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Functional and patient-reported changes in swallowing and voice after combined chemotherapy and radiotherapy for limited-stage small-cell lung cancer

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TITLE: Functional and patient-reported changes in swallowing and voice after combined chemotherapy and radiotherapy for limited stage small cell lung cancer

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ABSTRACT

Introduction: The purpose of this study was to describe the nature and impact of dysphagia and dysphonia in patients with limited-stage small cell lung cancer (SCLC) before and after chemoradiation.

Methods: A prospective cohort study was conducted on patients receiving chemoradiotherapy for limited-stage SCLC. Patients received either 40, 45 or 50Gy, commencing the second cycle of chemotherapy. Outcomes included: videofluoroscopy (VFSS) to investigate aspiration, swallowing function, and oesophageal motility; oral intake limitations; patient-reported dysphagia; and patient-reported dysphonia. Data were collected before treatment and one, three and six months post-treatment.

Results: Twelve patients were enrolled. Oropharyngeal swallowing was safe and functional at all times. Three patients exhibited oesophageal motility disorders before treatment, and a further three post-treatment. Oral intake was most compromised one month post-treatment with five patients either tube dependent or eating very limited diets. At all other times patients were eating normal or near-normal diets. Despite normal oropharyngeal swallowing on VFSS, three patients reported moderate or severe dysphagia one month post-treatment. Three additional patients reported moderate or severe difficulties three and six months post-treatment. Patients who reported dysphagia one month post-treatment all received a mean and maximum oesophageal dose of ≥15.7Gy and ≥42Gy respectively. Dose-response relationships were not apparent three and six-months post treatment. Voice problems varied, with worst scores reported one month post-treatment.

Conclusions: This study identified discordance between observed swallowing function and patient-reported problems, which has clinical implications for patient management, and highlights future research needs. Ongoing efforts to reduce mucosal toxicity in lung cancer patients are essential.

Keywords: dysphagia; swallowing; voice; quality of life; small cell lung cancer; chemoradiation

INTRODUCTION

Lung cancer remains the most common cancer in the world, with over 2 million estimated new cases and 1.7 million deaths worldwide in 2018[1]. Mortality and morbidity – from the disease as well as its treatment(s) – remain significant challenges for clinicians, and it has been identified that patients with lung cancer experience more symptom distress than those with other types of cancer[2]. Dysphagia (difficulty swallowing) and dysphonia (impaired voice) have been identified in patients with lung cancer as being significant problems, which may be caused by direct tumour invasion (from mediastinal disease or cervical lymphadenopathy), nerve compression (causing unilateral vocal-cord palsy), age, dyspnoea or deconditioning, and these problems may be further compounded by the treatment itself, which often comprises intensive chemoradiotherapy[3,4]. Dysphagia can result in malnutrition, aspiration pneumonia, associated hospital admissions, anxiety and depression, and a significant reduction in Quality of Life (QOL)[5].

Acute dysphagia has been recognised as a dose-limiting toxicity in patients with lung cancer receiving concurrent chemoradiotherapy, with between 30-51% of patients developing moderate (Grade 2) dysphagia, while 11-13% develop severe (Grade 3) dysphagia during the acute treatment phase[6,7]. However, the data is limited by the somewhat crude measurement of 'dysphagia', using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) scoring system which is based on subjective symptoms and does not identify the cause or nature of the swallowing problem. 'Dysphagia' may refer to swallowing difficulties due to oesophagitis-related pain, aspiration of fluids or a physical inability to clear solid food through the pharynx or oesophagus. These varying presentations have vastly different management strategies and impacts on patients, so an accurate appraisal of the nature of the problem using a variety of tools that measure all aspects of dysphagia is essential.

The need for well-designed, prospective research on the nature of dysphagia and dysphonia in lung cancer patients has been previously identified[3,8]. Understanding exactly what types of swallowing and voice problems patients develop and when, ensures accurate information can be provided to patients prior to treatment and allows clinicians to provide more timely preventative or therapeutic intervention, potentially avoiding dysphagia-related malnutrition or aspiration pneumonia, or the daily challenges resulting from dysphonia.

