Retrospective cohort examining the relationship between changes in nutritional status, as measured by the abridged Patient Generated Subjective Global Assessment, and changes in quality of life in people with cancer

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ABSTRACT

Malnutrition, present in approximately 40% of the general cancer population, negatively impacts quality of life (QOL) and treatment outcomes. Most nutrition screening and/or assessment tools are of limited clinical use as they omit nutrition impacting symptoms and physical performance known to be associated both with malnutrition and QOL. The purpose of this thesis was to evaluate whether differences in nutritional status, as measured by the abridged patient-generated subjective global assessment (aPGSGA), were able to predict differences in QOL, physical performance and short-term survival (< 3 y) in cancer patients. The Edmonton Symptom Assessment System (ESAS) was used to measure QOL and the 6-minute walk test (6MWT) to measure physical performance. Two-hundred and seven adult patients attending the cancer rehabilitation and cachexia clinic at the McGill University Health Centre between November 2013 and September 2015 were included. One-hundred and thirteen patients with information over four clinic visits formed a subgroup for repeated measures analysis of ESAS and aPGSGA score. Cross-sectional analyses (n = 207) included Pearson's correlations, multiple regression, one-way ANOVA and Kaplan-Meier survival analysis. Repeated measures analyses (n = 113) included repeated measures ANOVA and mixed models. Significance was accepted at $p < 0.05$. Total aPGSGA score was 9.6 ± 6.3 at the first visit with nutrition impact symptoms comprising 61% of the total score. A moderate strength correlation between total aPGSGA and ESAS scores ($r = 0.478$, $p < 0.001$) was observed at baseline. Baseline aPGSGA score predicted baseline ESAS score ($p < 0.001$) while controlling for age, diagnosis, ethnicity and sex. There was a difference of 71 m in 6MWT between highest and lowest aPGSGA scores ($p = 0.011$). In the 113 patients with full data total aPGSGA scores improved from 9.4 ± 5.8 to 5.3 ± 3.8 by the fourth visit ($p < 0.001$). Total aPGSGA score predicted changes in total ESAS score ($p < 0.001$),

with every 1 point change in aPGSGA score resulting in a corresponding change of 0.972 in total ESAS score over the study period. There were no significant differences in survival according to aPGSGA categories. Nutrition status, as measured by the aPGSGA, is able to detect differences in physical performance and QOL at baseline and predicts changes in QOL over time. Future studies are needed to further explore the impact of nutrition on both survival and cancer treatment outcomes.

RÉSUMÉ

La dénutrition, présente chez environ 40% des patients atteints de cancer, peut avoir un impact sur la qualité de vie ainsi que sur le résultat des traitements des patients suivis en oncologie. Le dépistage nutritionnel actuel tient compte des variations pondéral ainsi que de l'appétit. Toutefois, il ne considère pas les facteurs altérant l'état nutritionnel et la performance physique alors que ceux-ci sont bien connus pour avoir un lien avec la dénutrition et la qualité de vie des patients. L'objectif de cette étude était d'évaluer si l'Autoévaluation Nutritionnelle Globale Subjective – version abrégée (ANGSa) pouvait prévoir des différences au niveau de la qualité de vie, du fonctionnement physique et à la survie à court terme (< 3 ans) des adultes atteints de cancer. L'échelle d'évaluation des symptômes d'Edmonton (EESE) a été utilisée afin de mesurer la qualité de vie et le test de marche de 6 minutes afin de mesurer la performance physique. Deux-cent sept patients suivis à la clinique de réhabilitation et de cachexie du Centre Universitaire de Santé McGill ont été recrutés entre Novembre 2013 et Septembre 2015. Cent treize patients, suivis pendant au moins 4 rencontres, ont été considérés pour des analyses de mesures répétées du questionnaire de EESE et ANGSa. Le score global du ANGSa était 9.6 ± 6.3, avec la majorité du résultat (61%) provenant des facteurs altérant l'état nutritionnel (FAÉN). Des analyses transversales (n = 207) telles que des corrélations de Pearson, des régressions multiples, une analyse de variance à un facteur (ANOVA) et l'estimateur de Kaplan-Meier (fonction de survie) ont été réalisées. Des analyses de mesures répétées (n = 113) ont été faites avec le test de variances de mesures répétées ANOVA et des modèles mixtes. Une probabilité de $p < 0.05$ était considérée comme significative. Une corrélation entre l'ANGSa et EESE de puissance modérée ($r = 0.478$, $p < 0.001$) a été observée. Le pointage de l'ANGSa au premier suivi prédisait le pointage de l'EESE ($p < 0.001$) lorsque l'âge, le diagnostic, l'ethnicité et le

sexe du patient étaient contrôlés. Chez les 113 patients qui ont été suivis à au moins quatre suivis, le pointage de ANGSa s'est amélioré de 9.4 ± 5.8 to 5.3 ± 3.8 à la quatrième visite ($p < 0.001$). Une différence de 71 m a été observée entre le pointage le plus élevé de ANGSa (≥ 9) et le moins élevé (0 -1) pour le test de marche de six minutes ($p = 0.011$). Il n'y avait pas de différence notable de survie entre les catégories d'ANGSa. Le score totale d'ANGSa a prédit des changements dans l'EESE ($p <0.01$), avec chaque changement de 1 point d'ANGSa résultant en un changement correspondant de 0.972 dans le score d'EESE au cours de la période d'étude. Le statut nutritionnel, tel que mesuré par le ANGSa, était capable de détecter une différence au niveau de la performance physique ainsi que la qualité de vie au premier suivi et aussi de prédire les changements de qualité de vie au fil des suivis. De futures études seront nécessaires pour examiner l'impact de l'état nutritionnel sur la survie et sur les traitements contre le cancer.

AUTHOR'S CONTRIBUTIONS

J. di Tomasso is the primary author and major contributor of this thesis. He was involved in the conception and design of the study. J. di Tomasso collected information for the study from medical records, compiled it in a secure database and prepared the information for analyses. J. di Tomasso performed his own statistical analyses for the study, verified by a McGill statistician consultant.

Dr. Antonio Vigano is the attending physician of the McGill University Health Centre's cancer rehabilitation and cachexia clinic as well as director of the McGill Nutrition and Performance Laboratory. He was involved in conception and design of the study as well as editing of the manuscript and is the principle investigator as well as primary supervisor of J. di Tomasso.

Hope Weiler is the director of the Mary Emily Clinical Nutrition Research unit. Dr. Weiler as co-supervisor of J. di Tomasso, was responsible for coordinating the design of the present study and the editing of the manuscript.

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ABBREVIATIONS

6MWT: six-minute walk test

ANOVA: analysis of variance

aPSGA: abridged Patient Generated Subjective Global Assessment

BMI: body mass index

CON-CPG: Canadian Oncology Nutrition Clinical Practice Guideline (initiative)

ESAS: Edmonton Symptom Assessment System

ECOG: Eastern Cooperative Oncology Group

HGS: hand grip strength

ICD-10: 10th revision of the International Classification of Diseases

MNA: Mini Nutritional Assessment

MST: Malnutrition Screening Tool

MUHC: McGill University Health Centre

NIS: nutrition impacting symptoms

PGSGA: Patient Generated Subjective Global Assessment

PRO: patient-reported outcome

ROC: receiver operator curve

QOL: quality of life

SGA: Subjective Global Assessment

UNITS AND CONVERSATION FACTORS

Units

Kg: kilogram

h: hour

kcal: kilocalorie

m: meter

y: years

1.0 LITERATURE REVIEW

1.1 Introduction

The importance of nutrition is undisputed in oncology care. Significant weight loss (≥ 10% of total bodyweight over 6 months) is associated with both decreased survival and increased cancer recurrence [1-3]. Decreased food intake (≤ 1500 kcal/day) is associated with decreased physical function as measured by the Karnofsky Performance Scale [4]. Patients found at nutritional risk according to the Patient Generated Subjective Global Assessment (PGSGA) experience more frequent and longer hospital admissions [5]. Increasingly, studies show a strong positive association between worsening malnutrition and deteriorating health-related quality of life [6], with malnutrition acting as a major source of distress in cancer patients. While the prevalence of cancer-related malnutrition varies among countries, institutions, and cancer diagnoses, it is generally reported to approximate 40% [7].

To date, there is no consensus on how to systematically assess and monitor nutrition status in adult cancer patients. Dietitians, who are experts in nutrition assessment, cannot assess all cancer patients due to limited manpower [8]. Many of the nutrition screening and/or assessment tools available only measure weight changes and appetite [9]. These may be of little clinical value for the health professional working with cancer patients as they do not assess physical performance or nutrition impacting symptoms (NIS) (ex: nausea, vomiting, and pain) known to be associated not only with nutrition status, but also with survival, and quality of life [10]. A tool encompassing these dimensions (weight loss, food intake, NIS, and physical performance) could be used to simultaneously assess nutrition status as well as measure the effectiveness of nutrition interventions.

The use of the Patient Generated Subjective Global Assessment (PGSGA) has received widespread support from nursing and dietetic regulatory bodies [11,12]. The PGSGA is both a screening tool, able to rapidly identify malnourished patients and an assessment tool, used to evaluate nutritional status. The abridged Patient Generated Subjective Global Assessment (aPGSGA), a shortened version of the PGSGA which eschews the clinical (objective) evaluation by the health professional (i.e. disease state, metabolic demand, physical assessment), has been shown to be highly reliable and easy to implement [13]. Baseline aPGSGA scores predict certain outcomes in people with advanced cancer, such as survival and hospitalization [14]. Additionally, worsening of PGSGA scores over time are positively associated with worsening quality of life [15]. ***Therefore, the objective of this thesis is to evaluate whether nutritional status, as measured by the aPGSGA, is able to detect differences in QOL, physical performance and short-term (< 3 y) survival in people with cancer and; whether changes in nutritional status over time are able to predict changes in QOL and; to explore the value of clinic pathways in detecting differences in (<3 y) short-term survival.***

1.2 History of the aPGSGA

The origin of the aPGSGA can be traced back to the work of Detsky et al. on the Subjective Global Assessment (SGA) [16-18]. While not the first to perform nutrition assessments in hospitalized patients, Detsky et al. recognized that clinical information obtained during routine practice might be as effective as traditional measures. To this end, standard clinical information is separated into two sections with five features each, named "history" and "physical assessment". The history section includes: 1) weight change 2) change in food intake 3) gastrointestinal symptoms lasting at least two weeks 4) functional capacity and 5) disease state

and associated metabolic demand. The five features of the physical assessment target depletion of fat and muscle stores, notably: 1) loss of subcutaneous fat 2) muscle wasting 3) ankle edema 4) sacral edema and 5) ascites. Clinicians then use this information to assign a SGA rank categorizing a patient's nutrition status as either A (well-nourrished), B (moderate or suspected malnutrition) or C (severe malnutrition). The authors openly state that the assignment of this rank is subjective and there is no numerical weighing of each feature. Instead, clinicians are to focus on weight change, food intake and loss of muscle and fat to obtain SGA rank. The SGA has been found to be both accurate and reliable and continues to be used to this day [19].

Following on the expertise of Detsky, Ottery (1996) sought to improve the utility and ease of implementation of the SGA. Ottery (1996) preserved the original aspects from the SGA but divided it into two sections, one to be self-completed by patients and the other for a clinician-administered physical exam. This tool was named the Patient Generated Subjective Global Assessment (PGSGA) and is the true predecessor to the aPGSGA. The patient-completed portion is broken into four sections (weight history, food intake, symptoms and performance status), framed to the patient's perspective at a sixth to eighth grade reading level. The clinician-administered portion includes an assessment of metabolic demand, disease status, muscle and fat reserves as well as the presence or absence of edema. This second portion of the tool results in a letter rating similar to that of the SGA. It was not until later that a scoring system was added to the patient-completed portion of the test [20]. The total score corresponds to "triage recommendation ranges", describing the urgency for a nutrition intervention [21]. The PGSGA was also one of the first tools to be translated into a variety of different languages (now 21) to be used by clinicians and patients around the world [22].

Following the success of the PGSGA, a need for an abbreviated self-administered form was identified in view of high patient case-loads for all health care professionals. The aPGSGA, which eschews the physical exam in favour of brevity, relies on the patient reported component alone. It is thus a one-page questionnaire divided into four sections, or boxes, completed by patients. These boxes investigate various dimensions of malnutrition, namely: weight loss (Box 1), food intake (Box 2), NIS (Box 3), and functional status (Box 4). Scores obtained from each of the four boxes are totalled, ranging from 0 (best) to 36 (worst), in order to triage patients according to nutritional risk. Patients with a score of 0-1 are considered to be at no risk for malnutrition whereas patients scoring ≥ 9 demonstrate a critical need for nutrition interventions. This combined score has been shown to have high prognostic significance in people with advanced cancer (stages III/IV) [14], and was the scoring system used in this thesis research.

