–1·29; p=0·68; clustering effect p=0·052; figure 4).

The prevalence of geriatric assessment-guided management recommendations considered by oncologists in the intervention group is shown in the appendix (pp 3–6). Frequent toxicity checks, adjusting cancer treatment schedule or dosing, reviewing medications for duplications or interactions, providing education materials on ageing-related conditions, and referrals to relevant disciplines (ie, social workers or nutritionists) were among the most common recommendations selected by oncologists.

A lower proportion of patients had a new fall over 3 months in the intervention group (35 [12%] of 298 patients) compared with the usual care group (68 [21%] of 329 patients). Adjusting for a history of baseline falls, patients in the intervention group had a lower risk of having a new fall (adjusted RR 0·58, 95% CI 0·40–0·84; p=0·0035; table 3). Furthermore, a greater number of medications was discontinued in the intervention group compared with the usual care group before starting the new treatment regimen (mean difference 0·14 medications, 95% CI 0·03–0·25; p=0·015; table 3). We did not detect any significant between-arm differences for other geriatric assessment domains over 3 months (table 3).

	All patients (n=718)	Geriatric assessment group (n=349)	Usual care group (n=369)
Lung cancer regimens			
Pemetrexed-carboplatin with or without pembrolizumab	66/180 (37%)	13/64 (20%)	53/116 (46%)
Paclitaxel-carboplatin with or without monoclonal antibody	36/180 (20%)	20/64 (31%)	16/116 (14%)
Carboplatin-etoposide	20/180 (11%)	5/64 (8%)	15/116 (13%)
Carboplatin-nab paclitaxel	17/180 (9%)	7/64 (11%)	10/116 (9%)
Gastro-intestinal cancer regimens			
FOLFOX (leucovorin, fluorouracil, and oxaliplatin) with or without bevacizumab	65/246 (26%)	25/132 (19%)	40/114 (35%)
Gemcitabine-nab paclitaxel	44/246 (18%)	24/132 (18%)	20/114 (18%)
Capecitabine	23/246 (9%)	21/132 (16%)	2/114 (2%)
FOLFIRI (leucovorin, fluorouracil, and irinotecan) with or without bevacizumab	18/246 (7%)	12/132 (9%)	6/114 (5%)
FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) with or without bevacizumab	9/246 (4%)	3/132 (2%)	6/114 (5%)
Genito-urinary cancer regimens			
Abiraterone with or without prednisone	35/109 (32%)	22/56 (39%)	13/53 (25%)
Docetaxel with or without prednisone	32/109 (29%)	19/56 (34%)	13/53 (25%)
Enzalutamide with or without prednisone	13/109 (12%)	3/56 (5%)	10/53 (19%)
Gemcitabine-carboplatin	11/109 (10%)	3/56 (5%)	8/53 (15%)
Breast cancer regimens			
Palbociclib plus aromatase inhibitor	18/56 (32%)	6/19 (32%)	12/37 (32%)
Paclitaxel with or without trastuzumab	8/56 (14%)	1/19 (5%)	8/37 (22%)
Gemcitabine-carboplatin with or without trastuzumab	5/56 (9%)	2/19 (11%)	3/37 (8%)
Capecitabine	4/56 (7%)	0	4 (11%)
Lymphoma regimens			
Bendamustine-rituximab	18/46 (39%)	7/23 (30%)	11/23 (48%)
R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone)	9/46 (20%)	5/23 (22%)	4/23 (17%)
Gynaecological cancer regimens			
Paclitaxel-carboplatin	19/43 (44%)	10/29 (34%)	9/14 (64%)

Data are n/N (%). Data are only reported for commonly received regimens at cycle one.

