Geriatric Assessment as a Predictor of Tolerance, Quality of Life, and Outcomes in Older Patients With Head and Neck Cancers and Lung Cancers Receiving Radiation Therapy

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Received Aug 26, 2016, and in revised form Nov 18, 2016. Accepted for publication Nov 28, 2016.

Summary

In this prospective observational study of older head and neck or lung cancer patients, pretreatment dysfunction as measured by domains in a geriatric assessment were not associated with the predefined outcome of poor tolerance to treatment. However, dysfunction was

Purpose: To evaluate the association between functional status based on a geriatric assessment (GA) and outcomes of tolerance to treatment in patients with lung or head and neck cancer receiving radiation therapy (RT) or chemoradiation (CRT).

Methods and Materials: A prospective cohort study was conducted in patients aged ≥65 years with head and neck cancer or lung cancer undergoing curative intent RT or CRT. Pretreatment GA, health-related quality of life (HRQoL), and patient-reported outcomes (PRO) were obtained. Questionnaires were repeated biweekly during RT and at 6 weeks after treatment. Dysfunction was defined as scores <14 on the Instrumental Activities of Daily Living scale. Poor tolerance to treatment was defined by hospitalization, >3-day treatment delay, change in

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This study was presented in abstract/oral/and poster format at the American Society of Clinical Oncology 2015 Annual Meeting, May 29 to June 2, 2015, Chicago, IL; the American Society of Radiation Oncology 2015 Annual Meeting, October 18 to 21, 2015, San Antonio, TX; and the 2016 Multidisciplinary Head and Neck Symposium, Scottsdale, AZ.

The study was originally designed at the American Society for Clinical Oncology/American Association for Cancer Research Methods in Clinical Cancer Research, July 2012 Vail Workshop. The study was sponsored in part by the Alpha Omega Alpha 2012 Postgraduate Award, the Department of Radiation Oncology at the University of North Carolina, and the Geriatric Working Group of the Lineberger Comprehensive Cancer Center.

Conflict of interest: N.A.V. reports grants from Alpha Omega Alpha, during the conduct of the study; and grants from Conquer Cancer Foundation of the American Society of Clinical Oncology, outside the submitted work.

Supplementary material for this article can be found at www.redjournal.org.

associated with posttreatment quality of life and severity of patient-reported outcomes. Pretreatment geriatric assessment may help identify older patients who experience lack of recovery after treatment of their lung or head and neck cancers.

RT or CRT regimen, or death. Associations of dysfunction with tolerance to radiation therapy, HRQoL changes, and PRO ratings were evaluated.

Results: Of the 50 patients accrued, 46 had evaluable data. Mean age was 72.5 years (range, 65-92 years). At baseline, 37% had dysfunction. Poor tolerance to RT or CRT occurred in 39%. There was no association between dysfunction and tolerance. Patients with dysfunction had lower baseline HRQoL scores. From baseline to end of RT, those with baseline dysfunction had less of a decline in Role Functioning ($P = .01$) and Global Health Score ($P = .04$) domains. However, from end of RT to 6-week follow-up, those with dysfunction were more likely to continue to drop in the Physical, Role Functioning, and Social domains (all $P < .01$). Dysfunction at baseline was also associated with higher severity of certain PROs.

Conclusions: Pretreatment dysfunction was associated with continued decline and lack of recovery of HRQoL in this patient population. Larger studies could further elucidate the GA's predictive value.

Introduction

Cancer is primarily a disease of the elderly (1). It is estimated that more than 60% of all cases of cancer are diagnosed in those aged ≥65 years. As the US population continues to age, the number of older cancer patients is projected to rise significantly. Over the next 20 years, a 67% increase in the cancer incidence for older adults is expected (2). Despite this projected rise in incidence, there are few data to help guide clinicians as to the best ways to treat older patients, who are often diagnosed at higher stages, have significant comorbidities, are offered less-aggressive therapy, and are poorly accrued on prospective clinical trials (3-5). As age increases, functional reserve of multiple organ systems decreases. There are also increases in other medical problems in elderly patients (1). This, as well as perceived experience, has led many clinicians to assume that older patients have less tolerance for, and higher toxicity from, radiation therapy (RT) (6). Depending on the sites that are treated, RT is often thought to be well tolerated in older adults (7). However, with increasing number of older patients, increasing use of higher doses of RT, and increasing use of concurrent chemotherapy, it is important to study acute and long-term toxicity in this population in a systematic manner to understand what characteristics define the patient population that can, and cannot, tolerate aggressive RT regimens.