1.3 Box 1 of the aPGSGA: weight loss in people with cancer

Weight loss is often one of the earliest signs of malnutrition in people with cancer and can occur before overt symptoms appear [23]. The notion that weight loss impacts patient outcomes is not a new concept nor is it unique to people with cancer [24,25]. In people with cancer, involuntary weight loss may be driven by anorexia, metabolic or endocrine changes, presence of NIS, inflammatory response and fatigue [26]. If left unabated involuntary weight loss may result in decreased chemotherapy tolerance in middle-aged adults (median age 63) [27] and the elderly (70 years and older) [28].

The experiences of elderly cancer patients have been receiving more attention as of late, particularly in the area of malnutrition. A study of hospitalized elderly people with cancer found 71% of patients had experienced ≥ 10% weight loss and that 44% were underweight (body mass

index, BMI, < 20 kg/m^2) [29]. Elderly outpatients experience strikingly similar results (age ≥ 65 y), where approximately 40% of patients lose 10% or more of their usual bodyweight over 3 months [30].

While weight loss (≥ 5% over 6 months) is independently prognostic of survival, it often leads to detrimental losses of both skeletal muscle and function, worsening outcomes [31]. This phenomena, called sarcopenia, is defined as loss of muscle, strength and physical performance [32]. While traditionally associated with aging (primary sarcopenia), it is now often seen in the context of cancer and its treatment (secondary sarcopenia), as well as other chronic illness [32]. Sarcopenia is prevalent in people with cancer, particularly men [33]. Importantly, it is seen across all weight categories (underweight to obesity) and leads to poor outcomes [33]. While the aPGSGA does not assess the presence or absence of sarcopenia it does monitor relative weight changes over time regardless of obesity or underweight conditions upon presentation. Subjective recall of weight is closely associated with actual weight ($r > 0.90$; $p < 0.001$) [34] and is more accurately estimated than both height and BMI [35]. To avoid compounding errors in estimation of BMI the aPGSGA considers short-term (<1 year) weight recall which is highly accurate and long recognized as a clinically useful measure [36].

Weight loss in people with cancer is associated with QOL. For instance, weight loss is associated with lower global QOL as well as survival in cancer patients receiving palliative chemotherapy [37]. A multicentre, retrospective study of 1652 maxillofacial cancer patients examined the effects of a variety of physiological and psychological factors on diet. Gellrich et al. divided patients into three groups: patients who gained weight; patients who maintained their weight; and patients who lost weight. It was discovered that patients who lost weight had worse outcomes overall. Specifically, Gellrich et al. found those who lost ≥ 10 kg were most likely to

have body image issues, be on a modified textured diet, suffer depression, anxiety, hopelessness and lower global QOL [38]. Furthermore, among weight losing patients, those who lost ≥ 10 kg had worse outcomes than people who lost less than 10 kg; unfortunately data was not presented as a percentage of overall bodyweight, as is necessary to enable precise clinical interpretations. Authors of a three-year prospective, longitudinal study of 49 head and neck cancer patients asked a similar yet different question: can health-related quality of life predict weight loss in people with cancer [39]? The authors observed that weight loss ≥ 10% already present at diagnosis was associated with lower health-related QOL from diagnosis to three-year follow-up [39]. In addition, health-related QOL (particularly fatigue) was predictive of malnutrition and weight loss in this population. The aPGSGA is an appropriate tool for weight monitoring as it records weight history (current weight, one-month weight and six-month weight) and provides a weighted score for severity of weight loss.

1.4 Box 2 of the aPGSGA: food intake

Assessing food intake is of utmost importance as people with cancer are frequently hypermetabolic without a compensatory increase of energy intake [40]. Decreased food intake is a risk factor for mortality in hospitalized patients, including cancer patients [41]. Unsurprisingly, energy and protein intake is associated with QOL, especially in people with head and neck cancers [42]. Energy intake and QOL also improve following nutrition interventions [43]. Use of the aPGSGA allows for routine assessment of a patient's intake and thus the opportunity for earlier nutrition intervention. Nutrition interventions in people with cancer have been shown to reduce or reverse weight loss, preserve lean body mass [44] and improve food intake [45].

A patient's food intake can be used as an indicator of treatment tolerance and disease progression. In people with head and neck cancers protein intake decreased more in people with stage III/IV disease (median reduction of 89 g/day) than those with stage I/II disease (median reduction of 0.8 g/day, $p < 0.001$) during the study's follow-up period [42]. The patients with stage III/IV disease also had the most significant decrease in energy compared to their usual, pre-disease intake ($p < 0.002$) [42]. Similarly, Ravasco et al (2003) noted that self-rated health status, or, "the patient's perception of overall health" was strongly associated with overall energy and protein intake [43]. A multivariate analysis considering a variety of nutritional factors and symptoms found that only energy and protein intake was associated with a patient's self-rated health status [43]. A measure of food intake is a critical component of any nutritional assessment and even a subjective, self-assessment such as the aPGSGA can help direct interventions.

Dietitians have developed evidence-based guidelines directed at improving nutritional status in people with cancer which have been shown to be more effective than standard nursing care at improving energy and protein intake [46]. In this study, Isenring et al. observed that patients receiving weekly dietitian-led nutrition interventions throughout their radiotherapy treatment for head and neck cancer actually increased their protein and energy intake whereas the standard care group saw decreases in their intake. Following a nutrition intervention, patients with esophageal and stomach cancers (considered high risk of malnutrition) had a median increase of energy consumption of approximately 275 kcal/day; patients with colorectal and head and neck cancers experienced an increase of 410 kcal and 510 kcal/day respectively ($p < 0.03$) [43]. Weekly nutrition consulting by a dietitian along with supplementation in patients receiving chemotherapy resulted in a median increase of protein intake of 1.1 to 1.4 g/kg bodyweight per day and energy intake from 26 to 33 kcal/kg bodyweight per day, reaching minimum requirements for both

energy and protein [45]. However, not all interventions have proven successful in this regard. For example, biweekly nutrition interventions over a five-month period to patients receiving chemotherapy resulted in a daily increase of energy intake by a mean of 239 kcal and 10 g of protein as compared to controls, but did not result in improvements in clinical outcomes [47]. In this study the treatment group approached recommend energy targets of 1.5 times the basal energy expenditure as calculated using the Harris-Benedict equation, but the majority of patients did not meet this target, which could explain the negative findings. In contrast, a study with three treatment arms (nutrition counselling, supplementation with usual diet and usual diet alone) found nutrition counselling to be the most effective in increasing food intake; the group receiving nutritional counselling had improved survival, improved recurrence-free survival, less late radiotherapy toxicity, higher QOL and the highest oral intake [48]. The aPGSGA gives dietitians a means of assessing efficacy of their inventions over time through both the food intake score and overall aPGSGA score.

1.5 Box 3 of the aPGSGA: nutrition impact symptoms

The aPGSGA effectively captures how nutrition status is impacted by the number, type, and duration of symptoms. The number of symptoms present has been linked to nutrition status in cancer patients [49], and patients with multiple NIS have been found to weigh less and requiring more frequent medical interventions [50]. Weighted scores capture the concept that some symptoms, such as loss of appetite and pain, more acutely impact nutrition status and other clinical outcomes [51,52]. Asking patients to report only on recent symptoms ($\leq$ 2 weeks) can be traced back to Jeejeeboy et al (1987), who reported that persistent symptoms have a much greater impact on a patient's nutritional status than transient or previous symptoms [16]. The importance of

symptom assessment cannot be understated. Nutrition impacting symptoms contribute 24 of a maximum of 36 points to the overall aPGSGA score.

A prospective longitudinal survey of 219 oncology patients showed a weak association between PGSGA score and lower QOL at three distinct time points, r = -0.224, -0.350, -0.288, $p<0.05$. Total symptoms were found to have a moderate association between QOL at these same time points, r = -0.350, -0.406, -0.353, $p<0.05$ [10]. Similarly, Ravasco et al. (2004) found that malnutrition was associated with poorer QOL and worsening symptoms, such as anorexia, fatigue and diarrhea [42]. Both studies found NIS to be predictive of physical performance status, where people with worse symptoms are more likely to have lower performance. Tong et al. (2009) found no significant associations between NIS or PGSGA score with chemotherapy tolerance, but attributes these findings to a lack of power. Importantly, only half of the patients who were "at critical need for nutrition intervention" received a dietetic consultation, illustrating the dire need for systematic nutrition assessment in this population [10].

The type of symptoms experienced by patients also impacts the risk of malnutrition. It is for this reason that the list of gastrointestinal symptoms originally listed on the SGA has been expanded to encompass additional NIS deemed to be important. For example, chemosensory complaints such as taste and smell changes, are moderately associated with decreased global QOL ($R^2 = 0.2011$, $p <0.0002$) and particularly physical well-being ($R^2 = 0.3132$, $p <0.0001$) in people with advanced cancer [53]. A literature review performed by the Working Group of the Research Network of the European Association for Palliative Care examining the impact of NIS on prognosis in people with advanced cancer identified anorexia, problems swallowing and xerostomia as the most important [51]. The scored symptom checklist of the aPGSGA not only

identifies the presence or absence of such symptoms, but helps clinicians prioritize interventions by focusing on the most detrimental symptoms.

Time is an important aspect to consider when assessing NIS. The time symptoms first appear, how long they have been present for and whether or not symptoms persist on the day of evaluation will help prioritize nutritional interventions. The aPGSGA takes time into consideration by asking patients to rate their symptoms of the previous two weeks. This two week period is important, as it is well-known that symptoms will persist well beyond the end of cancer treatment [53] and it can take several weeks before an improvement in nutrition status occurs [45]. For example, taste changes experienced due to chemotherapy can last months after treatment ends [54] and can result in malnutrition. It is for this reason that patients should undergo routine nutrition assessment, in order to quickly identify emerging symptom issues before a patient's health deteriorates.

1.6 Box 4 of the aPGSGA: physical performance

There is a clear interrelationship between performance and nutrition status in people with cancer. In people with inoperable lung cancer both performance status and physical functioning were predictive of survival [55]. In people with advanced pancreatic cancer, weight loss (≥ 10%) and low energy intake (< 1500 kcal/day) have been associated with decreased physical function and strength [4]. This decrease in function, while associated with weight loss, is likely attributable to losses of lean body consistent with sarcopenia [56]. Malnutrition has also been shown to be associated with decreased QOL in both physical and social roles in people with head and neck cancer [57]. Surveys of community oncologists identified decreased function as the most troubling

patient concern [58]. Given that the aPGSGA provides both a nutrition assessment and a self-assessment of physical performance, it appears to be the ideal tool to use in people with cancer.

Physical inactivity has drawn widespread media attention for its obesogenic effects and more recently, as an independent risk factor for mortality in otherwise healthy people [59]. In healthy older adults (mean age 67 y) physical inactivity (forced bedrest) over just 10 days resulted in significant losses of total lean body mass and lean mass in the legs [60]. Recently, similar findings have been studied in people with cancer. Sedentary behaviour has been found to be associated with an overall decreased survival and increased cancer recurrence [61]. A prospective observational study of 573 women with colorectal cancer conducted by Meyerhardt et al. found that pre-diagnosis physical activity level had no association with mortality [62]. However, Meyerhardt et al. did show that physical activity levels after diagnosis, as well as their change over time (both positive and negative) did in fact predict mortality. The aPGSGA can quickly identify sedentary (bedridden) behaviour and if used as a repeated measure, show deviations from a patient's usual activity levels which may be indicative of a need for intervention.

Box 4 of the aPGSGA assesses physical performance status by asking questions similar to the often used Eastern Oncology Group Performance (ECOG) questionnaire, except from the patient's perspective. With the ECOG, clinicians rate a patient's performance status on a scale from 0 (normal activity) to 5 (death) [63]. The aPGSGA uses similar language to the ECOG and the stages are directly comparable with the exception that death is excluded from the aPGSGA (Table 1).

1.7 Patient-reported outcomes

In addition to the composite score it provides, the aPGSGA is a clinically useful tool for each question it asks. A systematic approach to symptom assessment in palliative cancer patients identified ten times as many symptom issues as did relying on patient report alone [64]. Similar results are found when assessing chemotherapy induced peripheral neuropathy in women with breast cancer. Physicians systematically underreport or underestimate the incidence of neuropathy when compared to a patient-reported outcome (PRO) tool [65]. Similarly, the use of a symptom checklist during patient interviews revealed a greater number of troubling symptoms (9.9 ± 5.9) than spontaneous report on its own (1.3 ± 1.4, $p < 0.001$) [66]. Structured patient-reported outcomes are increasingly being recognized [67], as adverse event reporting alone is inadequate to capture the true cancer patient experience [68] and likely too late to take preventive measures.