Most studies investigating symptoms in patients with lung cancer only include those with non-small cell lung cancer (NSCLC)[2]. Although small cell lung cancer (SCLC) makes up only about 13% of all lung cancers[9], management of limited stage disease often involves a hyperfractionated radiotherapy schedule delivered twice daily (BD); a schedule typically associated with increased rates of oesophagitis[10], which may also be associated with neutropenia and the development of acute dysphagia[7]. Those with SCLC also have a poor prognosis with a 5-year relative survival rate of 31-34%[11]. This higher morbidity and mortality profile highlights the importance of maximising QOL at all stages of treatment planning and delivery, so accurate data on the outcomes and risks of this vulnerable patient group is urgently required.

There are currently no studies that have reported on swallowing or voice outcomes in patients with SCLC, and the use of instrumental measures of swallowing function for any lung cancer patients is also lacking. The purpose of this prospective study therefore was to investigate the nature and impact of dysphagia and dysphonia in patients with limited-stage SCLC before and after treatment, using a range of measures to examine potential associations between post-treatment outcomes and treatment-related characteristics.

METHODS AND MATERIALS

Study Design and Participants

This was a prospective longitudinal cohort study, using repeated measures on a convenience sample of newly diagnosed patients with SCLC from [removed for blind review]. The study was approved by the [removed for blind review] ethics committee prior to commencement (HREC approval: [removed for blind review]) and all participants provided written informed consent prior to participation.

Patients with newly diagnosed limited-stage SCLC were recruited prior to receiving chemoradiotherapy at one of [removed for blind review]'s three radiotherapy sites across [city, country; removed for blind review]. Patients were eligible for inclusion if they were: over 18 years of age; had limited stage disease (no known distant metastatic disease and appropriate for radical chemoradiotherapy); able to read English; no previous radiotherapy to the head or neck; and no previous conditions or treatment that could cause swallowing or voice impairment.

Chemotherapy consisted of either carboplatin and etoposide or cisplatin and etoposide, given every 3 weeks for 4 cycles. Radiotherapy commenced with the second cycle of chemotherapy and was delivered using one of the following established protocols: 40Gy in 15 fractions over 3 weeks (1 fraction per day); 45Gy in 30 fractions over 3 weeks (2 fractions per day; BD); or 50Gy in 25 fractions over 5 weeks (1 fraction per day).

Data Collection

Data were collected on patients at four time points: prior to commencement of radiotherapy; 1 month post-completion of radiotherapy; 3 months post-completion of radiotherapy; and 6 months post-completion of radiotherapy. Study data were entered into and managed using the REDCap electronic data capture tool hosted at [removed for blind review][12].

Videofluoroscopic swallowing studies (VFSS; also referred to as the modified barium swallow) were used to analyse swallowing function. Swallowing images were recorded using the Philips Allura FD20 X-ray system and converted to .avi format for analysis. During the VFSS participants completed the following while seated in the lateral position: 3 x 5ml and 1 x 10ml liquid, 3 x 5ml semi-solid (pureed fruit), and a piece of solid food (½ cracker). All boluses were mixed or coated with barium to allow clear visualisation through the oral cavity, pharynx and upper oesophagus. An anterior-posterior view was also taken while the participant swallowed 5ml of semi-solid, to observe the presence of oesophageal motility disorder(s). Measures taken from the VFSS images were: (i) aspiration of liquids, using the Penetration-Aspiration Scale[13], an 8-point scale ranging from 1 (material does not enter the airway) to 8 (material enters the airway, passes below the vocal folds, and no effort is made to eject), (ii) overall swallow function of liquids, semi-solids and solids, using the Swallowing Performance Status Scale (SPSS)[14], a 7-point rating scale which takes into account how safely and effectively the bolus moves through the oral cavity and pharynx, and (iii) oesophageal motility disorder(s), rated as present or absent.

Oral intake was measured using the Functional Oral Intake Scale (FOIS) which rates the degree to which a person needs to modify the texture of food they eat and/or requires tube feeding. The scale ranges from 7 (total oral intake with no restrictions) to 1 (nothing by mouth) and has demonstrated validity and reliability[15].

Patient-reported swallowing and voice problems were measured using the Dysphagia Handicap Index (DHI)[16] and the Voice Handicap Index (VHI)[17] questionnaires respectively. The DHI comprise 25 items with

three response options (never; sometimes; always) and one global item, and the VHI comprises 30 items rated on a 5-point Likert-type scale.