Geriatric assessments (GAs) are used by some clinicians to evaluate an older person's functional status, comorbidities, cognition, psychological status, social functioning and support, nutritional status, and medications. The Instrumental Activities of Daily Living (I-ADL) measure (part of the functional status domain) is often used as a surrogate measure of an adult's ability to live independently in the community (8). In non-cancer patients, GAs have been used to guide interventions that reduce morbidity and mortality (9). In patients with cancer, GAs have revealed a high prevalence of functional and memory impairment, comorbidity, and malnutrition that had not been revealed by standard physician-reported performance assessments (10). Results from GAs (and specifically loss of function in I-ADLs) predicted which patients were more likely to suffer worse toxicity from chemotherapy (11) and surgery (12). Additionally, the GA has been used to help with the treatment decision process in older patients, and its use has been recommended by international committees (13-15).

There are limited data examining the utility of a GA tool in predicting poor tolerance to or toxicity from RT. However, because RT is a local/regional therapy, a GA may have different predictive values depending on the site of therapy. Both head and neck cancer (HNC) and lung cancer patients often receive combined-modality therapy, which may offer decreasing benefit in older patients (16, 17). Thus, a tool that could help predict which patients could tolerate intensive therapy could offer significant benefits in older patient populations. The purpose of this study was to investigate the association of dysfunction of I-ADL, as assessed via an abbreviated GA, with tolerance to, toxicity from, and quality of life during RT or chemoradiotherapy (CRT) in HNC and lung cancer patients aged ≥65 years, in addition to assessing the impact of treatment on short-term measures of independence.

Methods and Materials

The study "Predicting Tolerance to Radiation Therapy in Older Adults with Cancer" was an institutional, prospective, observational study. Patients were recruited from the Department of Radiation Oncology. English-speaking patients aged ≥65 years with newly diagnosed lung cancer or HNC scheduled to receive curative intent RT or CRT were eligible. From September 2012 until December 2014, 50 patients were accrued. Poor tolerance to RT or CRT was defined by experiencing any of the following outcomes: >3-day treatment delay secondary to treatment-related toxicity during RT, hospitalization secondary to

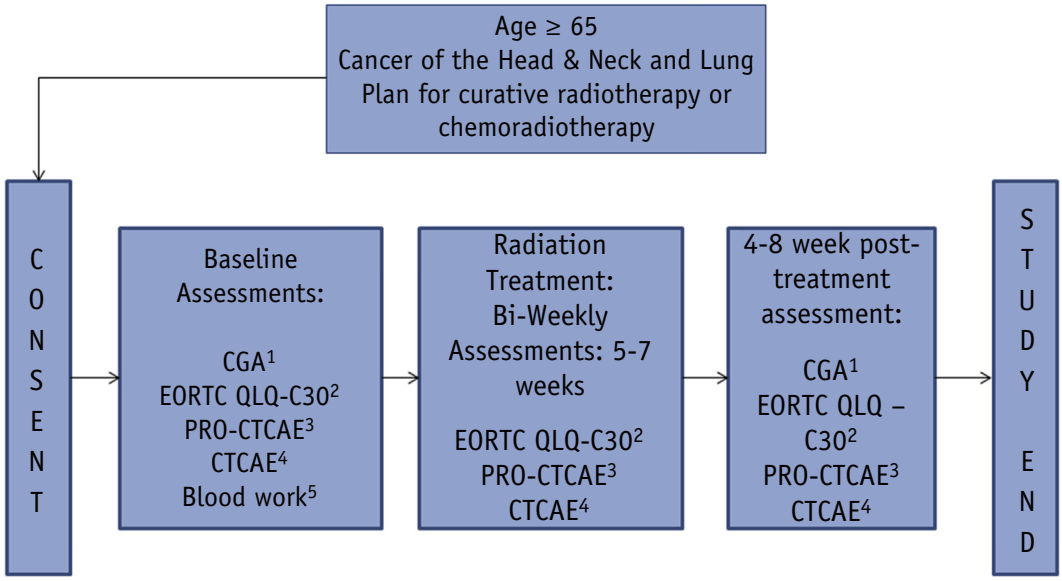
treatment-related toxicity during or up to 4 to 8 weeks after RT, unplanned dose reductions in either radiation or concurrent chemotherapy secondary to treatment-related toxicity during RT, unplanned change in chemotherapy regimen secondary to treatment-related toxicity during RT, or death. Secondary objectives included testing for associations between dysfunction and patient-reported outcomes (PROs) as measured by the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), as well as health-related quality of life (HRQoL) as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30). Additional secondary objectives included testing other components of the GA, and assessing the impact of treatment on functional status as measured by a repeat GA at follow-up. The study was reviewed and approved by the University of North Carolina institutional review board #12-1731. All patients signed informed consent forms before beginning the study. This study was registered with clinicaltrials.gov (NCT01752751).