Table 1: Comparison of ECOG Performance Status and aPGSGA Activities and Functioning

ECOG Performance Status*	aPGSGA Activities and Functioning
0: Fully active, able to carry on all pre-disease performance without restriction	Normal with no limitations
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	Not my normal self, but able to be up and about with fairly normal activities
2: Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	Not feeling up to most things but in bed or chair less than half the day
3: Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	Able to do little activity and spend most of the day in bed or chair
4: Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	Pretty much bedridden, rarely out of bed
5: Deceased	*Not applicable*

Legend Left: Statements and rating of performance status according to the ECOG Performance Status scale. Right: Statements and rating of performance status according to the aPGSGA activities and functioning

*[63]Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Canadians are familiar with the use of PROs as a result of widespread use of the Edmonton Symptom Assessment System questionnaire (ESAS). In 2008, Cancer Care Ontario began using the ESAS questionnaire with all cancer patients, now representing some 28,000 users monthly [69]. Oncologists (51%) and nurses (84%) felt that use of the ESAS questionnaire improved patient care and patients (93%) overwhelmingly agreed [69]. The ESAS questionnaire is now routinely being used for patient care [70,71] as well as clinical research [72]. Cancer Care Ontario plans to work hard to improve the quality, accessibility and organization of its services as well as trying to standardize care across its many sites [73]. Use of standardized nutrition assessment tools is part of that plan [74].

However, one must take care when choosing which PROs to use. Whenever possible, PRO tools should be tailored to the population under investigation [75]. This is especially true for assessing outcomes of nutrition interventions in people with cancer, as nutrition is often a complimentary therapy to medical treatment. While PROs are suitable outcome measures on their own, they are complimented by biological data such as laboratory tests, strength measures and survival [76]. In some instances, PROs are more predictive of mortality and physical functioning than laboratory testing (ex: hemoglobin) and physician-assessed physical performance status (ex: Karnofsky Performance Scale) [77]. The aPGSGA is a PRO tool designed specifically for use in oncology patients.

1.8 Nutrition care services are limited resources

The Canadian workforce of dietitians is an aging population; according to a report published by Dietitians of Canada, approximately half of the dietitian work-force is expected to retire by 2018-2019 and the number of difficult-to-fill positions (vacant for ≥ 90 days) is

increasing [78]. In the United States, the growth rate of the profession has halved (3.0% to 1.5%) from the 1990s to 2010 [79]. This could represent an emerging shortage of nutrition professionals and may result in difficulty accessing nutrition support services in a timely manner. It also demonstrates the need for effective, timely and efficient nutrition assessments in people with cancer as the current supply of nutrition professionals cannot meet patient demand.

The economic impact of malnutrition is enormous and often goes unrecognized. In hospitalized patients those with malnutrition have longer lengths of stay, more complications and a need for more medical treatment resulting in an increase of hospital costs by over 300% [80]. These findings have been confirmed, showing that the hospital cost of malnourished patients were three-fold higher than an average, well-nourished equivalent [81]. Lim et al. also found that malnourished patients were 1.5 times more likely to be readmitted within 15 days of discharge and that survival was lower at 1-year, 2-years and 3-years [81]. Despite the prevalence of malnutrition being 40% and sometimes higher, less than 5% of these patients receive any kind of nutrition intervention [80].

1.9 Other nutrition screening and assessment tools

There are a plethora of nutrition screening and assessment tools available, but there is little evidence-based consensus on which tool to use in which population. There are more general tools, such as the Malnutrition Screening Tool (MST) which considers recent weight loss as a percentage of usual weight and appetite [9]. The Mini Nutritional Assessment (MNA) has demonstrated success in assessing the elderly as it considers physical functioning and neuropsychological problems (ex: dementia) in addition to weight loss and changes in usual food intake [82]. The SGA and subsequently the aPGSGA were developed specifically for use in people

with cancer and can be considered disease-specific rather than general tools. Like the MNA, both the SGA and aPGSGA consider physical functioning. However, only the SGA and aPGSGA consider the all-important issues of NIS.

In November 2010 the Canadian Oncology Nutrition Clinical Practice Guideline (CON-CPG) Initiative provided recommendations on screening for malnutrition in adult cancer patients [83]. The CON-CPG combined a systematic literature review with an expert panel of interdisciplinary health professionals to reach their conclusions. The CON-CPG recommends systematic nutrition screening "at all Canadian health care facilities that deliver cancer care", with the Malnutrition Screening Tool (MST) being the tool of choice for this purpose [83]. The MST was chosen over the PGSGA as it was simpler and faster to use. The CON-CPG acknowledged the shorter aPGSGA to be a nutrition assessment tool in cancer patients, but could not recommend its use due to a lack of supporting evidence, particularly data on sensitivity and specificity.

New research has been published since the CON-CPG made their recommendations. In 2013, the aPGSGA was used as a screening tool for people with cancer and compared to the MST in a Canadian oncology setting [84]. The area under the receiver operating characteristic (ROC) curve was 0.956 for the aPGSGA compared to only 0.823 for the MST (Best = 1.0). The aPGSGA also had higher sensitivity and specificity when compared to the MST (Table 2). A previous study found similar results when comparing the scored PGSGA and the MNA, finding that the MNA lacked specificity (54%) when compared to the PGSGA [85]. Given its improved sensitivity and specificity over other screening tools, in addition to the useful information it provides on weight loss, food intake, NIS, and function, the aPGSGA appears to be the ideal nutrition assessment tool in oncology.

TABLE 2: Sensitivity and specificity of nutritional indices of malnutrition as determined by Subjective Global Assessment (SGA) global ratings

	PGSGA score ≥ 8	**aPGSGA score ≥6**	**aPGSGA score ≥7**	**MST ≥ 2**
Sensitivity (%)	96.9	93.8	84.4	81.3
Specificity (%)	86.2	77.6	89.7	72.4
Area under the curve	0.967	0.956	0.956	0.823

Legend: PGSGA = Patient Generated Subjective Global Assessment; **aPGSGA** = abridged Patient Generated Subjective Global Assessment; **MST** = Malnutrition Screening Tool

1.10 Rationale and Objectives

Malnutrition is prevalent in people with cancer (and survivors), but often goes unrecognized until it is too late. For example, malnourished cancer patients are more likely to need treatment with antibiotics, require more frequent and longer hospital admissions and severe malnutrition is independently associated with early death (Odds ratio 2.47, 1.40 – 4.36, p = 0.002) [86]. Nutrition assessments at the start of oncology treatment or diagnosis, while able to detect pre-existing malnutrition, can miss vulnerable patients as well as those who develop malnutrition as a consequence of their treatment and disease. Systematic use of a nutrition assessment tool, particularly one that captures weight change, changes in food intake, NIS and physical performance would assist in providing timely nutrition care services and serve as a measure of the effectiveness of nutritional interventions. Patients on different clinical pathways, notably restorative (disease-free survival), supportive (active disease) and cachexia (advanced disease) present with unique nutritional issues which may impact a patient's survival. Therefore the objectives tested in this thesis were:

1) To evaluate whether nutritional status, as categorized by the aPGSGA, are able to detect differences in QOL, physical performance and short-term (<3 y) survival in cancer patients using a cross-sectional analysis.
2) To evaluate whether nutritional status, as measured by the aPGSGA over time, reflect changes in QOL in cancer patients over time using a repeated measure analysis in a subgroup.
3) To evaluate whether the three pre-established clinic pathways have clinical utility by detecting differences in short-term (<3 y) survival.

H_{a1}: There will be a difference in QOL, physical performance and survival according to nutritional status measured by the aPGSGA in people with cancer.

Ho1: There will be no difference in QOL, physical performance and survival according to nutritional status as measured by the aPGSGA in people with cancer.

H_{a2}: Changes in nutritional status, as measured by the aPGSGA, will predict changes in QOL in people with cancer.

H_{o2}: Changes in nutritional status, as measured by the aPGSGA, will not predict changes in QOL and physical performance in people with cancer.

H_{a3}: There will be a difference in survival distributions according to clinic pathways.

H_{03}: There will be no difference in survival distributions according to clinic pathways.

2.0 MANUSCRIPT

The abridged Patient Generated Subjective Global Assessment predicts quality of life and physical performance, but not survival, in people with cancer

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2.1 Abstract

Introduction*:* The abridged Patient Generated Subjective Global Assessment (aPGSGA), a nutrition assessment tool encompassing weight history, food intake, nutrition impact symptoms (NIS) and physical performance status could simultaneously assess nutrition status, effectiveness of interventions and quality of life (QOL).

Objectives: 1) Evaluate whether nutritional status, as measured by the aPGSGA, can detect differences in QOL, physical performance and short-term (< 3 y) survival in cancer patients; 2) Evaluate whether aPGSGA score predicts changes in QOL over time; 3) To explore the value of clinic pathways in detecting differences in short-term (< 3 y) survival.

Methods: This retrospective cohort-study uses patient data from Cancer Rehabilitation and Cachexia clinic at the McGill University Health Centre from November 2013 to September 2015. Patients with four completed aPGSGA questionnaires were included. The Edmonton Symptom Assessment System (ESAS) was used to estimate QOL, six-minute walk test for physical performance and survival information came from medical records. Cross-sectional analyses (n = 207) included Pearson's correlations, multiple regression, one-way ANOVA and Kaplan-Meier survival analysis. Repeated measures analyses (n = 113) included repeated measures ANOVA and mixed models. Significance was accepted at $p < 0.05$.

Results: Total aPGSGA score was 9.6 ± 6.3 at the first visit with NIS comprising 61% of the total score. A moderate strength correlation between aPGSGA and ESAS scores ($r = 0.478$, $p < 0.001$) was observed at baseline. There was a difference in walk distance of 71 m between highest and lowest aPGSGA scores ($p = 0.011$). In repeated measures analysis aPGSGA scores improved from 9.4 ± 5.8 to 5.3 ± 3.8 by visit four ($p < 0.001$). Total aPGSGA score predicted change in ESAS, $F (1, 585.735) = 105.423$, $p < 0.001$, with every 1 point change in aPGSGA

score resulting in a corresponding change of 0.972 in total ESAS score across the follow-up period ($b = 0.972$, $SE_b = 0.094$, $p < 0.001$). There were no survival differences according to aPGSGA categories.

Conclusion: Nutrition status, as measured by the aPGSGA, is able to detect differences in physical performance and QOL at baseline and predicts changes in QOL over time. Future studies are needed to explore the impact of nutrition on survival and treatment outcomes.

2.2 Introduction

Cancer is the leading cause of death in Canada, responsible for approximately 30% of all deaths [87]. The incidence of cancer continues to rise with an estimated 196 900 new cancer cases in 2015, with estimated increases to 277 200 by years 2028-2032. There were an estimated 810 045 Canadian cancer-survivors as of 2009 and this number is also increasing; the relative five year survival for people with cancer has increased from 55.5% to 62.8% from the mid-1990s to the mid-2000s. It is estimated that roughly 40% of people with cancer experience malnutrition, yet just over half (57.6%) of them receive any kind of nutrition support (counselling, supplements, enteral or parenteral nutrition) [7]. The increasing prevalence of cancer along with longer survival has resulted in an increase in demand for cancer care services, particularly in the elderly.

The number of older Canadians ($\geq$ 65 years) is expected to more than double over the next twenty-five years, from 4.2 to 9.4 million people [87]. New cancer cases are also expected to more than double for this age group over the same time period. Older Canadians ($\geq$ 65 y) have much higher utilization of the health care system than their younger counterparts, including more frequent hospital admissions, longer lengths of stay, higher medication use and more demand for homecare services. This shift in demographics will require additional cancer screening, diagnosis and treatment. It also represents an increase in demand for allied health professionals, such as dietitians, to provide complimentary care during active treatment, palliation and survivorship. Malnutrition is also a common cause for disruption/change in cancer treatment [88].

Nutrition screening and assessment are of utmost importance as the timeliness of interventions directly impacts their effectiveness; the earlier nutrition services are provided, the better the outcome [89]. Not only are early nutrition interventions effective at improving nutritional

status, they have been demonstrated to improve QOL as well [90]. International nutrition societies and regulatory bodies recommend systematic nutrition assessment in all cancer patients [91] but there remains to be a widely accepted tool to accomplish this.

The aPGSGA, a dual-purpose screening and assessment tool, is able to identify cancer patients in need of a nutritional intervention as well as triage cases in order of urgency using a simple scoring system. The aPGSGA was developed specifically for use in an oncology population and is recognized and recommended for use by Cancer Care Ontario [74]. Recently, cross-sectional use for the aPGSGA has been shown to be associated with survival, underweight and treatment tolerance in people with cancer [14]. Few studies exist which use repeated measures of nutrition assessment, and fewer still exploring the relationship between nutrition and QOL. The purpose of this study is to evaluate whether nutritional status, as measured by the aPGSGA, is able to detect differences in QOL, physical performance and short-term (< 3 y) survival in people with cancer; 2) evaluate whether aPGSGA score predicts changes in QOL over time; 3) to explore the value of clinic pathways based on aPGSGA scores in detecting differences in short-term (< 3 y) survival.