Table 2: **Treatment regimens received at cycle one**

Discussion

To our knowledge, the GAP70+ trial is the first large nationwide cluster-randomised trial to show that providing a geriatric assessment summary with geriatric assessment-guided management recommendations to community oncologists significantly reduces serious treatment toxic effects in patients aged 70 years and older with advanced cancer and ageing-related conditions. The trial met its primary endpoint—the geriatric assessment intervention reduced the risk of serious toxic effects by over 20%. In the intervention group, more patients received reduced treatment intensity at cycle one (ie, primary dose reduction), indicating an effect on treatment decisions. Patients in the intervention group also had fewer falls and more medications discontinued, reducing polypharmacy. Importantly, reduced dose intensity in the intervention group did not compromise survival, which was similar between the study groups at 6 months and 1 year. The GAP70+ results are significant because weighing the risks and benefits of cancer treatment in vulnerable older adults is challenging, largely because they are disproportionately underrepresented in randomised clinical trials that establish the standards for cancer treatment.[6] Therefore, vulnerable older patients with advanced cancer often receive treatments that have greater risks than benefits. This study shows that simply providing information about health status through a geriatric assessment summary

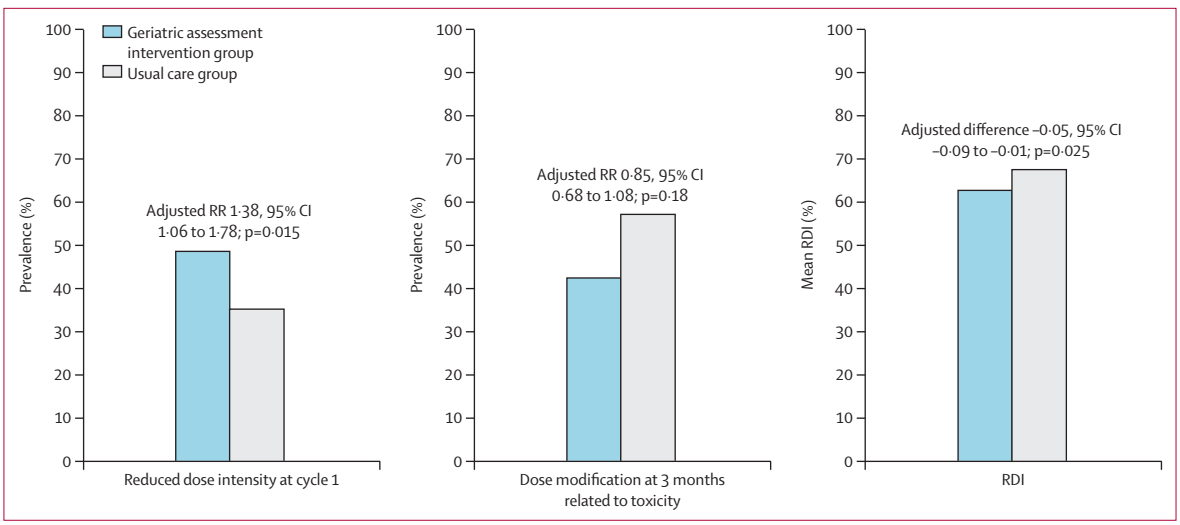

Figure 3: **Treatment intensity by study group**
(A) Prevalence of reduced treatment intensity at cycle 1. (B) Prevalence of dose modifications over 3 months. (C) RDI over 3 months. RDI=relative dose intensity. RR=risk ratio.