Study schema

Each patient completed a pretreatment abbreviated GA designed by Hurria et al (18), with the professional assessment performed by a dedicated research coordinator. To avoid influencing treatment decision, the results of the pretreatment GA were blinded to the treating physicians. The HRQoL measures, patient-reported outcomes, provider-reported toxicities (CTCAE version 4.02), pretreatment Karnofsky performance status (KPS), pertinent patient and tumor characteristics, planned chemotherapy regimens, health behavior questionnaire, and pretreatment serum samples for correlative studies (not included in this article) were collected at baseline. The HRQoL measures, PROs, and provider-reported toxicities were repeated biweekly during RT. They were repeated again, along with a repeat GA, at first follow-up between 4 and 8 weeks after RT (Fig. 1). When possible, patients completed their questionnaires on electronic tablets provided to them at their visits. Those patients uncomfortable with the use of a tablet completed their questionnaires with the help of a research coordinator. Provider-reported toxicity was collected via a Qualtrics e-mail survey sent to the patient's provider. Provider-reported toxicity results will be compared with patient-reported outcomes in a separate article.

Statistical analysis

On the basis of previous publications (11-13), we assumed a 40% rate of poor function on the I-ADL test of the GA.



[1]Comprehensive Geriatric Assessment
[2]EORTC QLQ-C30: European Organization for Reasearch and Treatment of Cancer Quality of Life Questionnaire.
[3]PRO-CTCAE: Patient Reported Outcomes of the Common Terminology Criteria for Adverse Events
[4]CTCAE v4.02: Common Terminology Criteria for Adverse Events
[5]$p16^{INK4a}$ collection from peripheral T-cells and baseline CBC.

Fig. 1. Study schema.

We also assumed a 75% prevalence of poor tolerance in the patients with at least 1 I-ADL dysfunction and a 25% prevalence of poor tolerance in the patients with no I-ADL dysfunction. The study was designed with 50 patients to give us 82% power to detect the difference in tolerance using a 2-sided Fisher exact test with $\alpha = 0.05$. Descriptive statistics are provided for all study measures, and Fisher exact tests were used to compare percentages between groups. As initially designed, dysfunction was defined as a score <14 on the I-ADL scale. Other GA components were assessed using an overall frailty score (19), which was defined as having deficits on 2 or more of the domains of the GA. Cutoffs for each domain are available in Table E1, available online at www.redjournal.org (20). Changes in HRQoL scores over time were compared between groups using 2 models. The first, a mixed linear model (21), used all available observations from baseline to end of RT (maximum of 4 per person). In the second model we hypothesized that changes observed over the course of treatment would remain steady, but patients' trajectories may change at the end of treatment and return to their pretreatment levels, so this model only included the end of treatment and the follow-up measurements. For any patient who completed at least 2 assessments of patient-reported outcomes after baseline, we took the maximum reported severity over the course of the study. These maximum reported severities were compared between groups using Jonckheere-Terpstra tests, which account for the ordered nature of responses. All analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, NC).