2.3 Methods

2.3.1 Study Design

This retrospective cohort study used data obtained from patients of the Cancer Rehabilitation and Cachexia clinic at the McGill University Health Centre (MUHC) enrolled November 2013 to September 2015; patients who started the clinic program prior to November 2013 but whose 4 follow-up visits extended into the study period were retained. Patients who completed aPGSGA and ESAS questionnaires at baseline are included in the data analysis. Patients with four clinic visits and complete aPGSGA questionnaires were used for repeated

measures analyses. Additional information was obtained from the patients' medical chart (survival, diagnosis). Ethics approval was sought and obtained from the institutional review board of the Montreal General Hospital of the MUHC prior to data collection in September 2015.

2.3.2 Inclusion and exclusion criteria:

Included: Adult (18 y of age and older) patients of the Cancer Rehabilitation and Cachexia Clinic having completed baseline aPGSGA and ESAS questionnaires. All cancer diagnoses were included.

Excluded: Participants missing baseline (first) aPGSGA questionnaire, ECOG score > 2 at baseline, estimated prognosis < 3 months according to referring oncologist and uncontrolled pain.

2.3.3 aPGSGA Questionnaire and weight

Scores were calculated as previously published using information gathered in 4 boxes [20]. In brief, points from Box 1 are derived from the absence or presence of weight loss (0 or 1 point) and from percentage weight loss experienced over the past month (0 to 4 points). Patients had their weight measured the day of the clinic to provide for current weight in Box 1. In Box 2, patients choose scored statements that reflects their food intake over the past month (0 to 4 points). Box 3 is the additive score from chosen symptoms, including an open-ended section for "other" symptoms (0 to 24 points). Lastly, Box 4 questions patients on their functional status (0 to 3 points). Points within Box 1 and Box 3 are additive, whereas Box 2 and Box 4 retain the selections with the highest points. Final aPGSGA score is obtained by summing the points from boxes 1 to 4, ranging from 0 (best possible score) to 36 (worst possible score). The aPGSGA score corresponds to four unique nutrition triage recommendations: 0 – 1 (no intervention required); 2 – 3 (patient education with symptom management); 4 – 8 (interdisciplinary

intervention of dietitians, nurses, physicians); ≥ 9 (critical need for intervention). In this study, malnutrition was defined as aPGSGA total score ≥ 9. Patients completed an aPGSGA at each clinic visit and questionnaires were scored either by a registered dietitian or trained research assistant who was supervised by said registered dietitian.

For the purposes of this study, a healthy BMI ranged between 20.0 and 24.9 kg/m^2. A BMI below 20.0 kg/m^2 was considered underweight, whereas overweight was between 25.0 and 29.9 kg/m^2 and obesity greater than 30.0 kg/m^2. While a healthy BMI is commonly between 18.5 – 24.9 kg/m^2 [92,93], the low cut-off of 18.5 kg/m^2 is inappropriate for this study due to the age of study participants (age > 65 y). Studies have shown that the older adults (≥ 65 y) as well as people with cancer already show significant signs of malnutrition at a BMI of 18.5 kg/m^2 and even higher [94-96] and instead propose a cut-off of at least 20 kg/m^2 [97], which is what was used in this study.

2.3.4 Physical performance measures:

Strength was measured by using the Jamar© handgrip dynamometer (Sammons Preston, Bolingbrook, IL). Measurements were taken at all clinic visits (visits 1 to 4) by either a registered dietitian or a trained research assistant using the patient's dominant hand. Patients repeated the test three times; the best score was retained. Patients were asked to squeeze for a period of three seconds before being given a 30 second rest between trials. Hand grip strength (HGS) was selected on the basis of being a measure of upper limb strength that correlates well with lower limb strength [98]. It has been used successfully as a measure of strength in people with cancer [99,100]. It has also been shown to be prognosis of survival in people with cancer [101].

All patients who were physically able based on a physiotherapist's clinical judgement performed a 6 Minute Walk Test (6MWT) at the first and final clinic visits. This is a simple and

easy to perform test valid in people with cancer [102,103] which also has prognostic significance [104]. The 6MWT entails walking for a period of 6 minutes while a professional records the distance traveled. In this study, patients walked in a 10 m long corridor and had their lap count recorded; patients ending partly through the corridor had their distance traveled measured in meters and added to the total obtained from the lap count. All 6MWT were performed by a professional physiotherapist.

Lastly, in addition to overall aPGSGA score the score from Box 4 was used in comparisons with the other physical performance measurements. As mentioned previously, Box 4 of the aPGSGA is a self-reported assessment of physical function and this dimension of the aPGSGA will be looked at independently of the rest of the tool.

2.3.5 Quality of life:

Quality of life was assessed using the ESAS. Patients were asked to rate their symptoms on an 11 point Likert scale, with 0 being the best score and 10 being the worst. The nine original questions of the ESAS relate to: pain, activity, nausea, depression, anxiety, drowsiness, appetite, shortness of breath and overall well-being. Both ESAS well-being and total ESAS score are considered measures of health-related QOL and have strong correlations with other measures of QOL [105]. Patients completed an ESAS questionnaire at each clinic visit.

2.3.6 Cancer Rehabilitation and Cachexia Clinic and Clinical Pathways

The Cancer Rehabilitation and Cachexia Clinic of the MUHC, is an ambulatory clinic aimed at improving nutritional status and physical performance in those affected by cancer. The Clinic is staffed by a palliative care physician, nurse clinician, physical therapist, occupational therapist and dietitian. During an initial assessment a patient will meet each clinician in five 30-minute blocks. Clinicians then discuss each case in order to agree upon a clinic pathway and

formulate a clinical plan. Follow-up frequency and duration are determined by the needs of the patient but typically vary between 2 and 4 weeks.

Clinicians recognized that patients' needs varied based upon their disease trajectory and developed three distinct clinical pathways to help personalize care (Appendix 1). Briefly, the three pathways are 1) Restorative: for patients who are disease free yet require assistance to return to usual activities 2) Supportive: for patients with active cancer, with or without treatment, requiring the help of an interdisciplinary team to overcome their disease and its side-effects and 3) Cachexia: for patients with incurable cancers, physical, metabolic and nutritional abnormalities. Consequently, specific inclusion and exclusion criteria for admission into the program were developed, specifically: patients needed the assistance of multiple professionals, have only moderately impaired physical performance status (Eastern Cooperative Oncology Group [ECOG] performance status ≤ 2) and could not have pain control as the reason for referral.

2.3.7 Statistical analysis

The estimated sample size for the present investigation was calculate for each objective. The first, to determine sample size for correlation between aPGSGA score and ESAS quality of life:

$$\text{The standard normal deviate for } \alpha = Z_\alpha = 1.960$$
$$\text{The standard normal deviate for } \beta = Z_\beta = 0.842$$
$$C = 0.5 * \ln[(1+r)/(1-r)] = 0.793$$
$$\text{Total sample size} = N = [(Z\alpha+Z\beta)/C]2 + 3 = 15$$

This calculation considers a correlation coefficient of 0.66, two-tailed alpha of 0.05, and 80% power found in similar research determining the correlation between PGSGA score and a different quality of life tool [106].

The second sample size calculation is a paired one sample t-test used to compare mean changes in quality of life from baseline to end of follow-up. Prior data suggests that to achieve a clinically relevant difference in ESAS subscales of 1.8 (with a standard deviation of 6.8) a minimum of 114 participants are required (alpha 0.05, beta 0.20) [107].

Descriptive statistics, such as mean and standard deviation or 95% confidence intervals, were used to summarize population characteristics (ex: cancer diagnosis, age, sex). Previously validated cut-off scores for aPGSGA were used to identify four groups of patients which corresponds to four unique nutrition triage recommendations: 0 – 1 (no intervention required); 2 – 3 (patient education with symptom management); 4 – 8 (interdisciplinary intervention of dietitians, nurses, physicians); ≥ 9 (critical need for intervention). Diagnostic groupings corresponded to The International Classification of Diseases, 10th Revision (ICD-10) [108]. The 'other' category includes bladder, brain, kidney, lymphoma, skin, neuro-endocrine, prostate, testicular, thyroid and head and neck.

Pearson's product-moment correlations were calculated to determine the relationship between QOL and aPGSGA score. Multiple regression via simultaneous entry was used to calculate the proportion of variability of QOL could be attributed to aPGSGA score. There was independence of residuals, as assessed by a Durbin-Watson statistic of 1.801. Examination of scatter plots and partial plots confirmed that the relationship between variables was linear. Homoscedasticity was assessed by visual inspection of a plot of studentized residuals versus unstandardized predicted values. Multicollinearity was ruled out by seeking out strong

correlations (≥ 0.700) between variables and testing tolerance. Normality was confirmed by inspecting all partial plots and the histogram of the standardized residuals. Chi-square tests of independence were used to examine the relationship between aPGSGA triage categories and categorical variables, such as clinic pathway and BMI, with an accepted significance level of $p < 0.05$. Post-hoc analysis with Bonferonni correction were used to identify where differences occured.

One-way ANOVA (analysis of variance) was used to determine differences in outcomes across aPGSGA triage recommendations. Data was normally distributed for each group, as assessed by Shapiro-Wilk test ($p > 0.05$); and there was homogeneity of variances, as assessed by Levene's test of homogeneity of variances. One-way repeated-measures ANOVA was used to detect differences in outcomes over the study period. The presence of outliers (± 1.5 standard deviations from the mean) and extreme outliers (± 3.0 standard deviations from the mean) were assessed by boxplot. All outliers were inspected to ensure accuracy of the data; extreme outliers were removed from analyses whereas outliers within 1.5 standard deviations from the mean were kept. Sphericity was assessed by Mauchly's test of sphericity and Greenhouse-Geisser corrections were applied where necessary. Data is presented as mean ± standard deviation unless otherwise specified. In analyses where there are an exceptional number of outliers and/or extreme outliers the Friedman test was used.

Mixed models were used to test whether or not changes in aPGSGA score over time reflected changes in ESAS: fixed effects included age, sex, ethnicity, cancer diagnosis, baseline aPGSGA and ESAS scores, follow-up duration in days and clinic pathway. The intercept was set as a random effect. Kaplan-Meier survival analysis was used to detect differences between

survival distributions. Significance was set at $p < 0.05$ level for all tests with corrections made for multiple testing using the Bonferroni correction, where applicable.

2.4 Results

Two-hundred and twelve patients between November 2013 and September 30th, 2015 were considered. Four were excluded for missing aPGSGA and ESAS questionnaires; one was excluded for being the only person in their demographic grouping (Aboriginal) leaving 207 (n = 207) for analysis. Baseline characteristics can be found in Table 1. The different ethnic groups, in ascending order, were: Black (4.4%), Asian (7.3%) and Caucasian (88.3%). The Caucasian group includes Arabs (5.8%) and Latin Americans (1.9% compared). The average clinic patient was overweight and visited 3 times (median = 3, mean = 3.7 visits). There was a statistically significant difference in men and women with respect to age and weight, but not BMI, with women being 4.9 y younger, $p = 0.008$ and weighing 6.6 kg less, $p = 0.005$.

Mean aPGSGA and ESAS scores can be found in Table 2. Nutrition impact symptoms represented the bulk of the score with 5.9 points or 61% of the total score at baseline and 3.4 points or 58% of the total by the fourth visit. Patients' aPGSGA score improved over time with aPGSGA score decreasing from visit 1 (M = 9.4), to visit 2 (M = 6.8) to visit 3 (M = 6.3) and visit 4 (M = 5.3). Post hoc analysis revealed that aPGSGA score was decreased from visit 1 to visit 2, visit 1 to 3, visit 1 to 4, and visit 2 to 4. There were also differences in weight score, food score and symptom score over the follow-up period. Patients' ESAS scores improved from visit 1 (M = 29.8), to visit 2 (M = 27.0), to visit 3 (M = 26.0), and visit 4 (M = 24.2). ESAS wellbeing improved from visit 1 (M = 4.5), to visit 2 (M = 4.1) and to visit 4 (M = 3.6). Differences in ESAS total score and Wellbeing subscore over the follow-up period are presented in Table 2.

Table 3 shows baseline subjective (aPGSGA and ESAS scores) and objective measures (weight, BMI, 6MWT, HGS) of participants according to aPGSGA triage categories. The 6MWT, total ESAS score and ESAS wellbeing differed significantly across aPGSGA categories.

However, BMI, weight and HGS did not differ significantly between groups. A chi-square test of independence was performed to examine the relationship between aPGSGA categories with BMI and clinic pathway. The relationship between aPGSGA categories and BMI was not significant, X^2 (9, N = 188) = 13.01, p = 0.162. There was a significant relationship between aPGSGA category and clinic pathway, X^2 (6, N = 194) = 17.14, p = 0.009. Post hoc analysis involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction. There was a greater proportion of patients in the cachexia pathway with an aPGSGA score > 9, $p < 0.05$.

