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Can frailty screening tools predict completion of chemotherapy and chemotherapy toxicity in patients with thoracic malignancy?

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1. Background

Treatments for thoracic malignancies have expanded significantly over the last decade and greater numbers of older patients are receiving systemic anti-cancer therapies (SACT) than ever before. This has highlighted a need to incorporate elements of geriatrics into management of patients with cancer including the recognition and appropriate management of 'frailty'. Comprehensive Geriatric Assessment (CGA) is seen as the gold standard assessment, but it is time and resource intensive and difficult to achieve in the treatment timescales mandated to meet cancer targets [1]. The 2015 International Society of Geriatric Oncology (SIOG) update recommends using screening tools to identify older patients in need of further evaluation by CGA. The consensus statement does not recommend one tool over another, rather, it advises that the choice of tool should depend on the clinical setting. The Geriatric 8 (G8) was acknowledged as having the most robust data compared to a number of different screening tools [2]. The Rockwood Clinical Frailty Scale (CFS) was developed as a convenient tool for assessing frailty in acute medicine. NHS England is currently piloting its use within oncology as part of its Specialised Clinical Frailty Network programme. The CFS has not however been widely validated in an oncology setting [3,4].

Several studies suggest that screening tools, including the G8, offer prognostic value for functional decline, chemotherapy tolerability, and overall survival in patients with cancer [5–7]. In lung cancer, frailty has previously been shown to be a predictor of first cycle toxicity [8]. This is a clinically valuable outcome which may highlight patients for whom oncogeriatrician review prior to treatment could offer the most benefit. It is less likely to be confounded by disease factors rather than survival outcomes.

This quality improvement project aimed to establish whether frailty screening is feasible in an oncology setting, which tool was most effective in identifying frail patients, and how these tools compare with routine oncological assessments such as performance status. This study was part of a development of a novel oncogeriatrics service, providing baseline evaluation of our population's frailty and outcomes.

We assessed 41 patients receiving platinum-based doublet chemotherapy for thoracic malignancy using the Geriatric 8 (G8), Rockwood Clinical Frailty Scale (CFS), Timed Get Up and Go (TGUG), Karnofksy Performance Status (KPS), and ECOG performance status (ECOG-PS). We looked at correlations between the tools and treatment related outcomes. We chose outcomes to assess chemotherapy tolerability including receiving the second cycle of chemotherapy on time at full dose (2CFDOT), completion of four cycles full dose (4CFD), and hospitalisation during and within three weeks of treatment. We also looked at concordance between frailty screening tools.

2. Methods

All patients with thoracic malignancies planned for four cycles of chemotherapy at Manchester Thoracic Oncology Centre at Manchester University NHS Foundation Trust, where they were screened for frailty between August and November 2018. Verbal consent was obtained and assessments were performed by trained clinicians prior to commencing chemotherapy. Approval was gained from the Trust Institutional Clinical Audit Department and respiratory directorate. Details of assessments can be found in Supplementary Items 1–3. Outcome data was collected from electronic patient records and chemotherapy prescribing software.

The Statistical Package for the Social Sciences (SPSS) software (Version 23) was used for quantitative data analysis. Spearman's rank order correlation was used to compare the frailty assessments. Mann-Whitney *U* test and Fisher's exact tests were used to compare the frailty scores for patients with different outcomes; choice of test depended on the variable properties. Logistic regression was performed to identify relationships between frailty scores and outcomes.

3. Results

41 patients (28 M, 13 F) were assessed with a median age of 71 (range 49–81). 32 patients were aged 65 or over (Supplementary table 1). 76% (31) patients scored ≤14 (indicating frailty) on G8. 75% (3) PS0, 70% (16) PS1, 83% (10) PS2, and 100% (2) PS3 were frail by the G8.