Results

Of the 50 patients accrued onto the study, 46 were ultimately considered eligible (4 patients did not complete the baseline I-ADL component and were removed from the study). Baseline patient characteristics are listed in Table 1. Sixty-one percent of patients had HNC, and 46% received concurrent CRT. Baseline KPS was ≤70 in 15% of patients (n=7), whereas baseline dysfunction in I-ADLs was present in 37% of patients.

Table 1 Patient characteristics (n=46)

Characteristic	n (%)
Age (y)	
65-69	18 (39)
70-74	14 (31)
75-79	8 (17)
80-84	4 (9)
85+	2 (4)
Sex	
Male	24 (52)
Female	22 (48)
Race	
Caucasian	40 (87)
African American	6 (13)
Cancer site	
Head and Neck	28 (61)
Lung	18 (39)
Smoking status	
Current	3 (7)
Previous	30 (65)
Never	6 (13)
Unknown	7 (15)
Stage	
I/II	6 (13)
III/IV	40 (87)
Baseline KPS	
80-100	39 (85)
≤70	7 (15)
Baseline I-ADL	
14	29 (63)
<14	17 (37)
Falls in last 6 months	
0	37 (86)
≥1	6 (14)
Frail Index	
Not Frail	31 (67)
Frail	15 (33)
Treatment	
RT alone	25 (54)
CRT	21 (46)

Abbreviations: CRT = chemoradiotherapy; I-ADL = Instrumental Activity of Daily Living; KPS = Karnofsky performance status; RT = radiation therapy.

Tolerance

Poor tolerance occurred to RT or CRT in 18 of the patients (39%) in total, 12 (43%) of the HNC patients, and 6 (33%) of the lung cancer patients. Reasons for poor tolerance are described in Table E2 (available online at www.redjournal.org). Baseline I-ADL dysfunction had no association with the primary outcome of tolerance to RT (38% vs 41%, $P=1.0$). There was no association whether looking at all patients or by tumor type (Table 2). Dysfunction in I-ADL also had no association with patients requiring percutaneous gastrostomy tube (g-tube) during RT. The receipt of CRT compared with RT alone was statistically associated with both poor tolerance to treatment in all patients (24% vs 57%, $P=.03$) and with requiring g-tube placement among HNC patients (29% vs 91%, $P=.002$).

Health-related quality of life

Forty-five patients completed the baseline HRQoL questionnaires. Thirty-six completed the questionnaires at the end of RT, and 26 patients completed the questionnaires at the final follow-up visit. There was a statistically lower score at baseline on the Physical Functioning, Role Functioning, and Global Health components (51 vs 86, $P<.001$; 47 vs 86, $P<.001$; 49 vs 71, $P=.001$) among patients with I-ADL dysfunction. Those with I-ADL

Table 2 Percentage of patients with outcomes of poor tolerance to therapy, compared by baseline characteristics

Outcome	Combined-modality therapy			I-ADL dysfunction			Frailty			Falls			Provider KPS		
	RT alone (%)	CRT (%)	*P*	=14 (%)	<14 (%)	*P*	Robust (%)	Frail/ Pre-frail (%)	*P*	0 (%)	≥1 (%)	*P*	≥80 (%)	≤70 (%)	*P*
All patients															
Poor tolerance	24	57	.03	38	41	1	39	40	1	38	67	.22	36	57	.41
HNC patients															
Poor tolerance	24	73	.02	43	43	1	40	50	.69	42	100	.20	44	33	1
G-tube	29	91	<.01	43	86	.08	50	63	.69	50	100	.48	52	67	1
Lung patients															
Poor tolerance	25	40	.64	25	40	.64	36	29	1	31	50	.58	21	75	.08

Abbreviations: G-tube = percutaneous gastrostomy tube; HNC = head and neck cancer. Other abbreviations as in Table 1.

dysfunction were less likely to have significant drops in their HRQoL during RT on the Role Functioning and Global Health components. However, those with I-ADL dysfunction at baseline were also more likely to continue to have decreased HRQoL in Role Functioning and Social Functioning after treatment (Fig. 2 and Table 3). Similar directions in HRQoL scores were seen among those considered frail (data not shown). Additional models including an adjustment for age were also evaluated and revealed no changes in the relationship between I-ADL/chemotherapy and EORTC scores.