A Pearson's product-moment correlation was run to assess the relationship between total aPGSGA score, the four individual domains of the aPGSGA and total ESAS score. Preliminary analyses showed the relationship to be linear with variables normally distributed as assessed by inspection of boxplot and there were no outliers. Total ESAS score had significant ($p < 0.001$) moderate strength correlations with total aPGSGA score as well as with the NIS and the activity subscales. Significant ($p < 0.001$), but weak correlations exist between total ESAS score and the food intake and weight subscales (Table 4). Associations between total aPGSGA score and its subscales are shown for completion.

Figure 1 displays aPGSGA and ESAS scores according to clinic pathway at baseline. Total aPGSGA score differed according to clinic pathway, with restorative patients having the best scores (6.8, SD 4.7) as compared to the cachexia patients (11.8, SD 7.2). However, there was no significant difference in ESAS scores according to clinic pathway (restorative 27.3 SD 14.5, cachexia 31.4 SD 17.7).

Kaplan-Meier analysis was conducted using the aPGSGA score categories but found no differences between survival distributions, X^2 (3) = 4.927, p = 0.177. However, a Kaplan-Meier curve based upon clinic pathway did show significant differences in survival distribution (Figure

2). Patients in the cachexia group had the shortest median survival of 777 days (95% CI, 585 – 968 days) when compared to 807 days (95% CI, 275 – 1338) in the supportive group; no median survival exists for the restorative group as the cumulative survival never dipped below 50% for these patients. There was a statistically significant difference in survival distributions for the restorative vs cachexia pathways, $\chi 2(1) = 13.899$, $p < .001$, restorative and supportive pathways, $\chi 2(1) = 3.972$, $p = 0.046$ and supportive and cachexia pathways, $\chi 2(1) = 5.036$, $p = 0.025$. However, after applying the Bonferroni correction statistical significant was accepted at the $p < 0.0167$ level and thus only the restorative and cachexia pathways remained significantly different from each other.

Multiple regression was performed using baseline data to determine how aPGSGA score predicted QOL. There was a moderate effect in the ability of the aPGSGA to predict ESAS scores (R^2 for the overall model was 24.2%, adjusted R^2 of 22.3%). Total aPGSGA score, age, diagnosis, ethnicity and gender statistically significantly predicted total ESAS score, F (5, 198) = 12.637, $p < 0.0005$. Only total aPGSGA score added significantly to the model; for each 1 point increase in aPGSGA score, ESAS score increases by 1.18. Clinic pathway ultimately was not included in the regression model. Table 5 contains a summary of the model.

Mixed model linear regression was used in order to determine if total aPGSGA score predicted QOL over time, with maximum likelihood being the method of estimation. Total aPGSGA score predicted change in ESAS, F (1, 585.735) = 105.423, $p < 0.001$, as did time from baseline (in days), F (1, 219.553) = 4.015, $p = 0.046$ and diagnosis, F (4, 186.535) = 2.668, $p = 0.034$. Ethnicity, clinic pathway, sex, and age did not significantly predict change in ESAS score. Model parameter information can be found in Table 6. For every 1 point increase in aPGSGA score there is a 0.972 increase in total ESAS score across the follow-up period. Conversely, for

every 1 day enrolled in the study/clinic total ESAS score decreased by 0.023, such that remaining in the study for 100 days would represent an average improvement of 2.3 points in total ESAS score. Patients with breast cancer or cancers of the female reproductive system had the worst ESAS scores whereas patients with haematological cancers had the best, although this difference was not significant. Patients in the restorative pathway had the best ESAS scores whereas patients in the supportive pathway had the worst, although these differences were again not statistically significant. There was a trend ($p = 0.052$) for Asian patients to have higher (worse) ESAS scores than either Black or White patients. The estimated variance of the intercept is about 78.664 which suggests that different individuals have different intercepts, $p < 0.001$, representing significant variance in ESAS scores between patients.

2.5 Discussion

This study demonstrated that malnutrition, as measured by aPGSGA score ≥ 9, is associated with worse total ESAS score, ESAS wellbeing and 6MWT using a cross-sectional dataset. Additionally, total aPGSGA score was able to predict QOL; for every 1 point difference in aPGSGA score, ESAS score would change by 1.2 points. Patients presented with a mean aPGSGA score of 9.6 and a median score of 9 at their initial visit. A score ≥ 9 triages patients into the highest malnutrition-risk category, suggesting that the prevalence of malnutrition in this population is high, approaching 50%. This finding is comparable to other studies that report an incidence of malnutrition above 40%[7] in people with cancer. A similarly structured cancer rehabilitation clinic found a median aPGSGA score of 13.5 (range 2 – 31) [109], confirming that patients referred to such multidisciplinary clinics have significant sequelae from their treatment and disease. The improvement in aPGSGA score seen in this study is clinically meaningful; the mean change of 4.1 points is enough to move patients from the highest risk category to the

preceding category and only 14% of patients had an aPGSGA score ≥ 9 by the end of the study period. A nutrition intervention in patients receiving radiotherapy noted a smaller improvement in aPGSGA of 1.6 over the 12 week period, however their control group worsened by 3.1 points [110]. An 8 week nutrition intervention in patients receiving chemotherapy saw a 9 point improvement in mean aPGSGA score over the study period, $p = 0.019$ [45]. Thus a mean improvement of approximately 4 points in total aPGSGA seems plausible and likely reflects a true improvement in nutritional status.

There were significant and meaningful differences in 6MWT between aPGSGA triage categories in this study. However, one must define what a clinically meaningful, or relevant, difference in 6MWT is. A longitudinal study of sedentary elderly (70 – 89 y) found a minimally significant change in a 400 m walking test to be 5%, with 10% resulting in "substantial" change from first assessment to 12 months [111]. A study of impaired older adults found that the smallest meaningful change in 6MWT was 20 m, with 50 m representing a substantial change [112]. In people suffering from COPD a 65 m mean difference between survivors (alive at the end of the 11 year follow-up period) and non-survivors [113] was identified. Additionally, patients were found to have a 20% increase in risk of dying for every 100 m difference in 6MWT [113], with patients walking > 350 m having the greatest chance of survival. A six week exercise intervention in palliative care patients noted an improved 6MWT of 29 m ($p = 0.007$) [114] and an interventional study of prehabilitation in patients with colorectal cancer demonstrated an improvement in 6MWT of 40 m after 33 days [115]. A trial of an immunomodulatory drug in people with advanced (stages 3 and 4) cancer noted an improvement in aPGSGA score from 10 to 5 which coincided with a 50 m (17%) increase in 6MWT [116]. Thus the minimal clinical difference of 6MWT is

approximately 5% or 30 m in the chronically ill, with differences of 10% or 50 m representing large changes.

The differences in 6MWT across aPGSGA categories at baseline exceeded the minimal clinical difference of 30 m; the difference in 6MWT between the highest and lowest aPGSGA scores was 71.4 m. However, while there is a tremendous amount of literature describing the importance of nutrition and exercise in people with cancer there are surprisingly few trials examining these aspects together, and fewer still which compare 6MWT with aPGSGA scores. In head and neck cancer patients both physical performance status (measured by ECOG) and aPGSGA score were worse in malnourished (involuntary weight loss ≥ 5% over 6 months) patients [117]. A study of people with COPD found a weak significant correlation of 6MWT with aPGSGA scores ($r = -0.245$, $p = 0.044$), but no difference in walking distance between those with high and low aPGSGA scores [118]. Lung transplant candidates with nutritional depletion (BMI < 90% of ideal and depletion of lean body mass) were found to have lower 6MWT as compared to those without depletion (52 m to 140 m, $P < 0.001$) [119]. A cancer rehabilitation program showed similar findings, where patients who dropped out of the program had both higher (worse) aPGSGA scores as well as lower 6MWT [109]. Thus, nutritional status not only influences initial walking distance, but the depletion of nutritional reserves may limit patients' ability to improve.

There were no detectable differences in HGS. Hand grip strength was used as a measure of physical performance because it is increasingly being used as an outcome measure in people with cancer. For example, HGS has been independently associated with survival, as well as other biological characteristics and physical performance tests in people with cancer [101]. Conversely, malnutrition (measured by the SGA) has been shown to be an independent determinant of HGS

(estimated effect size 11%, $p < 0.01$) in cancer patients [120]. In the clinic setting, HGS is used alongside other measures, such as the aPGSGA activity sub-score and body composition measured by dual-energy X-ray absorptiometry in order to determine the presence and severity of sarcopenia [121]. While HGS may be an important single measure in people with cancer this study was unable to detect differences in HGS, as it did using 6MWT, according to aPGSGA categories. This study suggests the ability of the aPGSGA to detect differences in more functional physical outcomes, such as walking, that are well known to relate to QOL [122].

Pearson's product-moment correlations showed that NIS were most closely correlated to QOL, followed by physical performance. Both have moderate strength ($0.3 < |r| < 0.5$) [123] correlations. Similarly, weight history and food intake had only weak ($0.1 < |r| < 0.3$), but significant, correlations with overall QOL. These associations have been confirmed elsewhere, with quality of life scores demonstrating mild ($r = - 0.224$, $p < 0.001$) to moderate ($r = -0.350$, $p < 0.001$) associations with PGSGA score, with emphasis on the importance of NIS [10]. Approximately 23% of the variation in QOL could be attributed to changes in nutrition. A study examining the relationship between QOL and nutrition status found that PGSGA score accounted for 26% of the variation in QOL [124]. A sample of mixed-diagnoses, home tube-fed patients found that severe malnutrition (BMI < 5th percentile of German population) contributed to 11% of the variation of QOL ($p = 0.037$) [125]. While their scale of measurements and intended purpose differ, four of the original nine ESAS symptoms do appear on the aPGSGA NIS list: nausea, fatigue, pain and appetite.

The sub-score of ESAS wellbeing also differed across aPGSGA categories and improved over the study period in a clinically meaningful way. Optimal cut-points in individual ESAS scores to distinguish between mild, moderate and severe symptom severity have been devised:

mild severity corresponds to an ESAS score < 4, moderate 4 – 6 and severe ≥ 7 [126]. In this study, patients scoring ≤ 1 on the aPGSGA only had mild symptom severity of well-being whereas malnourished patients (aPGSGA score ≥ 9) had moderate problems with well-being. A study aimed at determining minimal clinically important differences in ESAS sub-scores used ESAS well-being as its anchor and thus did not have a recommendation for meaningful changes in this measure [107]. However, meaningful changes in the other ESAS sub-scores at baseline as well as over time varied between 1.2 and 2.2. In the present study, a difference in ESAS well-being of 1.2 was found between the highest and lowest aPGSGA score categories at baseline, and the overall the group improved by 0.9 over the study period. Total aPGSGA score seems able to predict overall health-related QOL as well as the sub-score of wellbeing. However, the magnitude of the group change in well-being, while statistically significant, may not be clinically meaningful [107].

Malnutrition has long been associated with survival in people with cancer [1-3,31,48]. However, in this study, there was no difference in survival according to aPGSGA categories. The Kaplan-Meier test is used to compare difference in survival between pre-established groups or pairings and not between continuous variables [127]. The aPGSGA score is a continuous variable and while the original author defined triage categories their purpose was to direct nutritional care and not predict survival [20]. One study has shown differences in survival according to aPGSGA categories and it was done in patients exclusively with advanced cancer (stage 3 or 4) who were known to be cachectic and the comparisons were limited to patients with scores from 0 - 1, 2 – 8 and ≥ 9 [14], collapsing aPGSGA the middle aPGSGA categories together. This methodology was attempted in this study but there were no differences in survival, nor were there any differences

when only the cachectic patients were retained (data not shown). More research is needed to determine an optimal cut-off in aPGSGA score to be used in survival estimations.

Limitations which may impact generalizability of the findings of this study included underrepresentation of visible ethnic minorities typically seen in Montreal [128] as well as few cases of prostate cancer in men and an overrepresentation of haematological/lymphatic cancers in both genders compared to what is seen in Quebec, Canada [87]. Heterogeneity of follow-up duration, the high proportion of censored cases, a short follow-up duration for those entering the study later, and the use of clinic enrolment as the basis for survival duration limited the survival analysis [129]. Lastly, while improvements in this area are being made, only a minority of cancer patients have access to cancer rehabilitation services and improvements seen in QOL and aPGSGA score in this study may be larger than expected elsewhere.

In summary, malnutrition as assessed by the aPGSGA is able to detect differences in QOL and physical performance in adults with cancer and predict changes in QOL over time. Malnutrition remains a common problem in adults with cancer. Further investigation is needed to determine the relationship between aPGSGA score and survival as well as other oncology outcomes such as treatment tolerance and hospitalization.