The University of Washington QOL questionnaire (UW-QOL)[18] was used to measure health-related QOL. It includes 16 questions regarding pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety.

Demographic and treatment-related data were collected from the medical records. Data included: gender, age, nutritional status (using the Patient-Generated Subjective Global Assessment [PG-SGA][19]), radiotherapy regimen, chemotherapy agent, mean radiation dose to the oesophagus, maximum radiation dose to the oesophagus, oesophagitis (worst CTCAE score recorded and duration of worst CTCAE score recorded), required admission for neutropenia and delivery of prophylactic cranial irradiation (PCI).

Statistical Analysis

Descriptive statistics were used to summarise the demographic and clinical characteristics of the participants. These included counts and percentages for nominal valued variables; and means and standard deviations or medians, interquartile ranges and ranges for continuous valued variables.
For the purposes of analysis, the global item scores of the DHI were rated as normal (score of 1), mild (score of 2 or 3), moderate (score of 4 or 5) or severe (score of 6 or 7)[20].

RESULTS

Figure 1 shows the patient flow and data availability from recruitment to final data collection at 6 months post treatment. From a potential cohort of 34 patients diagnosed with limited-stage SCLC, complete – or near complete – data were collected on 12. Figure 1 outlines the reasons for non-participation or dropout and highlights the challenges of recruiting to studies with less common cancer types, as well as recruiting to supportive care research, particularly in the period immediately following diagnosis and prior to commencing treatment. Although we had intended to recruit 30 participants in total, the study was closed early as time and financial limitations did not allow for ongoing recruitment. Table 1 outlines the demographic and treatment characteristics for the 12 study participants.

INSERT FIGURE 1

INSERT TABLE 1

Swallow Function

No patient was observed to aspirate on VFSS either before or after treatment. SPSS scores were 1 (normal) or 2 (within functional limits) at all times, for all liquid, semi-solid and solid boluses (see Appendix A).

Three patients exhibited oesophageal motility disorders before treatment. These problems persisted post-treatment for those three patients, and there were an additional three patients who also exhibited these disorders at various times post-treatment – one patient at 3 months post-treatment only, one patient at 1 and 3 months post-treatment and one patient at all three post-treatment time points (see Appendix A).

Oral Intake

Table 2 outlines the oral diet patients were eating at each time point according to FOIS score. All patients were managing a normal or near normal diet pre-treatment. The most marked limitations occurred at 1 month post-treatment when one patient remained feeding tube dependent (score 3), two managed an oral diet of a single consistency (score 4), and two managed an oral diet with multiple consistencies, but requiring special preparation (for example, only pureed food or very soft with extra sauces; score 5). Oral intake returned to a normal or near normal consistency at 3 and 6 months post-treatment with the exception of one patient who remained limited to a special preparation diet (score 5).

Treatment-related toxicity data revealed that all five patients who required significant modification of their diet at 1 month post-treatment (scores 3-5) had experienced Grade 3 oesophagitis and required hospital admission for neutropenia during treatment. Nevertheless, pain had completely resolved for all patients at 1 month, other than one who remained feeding tube dependent due to persistent pain. Of the seven patients eating a normal or near-normal diet at 1 month post-treatment (scores 6-7) all had experienced a maximum of Grade 1-2 oesophagitis during treatment and had no diagnosis of neutropenia. There were no relationships apparent between FOIS scores and treatment data at 3 and 6 months post-treatment, nor was there an apparent relationship between FOIS score and BD treatment or PCI.

INSERT TABLE 2

Patient-Reported Swallowing Problems

For all domains – physical, functional and emotional – scores were worst at 1 month post-treatment and had improved by 6 months but not back to baseline (pre-treatment) levels (see Table 3). Scores from the global item of the DHI (a rating that "best describes the severity of your swallowing problem") identified that two patients reported moderate or severe swallowing difficulties at baseline, three (different) patients reported moderate or severe swallowing difficulties 1 month post-treatment, but these difficulties were reported as no more than mild at follow-up assessments for those patients, and three (different) patients reported a new onset of moderate or severe swallowing difficulties at 3 and 6 months post-treatment (see Figure 2).