Patient-reported outcomes

Over the course of the study, patients with I-ADL dysfunction reported statistically higher severity of shortness of breath, pain, cough, and wheezing, and less severity with taste (Fig. 3). There was no other statistical difference in patient-reported outcomes between those with I-ADL dysfunction compared with those with complete function at baseline.

Change in GA scores

Of the 46 patients who completed the GA at baseline, 28 patients (61%) completed a posttreatment GA as well. Forty-two percent of patients (8 of 19) independent on all measures of the I-ADL at baseline, no longer were independent in at least 1 of the measures of the I-ADL at follow-up. Fifty-two percent of patients (11 of 21) without frailty as measured by the overall frailty score at baseline were frail after completing their cancer treatment.

Discussion

In this small, prospective observational study of older patients with HNC or lung cancer an association between

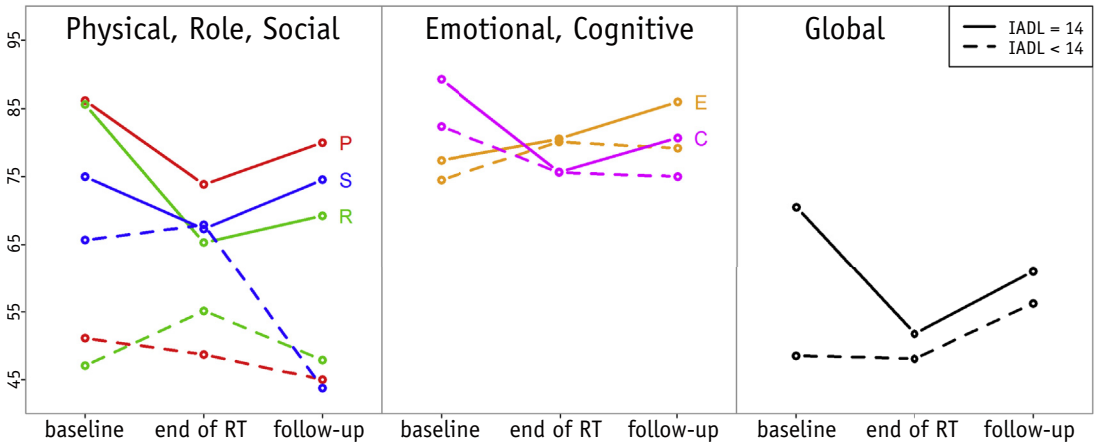


Fig. 2. Health-related quality of life changes. Solid lines: Patients with baseline Instrumental Activities of Daily Living (IADL) score of 14. Dashed lines: Patients with baseline IADL score <14. All available data at each time point were used for the figure. *Abbreviations:* C = Cognitive Function domain; E = Emotional domain; P = Physical Function domain; R = Role Function domain; RT = radiation therapy; S = Social Function domain.

Table 3 Mean baseline and change scores for EORTC QLQ scores, based on baseline characteristics

	Combined-modality therapy			I-ADL dysfunction		
Functional domain	RT alone	CRT	*P*	=14	<14	*P*
At baseline						
Global Health	59	66	.49	71	49	<.01
Physical	67	82	.13	86	51	<.01
Role	65	79	.26	86	47	<.01
Emotional	74	79	.29	77	75	.30
Cognitive	83	90	.30	89	82	.19
Social	73	70	.73	75	66	.10
Change from baseline to end of RT						
Global Health	−6.0	−22.2	.12	−21.1	1.9	.01
Physical	−1.9	−18.2	.03	−13.3	0.6	.05
Role	−2.3	−22.9	.01	−22.7	11.5	<.01
Emotional	11.5	−5.6	<.01	3.3	6.4	.70
Cognitive	−2.4	−21.1	<.01	−13.0	−5.1	.12
Social	0.8	−12.2	.18	−8.7	2.6	.19
Change from end of RT to follow-up						
Global Health	4.2	20.5	.55	14.2	5.6	.34
Physical	2.2	8.9	.65	10.4	−8.9	<.01
Role	−11.1	13.9	.54	13.0	−33.3	<.01
Emotional	−3.5	17.4	.10	8.3	1.4	.54
Cognitive	−1.4	16.7	.12	9.8	0.0	.52
Social	−4.2	4.6	.66	10.8	−30.6	<.01

Abbreviations: EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Other abbreviations as in Table 1.