2.6 Tables

Table 1: Baseline characteristics of patients enrolled in the Cancer Rehabilitation and Cachexia Clinic

	Total (N = 207)		**Men (n = 114)**		**Women (n = 93)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	63.9	13.4	66.2	13.0	61.2*	13.4
Number of visits	3.7	2.6	3.7	2.8	3.6	2.3
Height (m)	1.68	0.1	1.73	0.7	1.61*	0.1
Weight (kg)	71.6	17.0	74.6	15.2	68.0*	18.5
BMI (kg/m^2)	25.4	6.1	24.8	5.0	26.2	7.2
	No.	**%**	**No.**	**%**	**No.**	**%**
BMI category						
- **<20**	34	16.4	19	16.7	15	16.1
- **20 – 24.9**	67	32.4	40	35.1	27	29.0
- **25 – 29.9**	66	31.9	39	34.2	27	29.0
- **>30**	34	16.4	14	12.3	20	21.5
- **Missing**	6	2.9	2	1.8	4	4.3
Diagnosis						
- **Lung**	69	33.3	43	37.7	26	28.0
- **Female**	29	14.0	0	0	29	31.1
- **Digestive**	32	15.5	23	20.2	9	9.6
- **Lymphatic and Haematological**	42	20.3	20	17.5	22	23.7
- **Other**	35	16.9	28	24.6	7	7.5
Ethnicity						
- **Caucasian**	181	88.3	103	91.1	78	84.7
- **Asian**	15	7.3	5	4.4	10	10.9
- **Black**	9	4.4	5	4.4	4	4.3
Pathways						
- **Restorative**	43	20.8	16	14.0	27	29.0
- **Supportive**	81	39.1	40	35.1	41	44.1
- **Cachexia**	70	33.8	48	42.1	22	23.7
- **Missing**	13	6.3	10	8.8	3	3.2

Legend: BMI: Body Mass Index, Female: Breast cancer and cancers of the female reproductive system (ovarian, uterine, cervical, vaginal)

*: different from men, $p < 0.05$

Table 2: Total aPGSGA score and sub scores over the study period

	Visit 1	Visit 2	Visit 3	Visit 4	p-value
	n = 103				
Total aPGSGA score	9.4 (5.8)	6.8 (5.1)*	6.3 (4.7)*	5.3 (3.8)*,**	< 0.001
Weight score	1.1 (1.5)	0.4 (0.9)*	0.8 (1.3)**	0.5 (1.0)*	< 0.001
Food score	0.8 (0.9)	0.5 (0.9)*	0.4 (0.7)*	0.2 (0.4)*,**	< 0.001
Symptom score	5.9 (4.4)	4.6 (3.8)*	4.0 (3.7)*	3.4 (3.0)*,**	< 0.001
Activity score[a]	1.6 (1.0)	1.4 (0.9)	1.2 (0.9)*	1.1 (0.8)*	< 0.001
Total ESAS	29.8 (14.9)	27.0 (14.9)*	26.0 (15.1)*	24.2 (14.3)*	< 0.001
ESAS-Wb	4.5 (2.4)	4.1 (2.4)	4.1 (2.4)	3.6 (2.3)*	0.007

Legend: aPGSGA: abridged Patient-Generated Subjective Global Assessment, ESAS: Edmonton Symptom Assessment System, ESAS-Wb: Edmonton Symptom Assessment System wellbeing, p-value: Significance of overall ANOVA. Post-hoc tests done using the Bonferonni method, unless otherwise specified.

[a]: The physical activity subscale had n = 107 participants after removal of extreme outliers. Due to the violation of normality, the Friedman test was used in order to detect differences in the physical activity sub-score, $X^2 = 45.5$, $p < 0.001$.

*: different from visit 1, $p < 0.001$

**: different from visit 2, $p < 0.001$

Table 3: Subjective and objective measures of study participants according to aPGSGA triage recommendations

	0 - 1		2 - 3		4 - 8		>9		p-value
	n = 18 Mean (SD)		n = 25 Mean (SD)		n = 60 Mean (SD)		n = 104 Mean (SD)		
aPGSGA	0.8 (0.4)		2.5 (0.6)		6.4 (1.4)		14.6 (4.5)		
Weight (kg)	77.1 (16.0)		73.4 (11.3)		73.5 (18.7)		69.1 (17.1)		0.167
BMI (kg / m^2)	28.1 (5.5)		25.9 (3.7)		26.1 (6.6)		24.5 (6.2)		0.078
HGS (kg)	33.4 (13.1)		34.5 (10.4)		33.0 (10.7)		32.2 (11.4)		0.816
6MWT (m)	371.3 (137.1)		367.9 (136.3)		376.2 (103.1)		299.9 (136.0)*		0.011
ESAS	18.7 (10.7)		22.6 (13.4)		27.7 (13.7)		36.2 (15.9)*,**,***		0.001
ESASWellbeing	3.9 (2.6)		3.9 (2.6)		4.1 (2.5)		5.1 (2.6)**		0.023
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
Clinic pathway									
- **Restorative**	7	41.1	8	32.0	14	25.0	14	14.5	0.009
- **Supportive**	7	41.1	12	48.0	27	48.2	35	36.5	
- **Cachexia**	3	17.6	5	20.0	15	26.8	47	49.0	
BMI category									
- **<20**	0	0	1	4.2	10	17.2	23	22.7	0.162
- **20 – 24.9**	5	27.8	9	37.5	19	32.8	34	33.7	
- **25 – 29.9**	9	50.0	11	45.8	16	27.6	30	29.7	
- **>30**	4	22.2	3	12.5	13	22.4	14	13.9	

Legend: BMI: Body Mass Index, HGS: Hand grip strength, 6MWT: 6 minute walk test, aPGSGA: abridged Patient-Generated Subjective Global Assessment, ESAS: Edmonton Symptom Assessment System

*: different from aPGSGA triage category 0 – 1, $p < 0.05$

**: different from aPGSGA triage category 2 – 3, $p < 0.05$

***: different from aPGSGA triage category 4 – 8, $p < 0.05$

Table 4: Pearson's product-moment correlation between total ESAS score with total aPGSGA score and its four domains

	ESAS score	**aPGSGA-T**	**Weight**	**Food**	**NIS**
aPGSGA-T	0.478*				
Weight	0.111*	0.587*			
Food	0.206*	0.660*	0.430*		
NIS	0.498*	0.934*	0.329*	0.492*	
Activity	0.401*	0.548*	0.269*	0.315*	0.392*

Legend: aPGSGA-T: abridged Patient-Generated Subjective Global Assessment total score, ESAS: Edmonton Symptom Assessment System

* $p < 0.001$

Table 5: Summary of multiple regression analyses of total aPGSGA score in predicting total ESAS score

	B	**SE_B**	**ß**
Intercept	22.1	8.0	
aPGSGA total score	1.2	0.2	0.470*
Age	0.1	0.1	0.051
Ethnicity	-2.1	2.9	-0.045
Diagnosis	-0.2	0.7	-0.018
Gender	-3.4	2.0	-0.106

Legend: aPGSGA: abridged Patient-Generated Subjective Global assessment; ESAS: Edmonton Symptom Assessment System; B: unstandardized regression coefficients; SE: standard error of the coefficient; ß: standardized coefficient. Method of regression was simultaneous forced entry.

Dependant variable = Total ESAS score

* $p < 0.05$

Table 6: Fixed and random effects for model estimating change in ESAS scores

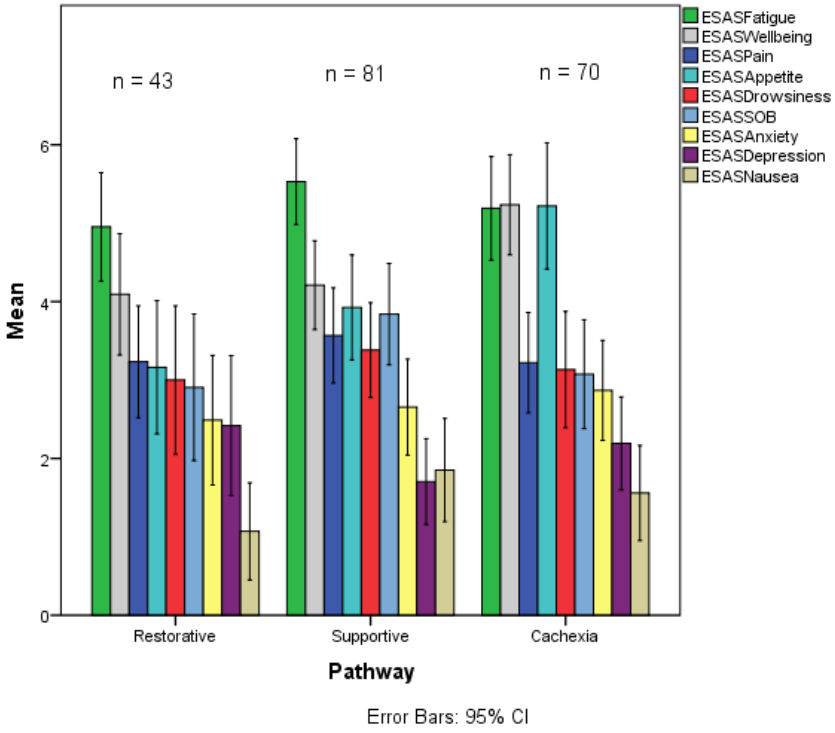
Parameter	b	SE_b	95% CI	P-value
Fixed:				
Intercept	13.391	6.142	1.275, 25.508	0.030
aPGSGA score	0.972	0.094	0.786, 1.158	< 0.001
Time	-0.023	0.011	-0.040, -0.001	0.046
Age (years)	0.030	0.070	-0.107, 0.167	0.665
Diagnosis: digestive	2.025	2.860	-3.616, 7.666	0.480
Diagnosis: lung	-0.908	2.453	-5.747, 3.929	0.711
Diagnosis: female	4.719	3.153	-1.501, 10.939	0.136
Diagnosis: haem	-3.621	2.472	-8.492, 1.250	0.144
Gender (female)	1.735	1.815	-1.844, 5.315	0.340
Pathway: restorative	-3.500	2.552	-8.536, 1.536	0.172
Pathway: supportive	1.123	1.123	-2.714, 4.961	0.564
Ethnicity: White	4.014	4.014	-5.474, 13.503	0.405
Ethnicity: Asian	6.078	6.078	-0.050, 12.207	0.052
Random:				
Intercept	78.665	15.541	53.407, 115.865	<0.001

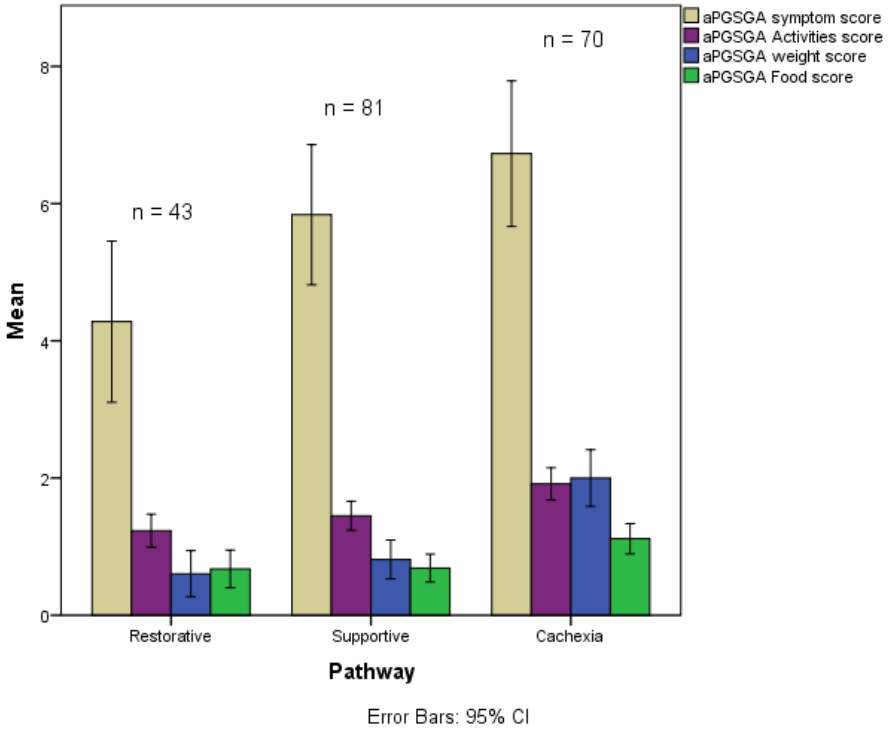
Legend: Female: Breast cancer and cancers of the female reproductive system (ovarian, uterine, cervical, vaginal), haem: lymphatic and haematological cancers, Time: measured in days, ESAS: Edmonton Symptom Assessment System, aPGSGA: abridged Patient Generated Subjective Global Assessment

Note: Dependant variable = total ESAS score. Reference category for diagnosis is 'other', for pathways it is cachexia and for ethnicity it is Black.