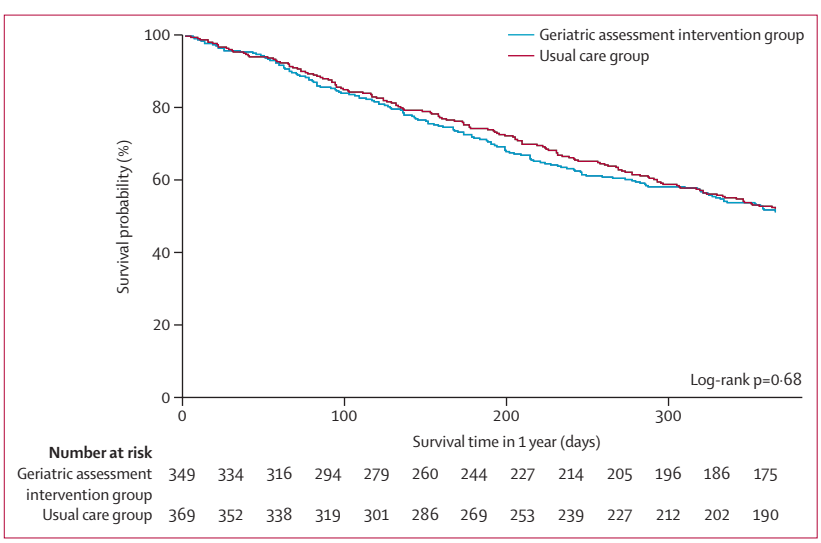

Figure 4: **Survival over 1 year by study group**

tied to management recommendations can improve upfront decision making for treatment and optimise clinically significant outcomes. The geriatric assessment intervention improved outcomes that are important to older adults with cancer, including serious treatment-related toxic effects, falls, and polypharmacy.[6]

To our knowledge, the GAP70+ trial is the first to enrol over 700 older patients with advanced cancer who were at high risk for adverse outcomes from palliative cancer treatment. The mean number of impaired geriatric assessment domains was greater than four, indicating a high prevalence of ageing-related conditions and frailty. The ASCO geriatric oncology guideline[2] and systematic reviews[9,14] highlight that older adults with ageing-related conditions receiving treatment for advanced cancer are at high risk of toxic effects, lower rates of treatment completion, and early mortality. The high prevalence of adverse outcomes shortly after starting treatment in this population offers an opportunity for utilisation of models of care and management that improve decision making regarding cancer treatments. The GAP70+ trial shows that, when available, community oncologists will use geriatric assessment information to personalise treatment decisions for vulnerable older patients with advanced cancer. The geriatric assessment intervention led to different treatment patterns (eg, a higher prevalence of single versus doublet chemotherapy) and reduced intensity treatment at cycle one.

Evidence has increasingly revealed that geriatric assessment-guided management improves clinical outcomes for older patients with cancer.[2,15] Randomised pilot studies have suggested that integration of geriatric assessment into oncology care is feasible,[16] can reduce treatment toxicity,[17] and can improve quality of life.[18] In a comparative study of two cohorts, older adults receiving chemotherapy who underwent geriatrician co-management were over four times more likely to complete cancer treatment.[19] A randomised controlled trial that enrolled vulnerable older adults with colorectal cancer who were receiving adjuvant or first-line chemotherapy found that a geriatric assessment intervention improved treatment completion, quality of life, and mobility.[20] We did an independent clinical trial in older adults that showed that this same geriatric assessment-guided intervention improved communication about ageing-related conditions and enhanced satisfaction for both older patients with advanced cancer and their caregivers.[3] The GAP70+ trial is unique—to our knowledge, it is the first nationwide cluster-randomised study to show that a multi-component geriatric assessment intervention delivered in community oncology practices can lower the

risk of serious toxic effects in older patients with advanced cancer and ageing-related conditions who were receiving palliative treatment.

Geriatric assessment can improve clinical outcomes in two ways: by influencing treatment decisions and by guiding interventions supported by the geriatrics' literature. A systematic review of 35 studies found that geriatric assessment influenced oncologists' treatment plans in a median of 28% of patients (range 8–54) and guided non-oncological interventions in a median of 72% (range 26–100).[9] In a large prospective observational study, older patients with breast cancer who were fit as defined by geriatric assessment were more likely to receive adjuvant chemotherapy.[4] In a sample of 321 older adults receiving palliative chemotherapy, 25% had a primary dose reduction; older age and comorbidity were associated with primary dose reduction.[21] In randomised clinical trials, older or frail patients with advanced colorectal[22] and gastric cancers[23] randomly assigned to reduced intensity chemotherapy had fewer toxic effects and similar survival to those who received standard dosing. In another randomised clinical trial, treatment allocation guided by geriatric assessment reduced treatment toxic effects without compromising survival in older patients with advanced lung cancer.[24] Therapeutic clinical trials should further examine tailored dosing strategies and use geriatric assessment as an essential component of the study design.