The mean change scores are estimated on the basis of patients with data at both time points.

functional deficits as measured by components of a GA and outcomes of tolerance to RT was not identified. However, baseline functional deficits were associated with decreased recovery in HRQoL after RT and with increased severity of certain patient-reported outcomes. Additionally, 42% of patients considered healthy according to I-ADL score at baseline lost at least one form of functional independence after cancer treatment.

At the time this study was designed there were no published studies on the predictive value of GAs on toxicity or tolerance to RT. A number of studies have since been published that help elucidate the potential clinical utility of GAs among patients receiving RT. Ulger et al (22) prospectively assessed 30 older patients undergoing RT for multiple different cancer types. Among their population, with a mean age of 70 years, all of the patients completed RT, none had greater than grade 2 toxicity, and there was no statistical association between toxicity and GA parameters (22). Spyropoulou et al (23) prospectively studied 230 patients over the age of 75 years receiving RT for curative or palliative intent to discern the association between the Vulnerable Elderly Survey 13 questionnaire and completion of RT. On multivariate analysis they found that a score of >3 (indicating vulnerability) was statistically associated with inability to complete RT (odds ratio 2.14, $P=.008$) (23). Baitar et al (24) studied the potential predictive value of the G8 assessment among 85 patients and ≥65 years receiving "(radio)chemotherapy" but only included 9 patients receiving RT. These 3 studies highlight the difficulty in the design of studies to determine the potential benefit of geriatric screening tools for RT decision making. The studies included different age cutoffs, different screening tools, different endpoints, different cancer types, and different treatment intent (curative vs palliative).

In contrast to the above studies, we limited our inclusion criteria to patients with HNC and/or lung cancer owing to the local/regional nature of RT. As opposed to a systemic treatment, RT toxicity is highly dependent on the area of the body that is being treated and the dose being delivered (25). With different expected toxicity profiles, the potential clinical benefit of a predictor of tolerance or toxicity may be very different among patients with primary tumors in different body locations. We chose to enroll patients with HNC and lung cancer because of the similar demographics and comorbidities of these populations, as well as the

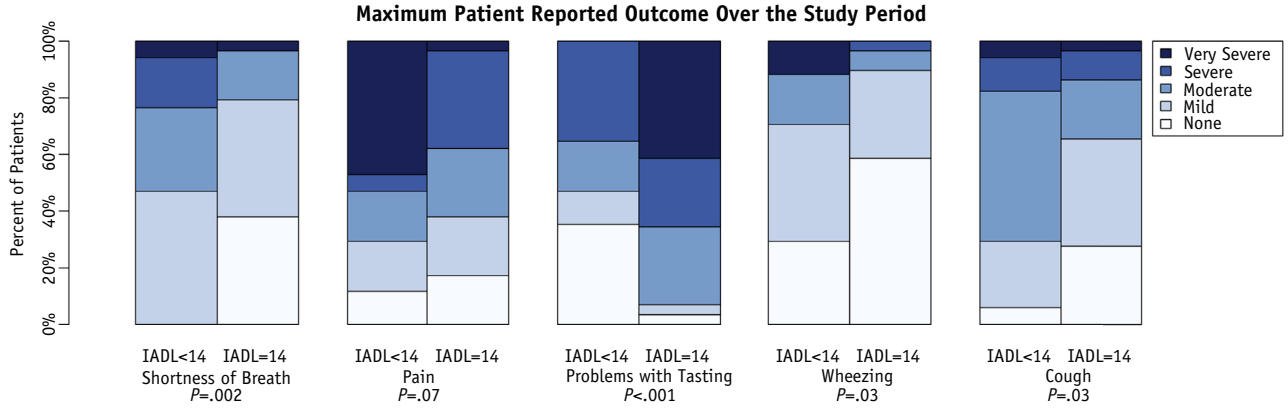


Fig. 3. Maximum-patient reported outcomes: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events. Darker shades of blue are higher severity of that particular patient-reported outcome. *Abbreviation:* IADL = Instrumental Activities of Daily Living.

morbid multimodality nature of the curative intent treatment. Additionally, we did not include patients receiving palliative RT. The goal of RT in the palliative setting is highly dependent on patient symptoms, and the decision to treat may be less dependent on patient functional status compared with the curative setting.