2.7 Figures

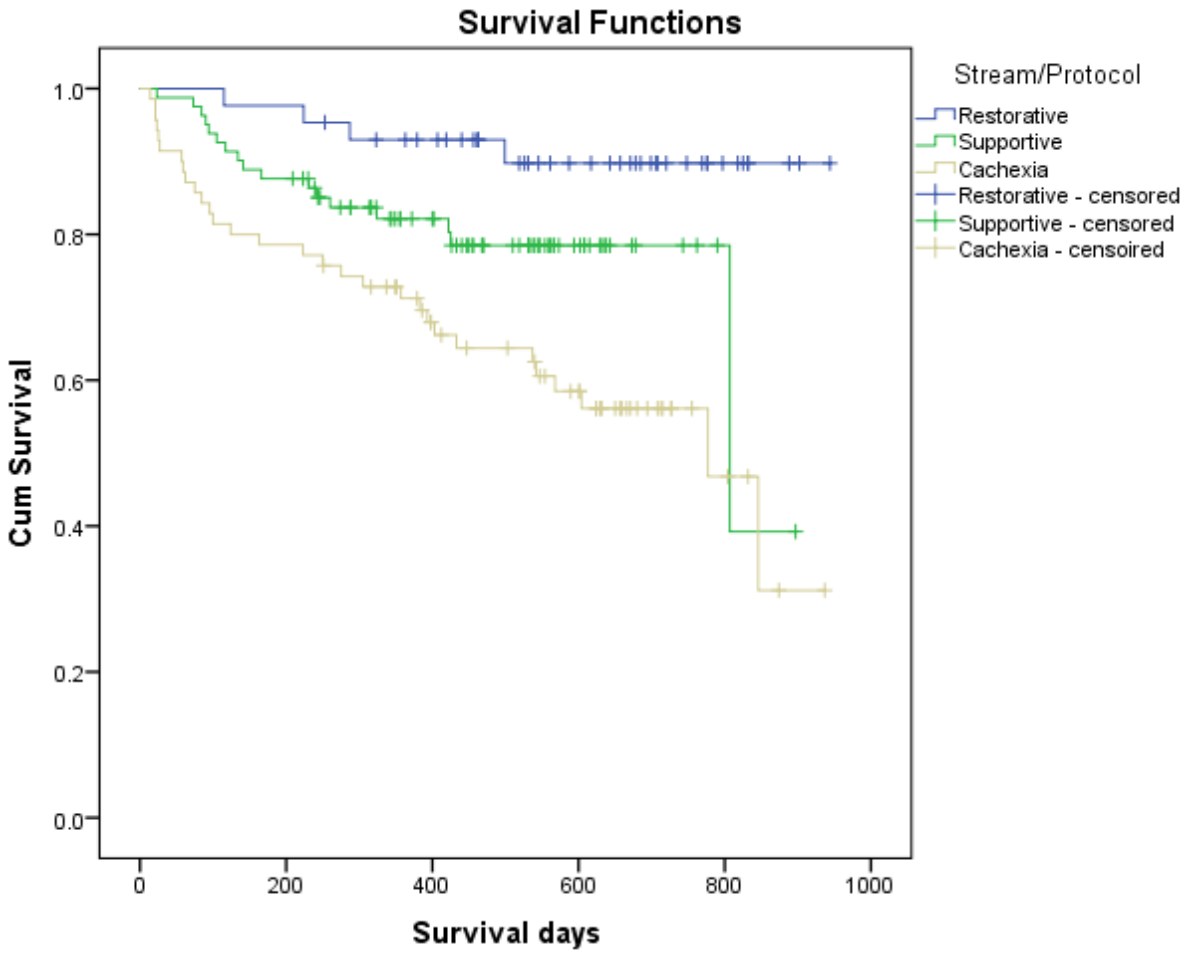
Figure 1: Mean ESAS and aPGSGA scores according to clinic pathway





Legend: ESAS = Edmonton Symptom Assessment System; aPGSGA = abridged Patient-Generated Subjective Global Assessment

Figure 2: Kaplan-Meier survival analysis according to clinic pathways



Legend: Restorative, Supportive and Cachexia represent the three clinical pathways of the MUHC's cancer rehabilitation and cachexia clinic. There was a statistically significant difference in survival distributions for the restorative vs cachexia pathways, $\chi 2(1) = 13.899$, $p < .001$.

3.0 GENERAL DISCUSSION

3.1 Major Findings

The aims of this study were to determine whether nutritional status, as measured by the aPGSGA, was predictive of QOL, physical performance and survival in people with cancer. Approximately 50% of adult cancer patients seen in a cancer rehabilitation and cachexia clinic were malnourished at the start of the study and the overall burden of NIS was high. A major finding was that baseline nutritional status as measured by the aPGSGA was predictive of QOL using both total ESAS score as well as the wellbeing sub-score. Additionally, aPGSGA categories were able to detect differences in 6MWT using a cross-sectional data-set. It was also shown that repeated measures of the aPGSGA predicted changes in total ESAS score when controlling for age, gender, ethnicity, diagnosis, clinic pathway and duration of follow-up.

This study made apparent the variation in criteria used to identify malnutrition, including but not limited to: percentage weight loss (ex: 2%, 5%, 10%) [97]; underweight or low BMI [95]; abnormally low biomarkers (ex: albumin) [130]; and the use of nutrition assessment tools, such as the aPGSGA and SGA [13,16]. There is often a variety of criteria used to detect malnutrition within a single centre, such as the Cleveland Clinic which has six criteria [130]. These criteria include unintentional weight loss, low BMI, visible muscle wasting, low food intake, presence of wounds and abnormal nutritional biomarkers. Additionally, dietitians in that centre used a tool to help identify malnutrition and consequently, found a higher prevalence of malnutrition compared to physicians who did not use a tool [130]. While these criteria are important, they neglect to include NIS or measures of physical performance. The aPGSGA is a standardized, repeatable and reliable tool which measures common features of malnutrition, including NIS and physical performance that is valid for use in people with cancer.

In this study the average BMI was 25.4 kg/m^2 and varied from 24.5 – 28.1 kg/m^2 across aPGSGA triage categories. Even patients classified into the cachexia pathway had a mean BMI of 22.8 kg/m^2 which is above typical norms for undernutrition [93]. Study participants had a greater BMI than what is typically found in other cancer rehabilitation (21.5 kg/m^2) [109] and cachexia clinics (21.0 kg/m^2) [131]. An international consensus of the definition and classification of cancer cachexia identified a BMI < 20 kg/m^2 and ongoing weight loss as being cachectic [97]. Furthermore, an extensive (n = 8160) retrospective chart review examining weight loss in people with cancer determined that a BMI < 20.0 kg/m^2 was associated with the worst survival and that any BMI < 25.0 kg/m^2 still negatively impacted survival, particularly in the presence of weight loss [132]. These findings demonstrate that patients suffer from malnutrition well before they attain a BMI < 18.5 kg/m^2 and supports the use of a BMI < 20, like in this study, to represent underweight. Additionally, BMI on its own may not be sufficient to determine malnutrition and other factors such as ongoing weight loss, NIS and poor physical performance can help confirm the presence of malnutrition.

While percentage weight loss was not retained in this study, the weight sub-score of the aPGSGA did describe severity of weight loss through its scoring system. Participants in the first three aPGSGA triage categories all had a median weight sub-score of zero, whereas patients with an aPGSGA score > 9 had a median score of 1 and mean of 1.9. Thus, patients at greatest risk for malnutrition in this study (aPGSGA score > 9) experienced the most weight loss. In people with cancer, a weight loss ≥ 2.5% increases risk of mortality regardless of BMI [132]. Patients often experience involuntary weight loss well before they are admitted into the clinic; weight loss is actually one of the reasons for referral into the rehabilitation program and consequently, it is

suspected that their rate of weight loss is higher just prior to clinic admission and rate of weight loss would be greater still had patients been accessed earlier.

It was demonstrated that QOL differed according to nutritional status where patients with the highest nutritional status had the highest QOL. There were no differences in QOL between clinic pathways: QOL did not differ based upon the presence or absence of disease (restorative versus other pathways) or disease severity (supportive and cachexia pathways). This disability paradox occurs when, "patients' perceptions of personal health, well-being and life satisfaction are discordant with their objective health status and disability" [133]. Even patients in a hospice setting preserved an acceptable QOL and a positive outlook [134]: a positive QOL becomes living well with, and perhaps despite, considerable illness [133]. This change in valuation of QOL is named the "response shift theory"; patients' perspective of QOL will change in consequence to their illness, but also as a function of time [135]. As patients move into the "intermediate post-injury" (ex: supportive pathway) and the, "long-term post-injury" (ex: restorative and cachexia pathways) phases of their illness they adapt to new conditions [135]. In contrast, malnutrition is an acute and temporary side-effect of cancer and treatment resulting in immediate decline of QOL driven by loss of weight and muscle, decreased food intake, NIS and a decline in physical performance, all of which are measured to some extent by the aPGSGA. Thus, differences in QOL due to varying aPGSGA score appear more important than the appurtenance to different clinic pathways.

While research examining the impact of nutrition on QOL in people with cancer is emerging there is a wealth of literature in other chronic diseases that confirm these findings. Self-assessed physical health and emotional well-being was found to be lowest in malnourished patients (according to SGA classification) receiving peritoneal dialysis [136]. Overall quality of life

has been shown to be lower in malnourished [137-141] and underweight [142] dialysis patients and improves or is maintained following a nutrition intervention [143,144]. Research in gastrointestinal diseases, including cirrhosis and inflammatory bowel disease, reach the same conclusions: nutrition status and NIS are closely linked to QOL, with malnourished and symptomatic patients experiencing worse QOL across the board [145,146]. In people with chronic obstructive pulmonary disease (COPD) health-related QOL was independently associated with malnutrition (BMI < 18.5) [147].

This study found that differences in 6MWT had corresponding differences in the physical activity score of the aPGSGA; both differed across aPGSGA score categories. One study found that prior to initiating treatment for head and neck cancer 47% of patients reported impaired physical performance according to the aPGSGA activity sub-score ≥ 1 [49]. Patients with an aPGSGA activity sub-score ≥ 1 were also more likely to experience NIS than those with scores of 0 (2.8 ± 0.17 compared to 1.0 ± 0.10, $p < 0.001$), experienced greater weight loss ($p < 0.001$) and had shortened survival [49]. The physical activity sub-score has been used to help characterize patients with cancer cachexia [121,148]. While the gold standard for measure of physical of performance remains the 6MWT, the activity sub-score of the aPGSGA seems a decent surrogate self-reported estimate.

Many studies have shown relationships between HGS and nutrition. For example, a three-month intervention with an oral nutrition supplement in malnourished patients according to SGA classification resulted in gains of lean body mass as well as HGS (26.1 kg ± 11.3 kg to 31.5 kg ± 10.1 kg, $p < 0.0001$) in people with non-neoplastic gastro-intestinal disease as compared to controls [149]. Oral nutritional supplementation in malnourished hospitalized elderly people (≥ 75 y) detected statistically significant improvements in HGS as compared to the control group, but

this change does not appear clinically meaningful as the difference amounted to approximately 1 kg [150]. A similar study of oral nutritional supplementation in community-dwelling older adults (≥ 65 y) detected statistical differences in HGS at the 8 week mark between the experimental and placebo groups, but these differences disappeared at the 24 week mark and again reflected only an increase of 1 kg [151]. Thus it appears that HGS is associated with nutrition status, but that changes over time appear to be limited to people who were malnourished at baseline, the magnitude of the change may not be clinically meaningful and the majority of studies are carried out in the elderly or in non-oncological populations which may not be directly comparable with cancer patients.

The usefulness of HGS as a repeated measure in people with cancer has recently been brought into question. Temel et al. (2016) recently published the results from a large scale, double-blinded placebo-controlled clinical trial examining the effects of a ghrelin-receptor agonist, Anamorelin, on physical performance and QOL in people with cancer [152]. This series of clinical trials used HGS as one of the primary end points for the study. While there was a significant increase in weight, lean body mass and improvement in NIS in the active treatment group compared to placebo, there were no changes in HGS. A trial of Enobosarm, an androgen receptor modulator, in cancer patients had similar findings, demonstrating improvements in weight and lean body mass but no detectable differences in HGS over the study period [153]. Studies that successfully demonstrate the usefulness of HGS as an outcome measure in people with cancer typically do so with cross-sectional data. For example, pre-operative HGS was a strong predictor of morbidity and mortality in esophageal cancer patients [154]. The present study is consistent with the large scale randomized clinical trials in that there were no differences

observed in HGS across aPGSGA categories at baseline nor were there differences over the study period, suggesting that HGS may best be used as a single, and not repeated measure.