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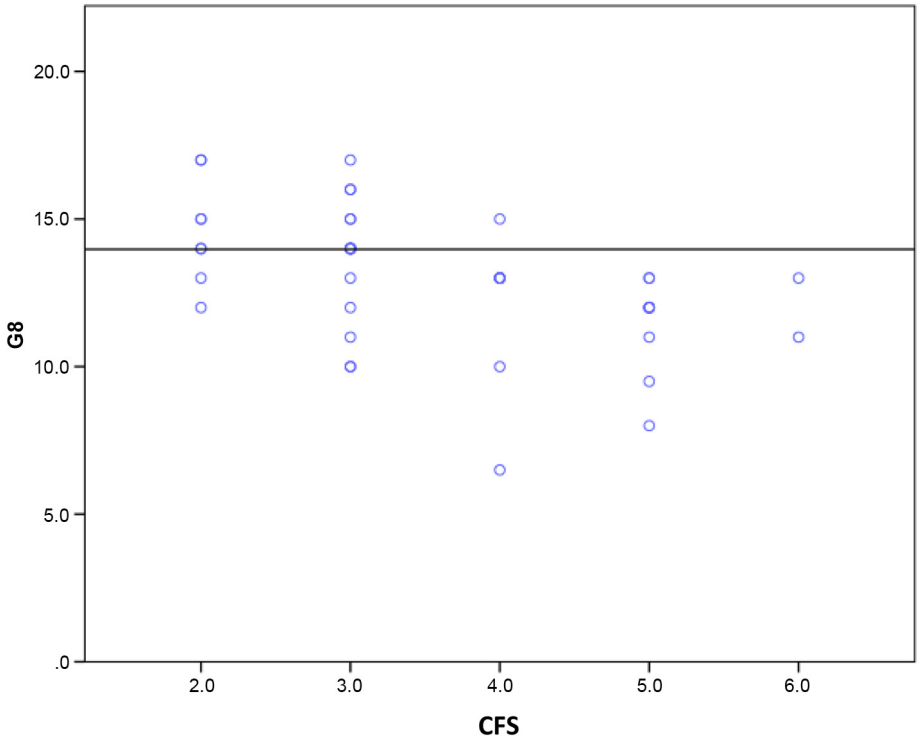

Fig. 1. G8 scores by Clinical Frailty Scale. CFS: Clinical Frailty Scale.

3.1. Correlating frailty screening tools

G8 score correlated significantly with CFS ($r = 0.560$, $p \leq .001$) and KPS ($r = 0.459$, $p = .003$), but not with ECOG-PS ($r = -0.168$, $p = .294$). This may reflect the wide distribution of G8 scores within ECOG-PS1, which represents 56% of the population (Supplementary fig. 1). In addition, 75% of ECOG-PS0 patients were found frail by G8 albeit from a small sample of four patients. All those found moderately frail (a score of ≥5) by CFS would have been found frail by G8 (Fig. 1). However, a number of patients scoring <5 on CFS were frail by G8. G8 and TGUG did not correlate significantly. Patients with lung cancer receiving palliative care were frailest by all measures. Patients with mesothelioma had the highest proportion of never smokers (38%) and lower mean medications (3.7) compared to patients with lung cancer (5.7).

3.2. Correlating frailty screening tools with outcomes

24% (10) patients didn't receive their second cycle at full dose on time (2CFDOT). All cycle 2 delays or dose reductions were toxicity related (Supplementary table 2). Only 39% (16) patients completed four cycles at full dose (4CFD) and 39% (16) were hospitalised. Four of the 25 patients who did not receive 4CFD had progressed through treatment (all mesothelioma). Median CFS and KPS scores for patients receiving 2CFDOT were significantly better (i.e less frail) ($p = .04$ and $p = .05$ respectively), but no significant difference was seen in the median G8/TGUG scores ($p = .066/0.134$ respectively) (Supplementary table 3). A G8 cut-off of ≤14 is the most widely used cut-off to identify a frail population, although other classifications have been suggested [9]. Dividing the cohort using a G8 ≤ 14 was not significant ($p = .4$), but a cut-off of 13 was ($p = .03$) for receiving 2CFDOT (Supplementary table 4). No significant difference was seen for hospitalisation or 4CFDOT (Supplementary tables 4,5,6). Interestingly, in this small cohort, ECOG-PS was not associated significantly with any outcomes. Logistic regression was performed for age, G8, and KPS ($p = .26, 0.09, 0.07$ respectively). None were significant predictors of 2CFDOT, 4CFD, or admission.

G8 was the most sensitive tool for receiving 2CFDOT, 4CFD, and admission, however this is reflected in a lack of specificity; specificity was improved by a cut-off of ≤13 (Table 1). The CFS had greatest specificity at a cost to sensitivity. 76% of the sample population was found frail by G8 ≤ 14 which is reflected in the lower specificity, but is comparable to the levels of frailty found in other studies using G8 [6,7].

4. Discussion

Existing oncology tools for assessing functional status (such as ECOG-PS and KPS) are currently used to assess fitness for treatment, clinical trials, and predict prognosis. However, these have been developed and validated in younger populations who may not exhibit the complex comorbidities of older patients. Conversely, tools used by

Table 1
Sensitivity and specificity of frailty screening tools for predicting outcomes.