INSERT TABLE 3

INSERT FIGURE 2

Exploration of treatment-related toxicity data revealed that patients who reported any swallowing difficulties at 1 month post-treatment (mild, moderate or severe) had all received a mean radiation dose to the oesophagus of 15.7Gy or more, and a maximum dose of 42Gy or more. In contrast, those who reported no swallowing difficulties at 1 month all received mean and maximum radiation doses to oesophagus less than these doses. The relationship between DHI scores and treatment data was no longer apparent at 3 and 6 months post-treatment. There were no obvious relationships between DHI scores and oesophagitis, neutropenia, BD treatment or PCI.

Patient-Reported Voice Problems

Patient-reported voice problems were minimal, with median scores of 0 or 1 ('never' or 'almost never' experience the problem) at all time points for the functional, physical and emotional domains (see Appendix B). The most frequent or highest scores were given to questions rating the statements: "My voice sounds creaky and dry", "I run out of air when I talk" and "The sound of my voice varies throughout the day". The greatest spread of scores occurred at 1 month post-treatment although patients continued to report problems (though to a lesser degree) across voice-related physical, functional and emotional domains at 3 and 6 months post-treatment.

Health-Related Quality of Life (QOL)

Scores for all QOL domains varied at all time points with no clear patterns evident. See Appendix C for the scores for each symptom scale presented as per UW-QOL v4 guidelines.

Nutritional Outcomes

Three patients were moderately malnourished at baseline (PG-SGA category B). PG-SGA scores were worst at 1 month post-treatment with a median point score of 8, indicating the need for nutrition intervention, bordering on a 'critical need for improved symptom management and/or nutrition intervention' (see Table 4). Scores at 1 month post-treatment also identified that 50% of patients were moderately malnourished (PG-SGA category B), with the remaining 50% being well nourished (PG-SGA category A). No patient was identified as being severely malnourished (PG-SGA category C) at any point. Exploration of treatment-related toxicity data revealed that patients who were moderately malnourished and in need of nutrition intervention at 1 month post-treatment had all received a mean radiation dose to oesophagus of 15.7Gy or more, and a maximum dose of 42Gy or more.

INSERT TABLE 4

DISCUSSION

This study is the first time that detailed functional and patient-reported data on swallowing and voice outcomes in patients with SCLC has been reported. Although patient numbers were small due to challenges recruiting from this uncommon patient cohort, the prospectively collected data is comprehensive and has implications for the multidisciplinary management of these complex patients.

A small number of patients were identified or reported as having problems at baseline, suggesting that issues such as oesophageal dysmotility (n=3), moderate-severe patient-reported dysphagia (n=2) and moderate malnourishment (n=3) may be caused by the cancer itself. Nevertheless, in our cohort the majority of problems were recorded post-treatment (particularly at 1 month post), implicating chemoradiotherapy as the cause, rather than the cancer itself.

Detailed assessment of swallowing function using VFSS identified that in our cohort swallowing was safe and effective at all times. There is limited data in the literature regarding the prevalence of dysphagia in patients with lung cancer. In a study of 72 patients with advanced lung cancer (8% of whom had SCLC) receiving palliative chemotherapy, 18% identified as having dysphagia on the self-rated EAT-10 tool[21]. This could represent an over-estimation, as some patients had neurological co-morbidities or a history of radiotherapy to the head and neck, or it could be an under-estimation, as only outpatients undergoing (single modality) palliative chemotherapy were recruited. A small number of subsequent studies have attempted to identify the prevalence of dysphagia in heterogenous cohorts of cancer patients who were during or post cancer treatment (including those with lung cancer, but without detail regarding NCSLC vs

SCLC). Kenny et al.[5] found that of the 59 lung cancer patients in their total cohort of 385 oncology patients, 25% had dysphagia as confirmed through clinical evaluation. In a recent study from our centre, 78% of lung cancer patients reported dysphagia for solids and 33% reported dysphagia for liquids[22]. While these symptoms were usually rated as mild, responses to the statement "I have trouble eating certain solid foods" were often severe. As all of these prior studies have been cross sectional, it is not known whether the problems identified or reported were cancer related, or treatment related. The low prevalence of oropharyngeal dysphagia in this current study – the majority of which appears to be treatment related – may be an artefact of the small sample and selection bias; in particular, our careful exclusion of patients with dysphagia-associated comorbidities.