To our knowledge, the GAP70+ trial is the first to show that a geriatric assessment intervention can reduce the risk of falls and polypharmacy. Both falls and polypharmacy are more common in older patients with cancer and can increase the risk of adverse clinical outcomes, such as functional impairment, hospitalisations, and mortality. Furthermore, polypharmacy increases the risk of falling.[25] Consistent with other research,[25] the prevalence of falls in the patients receiving usual care in our study was high, with over 20% having a new fall within 3 months of starting a new cancer treatment. Evidence-based geriatric assessment-guided recommendations for falls prevention[26] were provided to most of the participants in the intervention group, since impairment in the physical performance domain was highly prevalent. Deprescribing high risk medications (eg, benzodiazepines) might also have reduced serious treatment-related toxic effects and falls.[27]

Other randomised clinical trials studying geriatric assessment for patients with cancer will add to the knowledge about other clinical outcomes, populations, and models for guiding ageing-appropriate care.[2] Several other large randomised trials presented at the 2020 ASCO annual meeting showed the benefits of geriatric assessment-guided interventions on clinical outcomes in older adults.[2,28] A geriatric assessment-guided intervention led by a nurse practitioner at an academic cancer centre in the USA showed reduced toxicity for older patients who received chemotherapy in a clinical trial that was randomised at the patient level. Another randomised trial showed the benefits of geriatrician co-management on health-related quality of life and healthcare utilisation for older patients with cancer in Australia. These ongoing trials will add valuable information to guide clinical care in older patients with cancer who are less frail (ie, without clinically significant ageing-related conditions), who are receiving cancer treatment with curative intent, and who have specific tumour types. The GAP70+ study is unique in that our intervention was delivered by community oncology practice staff to older adults with ageing-related conditions and advanced cancer who were at a high risk of adverse outcomes from cancer treatment. Future research should build upon these efficacy studies to evaluate implementation strategies for ageing-sensitive interventions that integrate geriatric assessment and geriatric assessment-guided management into oncology clinical care.

This study has limitations. The intervention was done only at a single timepoint, although the intervention affected outcomes for 3 months. The low intensity of the intervention and delivery by oncologists rather than geriatricians might have limited the ability to improve geriatric assessment outcomes beyond falls and polypharmacy. Integrated and longitudinal co-management between oncologists and geriatricians might provide even greater benefits for functional and quality-of-life outcomes because of better adherence to recommendations. However, access to geriatricians is restricted in many places, which could prevent implementation of co-management models.[29] Since

	Range	Overall between-arm difference (geriatric assessment–usual care) or RR (95% CI)	p value	p value for site clustering effect
Instrumental Activities of Daily Living scores over 3 months*	0–14	−0·13 (−0·58 to 0·31)	0·50	0·28
Short Physical Performance Battery scores over 3 months*	0–12	−0·33 (−0·80 to 0·14)	0·15	0·36
OARS physical health subscale scores over 3 months*	0–20	−0·24 (−1·15 to 0·65)	0·55	0·28
Geriatric Depression Scale scores over 3 months*	0–15	−0·04 (−0·52 to 0·43)	0·84	0·20
Number of prescription medications discontinued before starting cancer treatment regimen†	0–11	0·10 (0 to 0·20)	0·03	NA
Number of overall medications (prescription and non-prescription) discontinued before starting cancer treatment regimen†	0–13	0·14 (0·03 to 0·25)	0·02	NA
Any fall over 3 months‡	0–1	RR 0·58 (0·40 to 0·84)	<0·01	NA

Higher scores indicate better health except for depression scale and medications. Models with practice site random effect did not converge. NA=not applicable. OARS=Older Americans Resources and Services. RR=risk ratio. *Measures were analysed using linear mixed models adjusted for baseline values. †Polypharmacy was analysed using adjusted linear regression models. ‡Any fall over 3 months was analysed using generalised linear regression models (binary distribution with log link) adjusted for baseline values.