	G8 ≤ 14			G8 ≤ 13			TGUG < 10			CFS ≥ 5			ECOG-PS ≥ 2		
	No 2CFDOT	No 4CFD	Admission	No 2CFDOT	No 4CFD	Admission	No 2CFDOT	No 4CFD	Admission	No 2CFDOT	No 4CFD	Admission	No 2CFDOT	No 4CFD	Admission
Sens	90.0%	80.0%	87.5%	90.0%	68.0%	75.00%	60.0%	54.2%	56.3%	50.0%	32.0%	31.3%	50.0%	32.0%	31.3%
Spec	29.0%	31.3%	32.00%	51.6%	43.8%	52.00%	60.0%	43.8%	45.8%	80.7%	81.3%	76.0%	71.0%	62.5%	64.0%

TGUG: Timed Get up and Go, CFS: Clinical Frailty Scale, ECOG-PS: Eastern Cooperative Oncology Group Performance Status, 2CFDOT: Second cycle full dose on time, 4CFD: Four cycles full dose.

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geriatricians to identify frail patients are still being validated in the oncology setting where they are not routinely used.

We found that ECOG-PS and G8 did not significantly correlate. The small size of the subgroups makes it difficult to compare the performance of frailty screening tools with performance status. Previous work in patients with lung cancer found ECOG-PS to correlate well with a number of geriatric indices (not including G8), and argued ECOG-PS was a good parameter in assessing older patients [10]. However, another study found that G8 was more discriminating for poor prognosis in a cohort of largely ECOG-PS 0–1 cancer patients [9]. The majority of our population were ECOG-PS1 and of these patients, 48% had hospital admissions, and 65% did not receive 4CFD. In this group, the greater discriminatory power of frailty screening tools could be valuable in identifying those of 'good' performance status who are at risk of poorer outcomes, but this requires further research with a larger population.

A limitation of this study was the heterogenous population. Patients with mesothelioma were less likely to have significant co-morbidities and smoking history. However, mesothelioma itself can cause significant frailty due to cachexia and breathlessness. Weight loss was often a factor in patients with mesothelioma who scored lower on the G8 but had good functional status by KPS or CFS. This highlights the difficulties in attempting to develop a single frailty screening tool suitable for the vast variety of cancer populations that exist.

The heterogeneity of treatment regimens may be a confounding factor when interpreting relationships between frailty and outcomes. This limitation is likely to impact attempts to study frailty in a 'real-world' population where clinician treatment choice will be influenced by a patient's performance status. The sample size was relatively small because this was data collected as part of a service development project. We acknowledge the limitations the sample size and heterogeneity of the population place on drawing conclusions from this data.

CFS and KPS scores were significantly associated with 2CFDOT. Using a G8 cut-off of ≤13 was significantly predictive of receiving 2CFDOT, whilst a cut-off of ≤14 was not. Although our study suggests a G8 cut-off of 13 rather than 14 may have more utility, we recognise it is not possible to draw this conclusion from this small population. The significant relationship of these tools with 2CFDOT was felt to be clinically important, as patients who struggle to tolerate chemotherapy from the initial cycle are a cohort who may benefit most from geriatric intervention prior to starting treatment. However, the lack of significant relationship between any of the tools with completion of FCFD or hospitalisation suggests a limitation in using these tools to predict chemotherapy tolerability. Completion of 4CFD and hospitalisation were affected by cancer progression, making these less useful outcome measures.

TGUG does not add to the sensitivity of the G8, but it is an objective measure which can provide useful information on mobility/musculoskeletal health.

Ideally, all older patients would undergo CGA but few centres have the capacity to offer this assessment. Tools such as the CFS or G8 may allow selection of the patient group that would benefit most from oncogeriatric input. Choice of tool and cut-off may depend on the capacity of a service to offer CGA to all those screened as frail.

5. Conclusion

Frailty screening is feasible in an oncology setting and a large proportion of patients receiving thoracic malignancy are found frail by commonly used frailty screening tools, including a high proportion of ECOG-PS 0/1 patients.

This study shows a limited predictive value of these screening tools and suggests they are not discriminatory enough alone to guide treatment decisions, but they may complement and streamline the identification of patients who will benefit from more comprehensive geriatric input.

Going forward, this tertiary service has implemented routine G8 screening for all patients considered for SACT with scores below thresholds, which triggers review by a dedicated oncogeriatrician.

Author contribution

Study concepts: Ann Tivey, Laura Cove-Smith, Cassandra Ng
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Data acquisition: Ann Tivey, Mohammed Ullah, Alison Beech
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Data analysis and interpretation: Ann Tivey, Alison Beech
Statistical analysis: Ann Tivey
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Manuscript review: Ann Tivey, Laura Cove-Smith, Cassandra Ng

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2020.03.002.

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