Oral intake limitations, patient-reported swallowing function and nutritional status were most compromised at 1 month post-treatment, even though oropharyngeal swallow function had been identified as safe and normal (or near normal). For the patient with the most significant swallowing issues at this time, their UW-QOL pain score was 'moderate', but for all other participants there was no clear association between swallowing complaints and reported levels of pain, indicating an alternative cause to their issues. It is possible that residual sensory changes following the resolution of treatment toxicities contributed to these patients' diet limitations, reports of dysphagia symptoms and compromised nutritional status. The relationship between radiation dose to the oesophagus and acute oesophagitis is well-established[23], as is the relationship between oesophageal dose and nutritional status[24]. More recently, neutropenia has also been identified as a risk factor for higher grades of acute oesophagitis[7,25]. While these studies refer to NSCLC, it is likely that results can be extrapolated to patients receiving chemoradiation for SCLC. In the current study, limitations in oral intake, patient-reported dysphagia and compromised nutritional status at 1 month post-treatment were only observed in patients who had received a higher oesophageal dose, as well as those who had experienced Grade 3 oesophagitis and neutropenia. It therefore seems plausible that more severe toxicities and mucosal damage contribute to residual sensory changes, even after those toxicities have resolved, and this hypothesis warrants further investigation. Reducing this risk requires ongoing efforts to optimise mucosal protection during radiotherapy, and approaches such as IMRT that keep the oesophageal dose as low as reasonably achievable are essential. Acknowledging that the oesophageal doses within our study were within acceptable constraints, supporting these patients through referral to a Speech Pathologist (for comprehensive swallow evaluation, advice and, where indicated, instrumental assessment) and a Dietitian (for optimisation of nutritional support) are recommended. Interestingly, there was no apparent relationship between the three patients who received BD treatment and their treatment-related toxicities or swallowing outcomes. As the BD treatment regimen is typically associated with

increased rates of oesophagitis[10] our small numbers may have failed to identify a relationship, so treatment regimen should be taken into account in future larger studies.

At 3 and 6 months post-treatment, the potential influencing factors to patients' perceptions of swallowing problems are less clear. Indirect factors such as prophylactic cranial irradiation (PCI), associated de-conditioning and sarcopenia, functional decline and fatigue could all contribute[3-5,26]. While 7 of our patients received PCI, the timing of this did not systematically coincide with swallowing data collection, and there was no clear association between this treatment and reported swallowing problems. Future studies with larger numbers would help identify whether such an association exists.

The discordance between observed and reported dysphagia has been well-documented in the head and neck cancer literature[27]. Across all cancer types, a modest agreement at best has been shown between NCI CTCAE ratings and patient-reported outcomes[28]. In NSCLC patients specifically, a discrepancy between clinician-rated dysphagia (based on the NCI CTC) and patient-reported QOL and pain measures has also been reported[29]. This is the first time that a discrepancy has been identified between physiological swallow function (using VFSS) and patient-reported dysphagia in lung cancer (either NSCLC or SCLC). The value of instrumental assessment – specifically VFSS – cannot be understated. These tools can identify functional problems but they can also differentiate between a physiological problem and other issues, such as residual sensory changes. These findings highlight the importance of measuring different aspects of swallowing in dysphagia on all populations, including lung cancer. There are also implications for the clinical management of patients following chemoradiotherapy, as identifying the nature and extent of dysphagia will be highly dependent on the tools used. The subsequent management of dysphagia relies on this accurate classification of the problem, and assists in patient education and support approaches such as speech pathologists and dietitians working together to optimise oral intake and nutritional status.

Voice problems in our cohort were minimal overall. Previous research investigating lung cancer patients reported that 90% of them were perceptually dysphonic, however only 27.5% were concerned about their voice[30]. This again highlights the discrepancy between observed and reported problems; indicating an application to dysphonia as well as dysphagia. The minimal problems found in our study may reflect this discrepancy as we only collected data on patient-reported voice problems without any instrumental or clinician-rated validation.