Another difference between our study and the prior studies is the inclusion of HRQoL and PRO data. Although tolerance and the ability to complete treatment is an important endpoint, quality of life and maintaining independence after treatment can be an equally important endpoint to many older patients (26). Our study suggests that 42% of patients may lose their ability to maintain independence at first follow-up after curative intent RT or CRT. This information should be an important component of the decision-making process between older adults and their clinicians. Several studies have published results on HRQoL changes among older patients with HNC (27-29) and lung cancer (30). These and other studies suggest that age itself may not predict lower HRQoL (31). Though older patients may have lower physical function, they often have higher social function and less financial difficulties than their younger peers (31). In contrast, our study demonstrates that baseline dysfunction may predict for inability to recover HRQoL after antineoplastic therapy.

There are limited data on the topic of predicting decline in HRQoL in older patients with cancer. Deckx et al (32) assessed 354 patients over the age of 70 years, 134 of whom had cancer, in a prospective cohort study. More than 50% of the cancer patients in their study underwent RT as part of their treatment. Patients completed multiple geriatric screening tools, including an abbreviated GA, G8, and the Vulnerable Elderly Survey 13. They found that none of the geriatric screening tools were associated with decline in HRQoL. However, Pottel et al (19) identified a significant association between frailty (as measured by G8 and ComprehensiveGA) and decreased HRQoL and lower quality-adjusted survival in a prospective study of 100 older HNSCC patients receiving CRT. Similarly, our study suggests that functional deficits based on the GA at baseline may be associated with differences in both decline and lack of recovery of HRQoL during and after RT among HNC and lung patients. If true, then it is feasible that clinicians could use a GA to identify those patients who could benefit from pretreatment interventions (such as physical therapy) that could help older patients avoid continued decline of physical function after cancer therapy.

Our study has several limitations. With 46 patients, this small, single-institutional study was limited in scope and should not be used as proof that RT is well tolerated in patients with functional deficits at baseline. This study was performed at a single academic institution in which older patients received significant supportive care from their physicians, residents, nurse practitioners, dedicated nurse navigators, nutritionists, and speech therapists. In a setting with fewer resources it is possible that a larger number of events would have led to associations between baseline dysfunction and tolerance. Additionally, the results of this study in HNC and lung cancer patients should not be extrapolated to patients receiving RT for other cancer types and other anatomic locations. Antineoplastic therapy was not defined in the protocol, and treatment decisions were left up to the treating physicians. Although the treating physicians were blinded to the results of the GA, it is possible that those patients with poorer functional status received less-aggressive therapy (ie, lack of concurrent chemotherapy, lower radiation dose, or smaller radiation fields). Follow-up was limited to 8 weeks after RT. Longer follow-up is important to understand long-term side effects, long-term HRQoL, and survival differences between those with and without dysfunction at baseline. The original design of the study was limited to assessing the I-ADL component of the GA, which is a small component of a larger screening test. Although an overall frailty score was used as part of this analysis, the study was not primarily designed with this score in mind and was underpowered for that reason. Last, owing to the small number of events, associations between poor tolerance (including hospitalizations), PRO, and HRQoL results could not be assessed in a multivariate model.

Conclusion

In this prospective study of older patients with HNC and/or lung cancer, I-ADL dysfunction at baseline was not associated with outcomes of poor tolerance to RT. However, I-ADL dysfunction was associated with lack of recovery of important components of HRQoL after RT and with higher severity of certain PROs. Additionally, 40% of independent patients at baseline lost at least one aspect of their independence after their antineoplastic therapy. Ongoing and future larger site-specific studies examining assessment-based treatment decisions or interventions should help clinicians elucidate the potential clinical benefits of screening GAs among older patients receiving RT-based treatments.

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