Table 3: **Effect of the geriatric assessment intervention on geriatric assessment outcomes**

survival was a secondary aim and only captured for 1 year, the study was not designed to examine non-inferiority between the study groups; further research is required to evaluate the effects of geriatric assessment interventions on survival as a primary aim and for tumour control. Oncologists determined the risk of toxic effects of regimens for eligibility, which might lead to bias. To reduce potential bias, the masked clinical team at the Research Base reviewed the toxic effect risk for all regimens.[10] Future research could consider incorporating standardised tools, such as the MAX2 index, to determine risk of toxic effects.[30] Imbalances in patient characteristics due to potential selection bias from differing practice characteristics inherent to cluster randomisation might have affected results. Some characteristics, such as receipt of previous chemotherapy, might have increased the prevalence of toxic effects in the intervention group. Other characteristics, such as impaired physical performance, might have increased toxic effects in the usual care group. Furthermore, less accrual from individual practices randomly assigned to the usual care group might reflect differences in care patterns. However, in an analysis of baseline data, oncologists' characteristics were not associated with the decision to provide chemotherapy, suggesting that oncologists might make decisions similarly.[8] Differential response rates for patient-reported outcomes and missing data might have influenced results. For example, a higher prevalence of patient-reported outcomes completed in the usual care group might have led to higher reporting of falls. However, a strength of this study is that the response rates for patient-reported outcomes was high in both study groups. This study enrolled a heterogeneous group of older patients with advanced cancer who were receiving palliative treatments for various cancer types with a high risk of toxic effects, consistent with the population that is cared for in community oncology practices. Nevertheless, stratified analyses showed benefits across history of previous treatment, cancer type, and treatment type. Thus, our results appear to be relevant to many older adults with ageing-related conditions and advanced cancer, which is a substantial strength.

In conclusion, to our knowledge, the GAP70+ trial is the first nationwide cluster-randomised clinical trial to show that geriatric assessment and geriatric assessment-guided management, when integrated into oncology care, can significantly reduce treatment toxic effects, falls, and polypharmacy in older patients with advanced cancer who are receiving treatment. Although a higher proportion of patients in the intervention group received reduced intensity treatment at cycle one, survival did not differ by study group. Geriatric assessment and geriatric assessment-guided management should be considered as the standard of care for older patients with advanced cancer and ageing-related conditions who are starting a new treatment regimen with a high risk of toxic effects.

Contributors

SGM, the principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis. HX and EC did the statistical analyses. MRM, AM, MAF, KPL, ER, and RFD were involved in the masked review of treatment regimens and toxic effects at the UR NCORP Research Base. LL, MJ, and KM provided extensive input on the original study design development and provided advice and support throughout the study. JOH, JB, and NA are community oncologists who provided input on design of the study and facilitated recruitment at their practices. TW and WD provided feedback on design, analyses, and the final manuscript. All authors had full access to all the data in the study, reviewed and provided feedback on the manuscript, and had final responsibility for the decision to submit for publication. SGM, the statisticians (HX and EC), and senior study staff (SO, NG, SP, AP, and MW) accessed and verified the data.

Declaration of interests

KPL reports consultant fees from Pfizer and Seattle Genetics and honoraria from Pfizer. RFD received honoraria for consulting from Exelixis. TW reports research funding from Janssen and consultant fees from Seattle Genetics and Carevive. All other authors declare no competing interests.

Data sharing

The following data will be made available through NCORP Data Archives (https://nctn-data-archive.nci.nih.gov/), including de-identified individual participant data and data that underlie the results reported in this article. The data will be available beginning 12 months (or until entered into archive per NCI deadlines) with no end date following article publication. The study protocol, statistical analysis plan, informed consent form, and clinical study reports will be made available on the Cancer and Aging Research Group website (https://www.mycarg.org/). These documents will be available beginning 6 months and with no end date following publication of the article. The above data and materials are made available to anyone who wishes to use the data in the NCORP Data Archive or the study related materials. For any further data or materials, research proposals can be directed to SM (supriya_mohile@urmc.rochester.edu). Opportunities for further analyses will be made available to investigators of the Cancer and Aging Research Group. There is no cost to be a member of the Cancer and Aging Research Group (see https://www.mycarg.org/ for membership information).

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