The small numbers in this study presented a number of limitations. We were unable to characterise the prevalence of dysphagia in SCLC or to robustly explore the potential associations between dysphagia and radiation treatment factors. Nevertheless we were able to demonstrate the feasibility of objective dysphagia assessment using VFSS and the ability to collect data across a variety of functional and patient-reported domains. Further research is now required to better understand the apparent discrepancy between observed and reported dysphagia in this population, and to investigate the potential link between mucosal damage and its impact on swallowing function or sensory changes.

CONCLUSIONS

This study is the first time that patient-reported dysphagia following chemoradiation for SCLC has been reported and it has been identified despite an absence of objectively impaired swallow function. Patient-reported dysphagia is multi-factorial and our findings suggest that treatment factors such as radiation dose to the oesophagus and oesophagitis may all have an impact. Despite our best efforts, side effects from intensive treatment for SCLC are unavoidable. Acknowledgement and early identification of patient reported dysphagia in SCLC patients may enable timely, appropriate support and intervention. .

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Table 1: Patient and treatment characteristics

Characteristic	n	%
Gender		
Male	5	42
Female	7	58
Age		
Median (range)	67.5 (51 – 79)	
Radiotherapy treatment		
40Gy / 15 fractions	7	58
45Gy / 30 fractions[#]	3	25
50Gy / 25 fractions	2	17
Chemotherapy		
Carboplatin/etoposide	10	83
Cisplatin/etoposide	2	17
Mean dose to oesophagus (Gy)		
Median (range)	18 (10 – 32)	
Maximum dose to oesophagus (Gy)		
Median (range)	42 (25 – 46)	
Admission for neutropenia during treatment		
Yes	5	42
No	7	58
Prophylactic Cranial Irradiation (PCI)		
Yes	7	58
No	5	42
Time between radiotherapy and PCI (months)		
Median (range)	3 (3-7)	

[#]BD treatment

Table 2: Functional Oral Intake Scale scores by timepoint

		Timepoint							
		Baseline (n=12)		1 month (n=12)		3 months (n=12)		6 months (n=10)	
FOIS rating		n	%	n	%	n	%	n	%
Tube dependent									
1	Nothing by mouth								
2	Tube dependent with minimal attempts of food or liquid								
3	Tube dependent with consistent oral intake of food or liquid			1	8				
Total oral intake									
4	Total oral diet of a single consistency			2	17				
5	Total oral diet with multiple consistencies, but requiring special preparation			2	17	1	8	1	10
6	Total oral diet with multiple consistencies, without special preparation, but with specific food limitations	3	25	3	25	3	25	3	30
7	Total oral diet with no restrictions	9	75	4	33	8	67	6	60

Table 3: Dysphagia Handicap Index scores by subscale for patient-reported swallowing problems

	Timepoint			
Subscale/Statistic	Baseline (n=12)	1 month (n=10)	3 months (n=10)	6 months (n=10)
Physical (max 36)				
Median	1.6	3.8	5	2
Interquartile range	0 to 6.4	2.5 to 6.8	1.5 to 6.3	1 to 5
Range	0 to 9	0 to 10	1 to 9	0 to 10
Functional (max 36)				
Median	0	8	3	2
Interquartile range	0 to 5.5	0.8 to 10.3	0.5 to 5	0 to 4.4
Range	0 to 11	0 to 18	0 to 7	0 to 9
Emotional (max 28)				
Median	0.5	3	2	1
Interquartile range	0 to 4.5	0 to 7.3	0 to 2	0 to 2.7
Range	0 to 6	0 to 10	0 to 5	0 to 7

Lower scores represent better outcomes

Table 4: PG-SGA scores indicating nutritional status by timepoint

	Timepoint							
	Baseline (n=11)		1 month (n=12)		3 months (n=10)		6 months (n=8)	
	n	%	n	%	n	%	n	%
Total PG-SGA score								
Median	5		8		3.5		4.5	
Interquartile range	3 to 9		3 to 11		2 to 6		2 to 10	
Range	1 to 10		2 to 15		2 to 10		2 to 11	
Global PG-SGA rating								
A (well nourished)	8	73	6	50	8	80	6	75
B (mod malnourished)	3	27	6	50	2	20	2	25

PG-SGA scores indicate level of intervention required: 0-1, no intervention; 2-3, education required; 4-8, requires intervention; >9, critical