The presence of a sub-sample of cancer survivors, a group for whom interest is growing rapidly as the number and life expectancy of survivors increases [155,156], allowed for further analysis of the aPGSGA. The mean aPGSGA score for the restorative pathway, representing cancer survivors, was 6.8 at baseline which would classify patients as at moderate risk for malnutrition and in need for a nutrition intervention by a health professional. Information regarding posttreatment or cancer survivor malnutrition is limited, with the majority of work focused on oral cavity, pharynx and digestive organ malignancies. In these populations, posttreatment malnutrition (involuntary weight loss ≥ 10% posttreatment) varies between 16 – 55% [157-159]. In total 14 (32.6%) of restorative patients were malnourished at baseline (aPGSGA score ≥9). Of those who scored ≥ 9 on the aPGSGA their mean total score was 12.5 with an impressive 8.6 points coming from NIS, highlighting the persistence of symptoms even after successful treatment. A survey conducted with 4903 cancer survivors echoes this finding: 92% complained of a symptom related to their disease or treatment, with a quarter of survivors experiencing a high symptom burden [160]. These patients typically had stabilized their weight and improved food intake but still had persistent NIS. This finding highlights how NIS persist even after (successful) completion of treatment [161], and that repeated measurements using the aPGSGA should continue at oncological follow-up visits to monitor these symptoms.

3.2 Strengths

A wealth of literature supports the use of the ESAS questionnaire and aPGSGA as valid assessment tools for use in people with cancer [105,162]. These tools offer time savings for health professionals as they are self-administered and have low response burden. Importantly,

information captured by the aPGSGA is of clinical use above and beyond its total score; answers provided in the questionnaire provide clinicians with a thorough assessment and guide for interventions aimed at improving nutritional status in cancer patients [163]. For example, if a patient identifies nausea and vomiting as NIS of concern, the treating clinician will be able to target those complaints and provide assistance in a timely manner. The use of PRO is likely only going to increase with time as reimbursement for medical care and drug approval may rely on them in the near future [164].

The size of the available sample, both at baseline (n = 207) and for repeated measures (n = 113), was a strength of this study; it met the minimum required sample for relationship testing (estimate of 15) as well as repeated measures (estimate of 114). This allowed for robust statistical analyses and the ability to detect even small differences between groups which were often also clinically meaningful. This distinction is important as clinical research often finds statistically significant results that have little, if any, clinical value. For example, the differences in 6MWT across the lowest (best) and highest (worst) aPGSGA categories was highly significant but also clinically relevant; a mean difference of 71 m is above well above 30 m, which is considered the minimal clinically important difference. Patients with severe chronic obstructive pulmonary disease noted a difference of 54 m (95% confidence interval, 37 – 71 m) in 6MWT represented an appreciable difference in exertion; the American Thoracic Society suggests the upper limit of the confidence interval of 70 m is a significant difference in 6MWT [165,166]. Similarly, the difference in ESAS wellbeing sub-score of 3.9 (aPGSGA score $\leq$ 1) to 5.1 (aPGSGA score $\geq$ 9) can categorize patients into different symptom severity indices, from mild to moderate severity [126]. The ability of the aPGSGA to detect these clinically meaningful

differences above and beyond statistical significance supports its use in both clinical and research domains.

3.3 Limitations

Observational retrospective studies are considered less rigorous than a prospective interventional trial and fewer inferences of causality and directionality cannot be made. However, observational studies may still be helpful with confirming generalizability and applicability of findings from other studies [167]. For example, this study was able to support findings from a prospective interventional trial showing a relationship between QOL and nutritional status in head and neck cancer patients [124]. Prospective clinical trials are limited by their inclusion criteria, which often restrict study participation to patients with specific cancer diagnoses, cancer stages and age groups. These restrictions are not reflective of real-world scenarios.

The generalizability of this study was limited by the underrepresentation Black, Latin American and Asian people as compared to the population of Montreal [128]. This is not surprising, as visible minorities traditionally have lower levels of access and utilization to health care services [168]. The most common diagnoses found in this study were different to those found in the province of Quebec. The most common cancer diagnoses in Quebec are digestive, prostate and lung for men and female oncological, lung and digestive for women [87]. In this study there was an over-representation of haematological/lymphoid and lung cancers in both genders and a dearth of prostate cancer in men. As a tertiary/quaternary health care provider, the McGill University Health Centre (MUHC) receives more difficult to treat and advanced cancers than community (primary/secondary) hospitals. Additionally, patients with lung and haematological/lymphoid cancers present with complex sequelae, including malnutrition, and are more likely to be referred

to rehabilitation clinics focusing on nutrition and exercise [169,170]. Furthermore, treatments for prostate cancer generally result in fewer functional limitations and needs for referral to cancer rehabilitation than treatments for other cancers [160]. The typical problems experienced by survivors of prostate cancer, such as sexual dysfunction, urinary and bowel incontinence, are best suited to a clinic specialized in these areas and not a clinic geared at nutritional and physical therapy [171,172]. Moreover, the attending physician in the cancer rehabilitation and cachexia clinic was also working at the MUHC's lung cancer rapid-investigation clinic resulting in a larger number of people with lung cancer being enrolled into the study. Despite this greater case-complexity, the aPGSGA was still able to detect differences in QOL and physical performance, as well as changes in nutritional status over time in this population.

Only a minority of Canadian health care institutions offer any type of cancer rehabilitation services [173] and consequently, patients in this study might have experienced more favorable outcomes than the general population of cancer patients, such as their ability to improve their QOL, nutritional status and physical performance. Fortunately, the need for such rehabilitative services is now being recognized and will hopefully be the standard of care in the years to come [174,175]. Furthermore, findings in this study with respect to the prevalence of NIS and malnutrition were consistent with other cancer rehabilitation [109] and cachexia clinics [131].

Limitations with the survival analysis included the use of enrollment into the clinic (as opposed to date of cancer diagnosis) as baseline for survival calculation and heterogeneity of follow up duration [129]. Patients who entered the study towards the end of the inclusion period had less than a year of survival follow-up; while included in the analysis, most were still alive at the time resulting in a high degree of censored cases. Precise time of cancer diagnosis is not always known nor practical to collect retrospectively. It is argued that entry into the clinic represents a

meaningful milestone in the patient's treatment trajectory (ex: beginning of disease-free survival or change towards more palliative treatment). While follow-up duration was limited, inclusion into the study went as far back as possible in consideration of the restructuring of the MUHC's cancer rehabilitation program which took place in the fall of 2013. These limitations may account for the inability to detect differences in survival distribution across aPGSGA triage categories and could be addressed in future, ideally prospective, studies.

3.4 Conclusion

This study demonstrated that the aPGSGA, an easy-to-use nutritional assessment tool, is associated with physical performance and QOL in a heterogeneous group of adults with cancer. The clinic pathways devised by clinic members relies upon aPGSGA scores and has been validated by its ability to predict short-term survival. This study adds to the body of evidence supporting the use of the aPGSGA in routine clinical oncology practice as an important nutrition assessment tool and that its use as a repeated measure could rapidly detect the shifts in nutritional status often encountered by patients under treatment.

3.5 Future Directions

A prospective study should take place to confirm the relationships between physical performance, QOL and nutritional status in cancer patients which were found in this study. Future studies could explore the relationship between aPGSGA and tolerance and efficacy of oncological treatment. More work is needed to identify optimal groupings in aPGSGA score to predict survival and hospitalization. Future studies should use a continuous score of the aPGSGA to perform a Cox regression with time-dependent co-variates. Prospective studies should take advantage of the digital version of the aPGSGA in order to facilitate record-keeping and the referral process (see: http://pt-global.org/).

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5.0 Appendices

Appendix 1: Cancer Rehabilitation Pathways

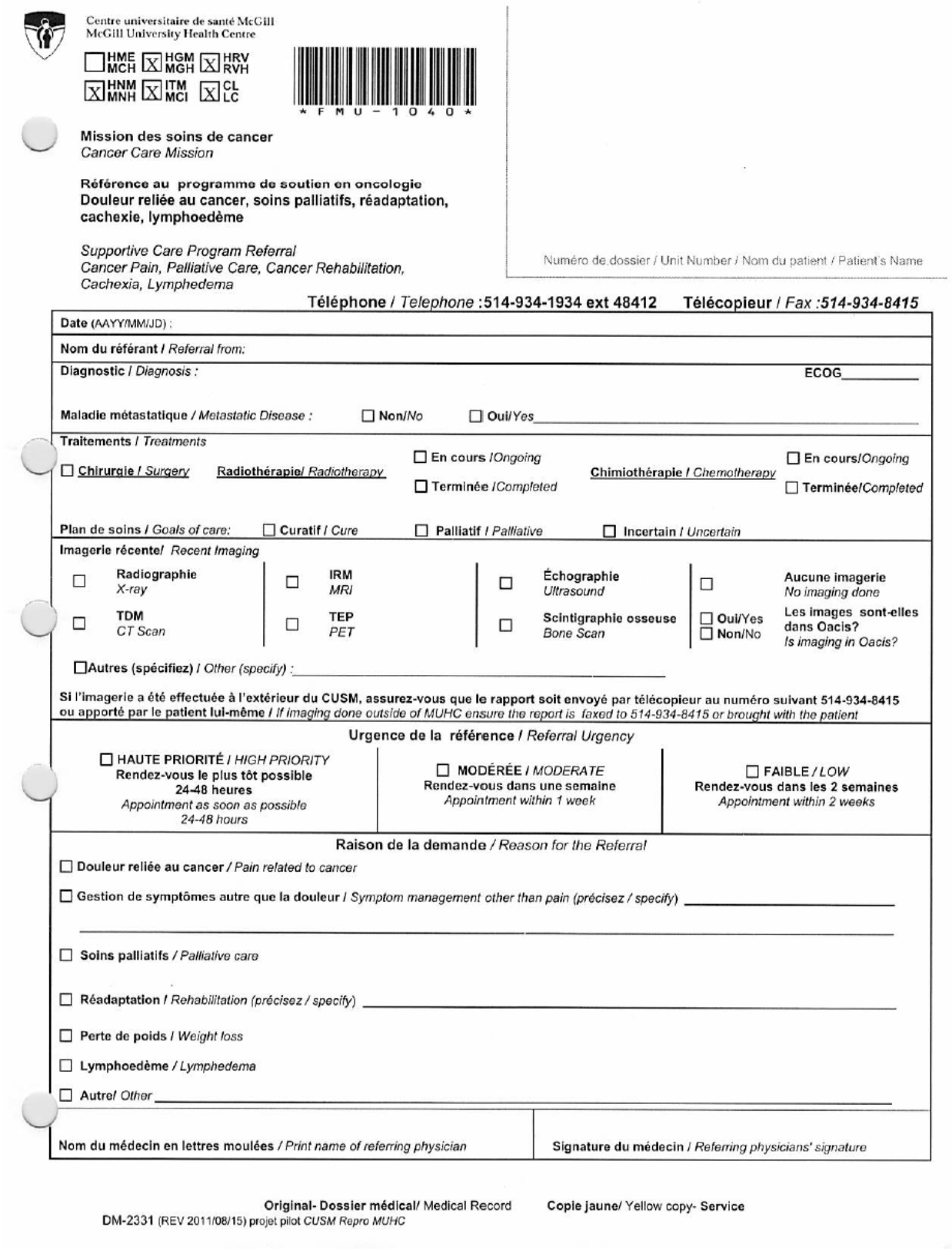
RESTORATIVE REHABILITATION		
Prognosis	No signs of active disease	
Patient Population	- Patient is experiencing problems secondary to cancer and/or its treatments such as deconditioning, fatigue, weakness, nutritional and digestive problems or cognitive loss requiring an interdisciplinary approach (Physician, Nurse, Occupational Therapist, Physical Therapist, Dietitian) - Patient has been seen for post treatment evaluation by oncology and is at least 1 month after treatment is completed	
Goals	- Optimize physical, nutritional and functional status - Return to usual activity - Minimize impact of cognitive dysfunction in daily living - Educate and empower patients to make healthy life choices	
Assessment Tools	First visit (all patients): - Edmonton Symptom Assessment System (ESAS) - Distress Thermometer (DT) - abridged Patient-Generated Subjective Global Assessment (aPG-SGA) - 6 minute walk - Sit to stand - Single Leg Stand (SLS) - Modified CHAMPS (Community Healthy Activities Program for Seniors) - Blood work (chem panel, c-reactive protein, albumin, complete blood count,) - **Hand grip – 1 year pilot** - **Mini-Cog – 1 year pilot** - **Fatigue Symptom Inventory - 1 year pilot** As needed: - Montreal Cognitive Assessment (MOCA) - Blood work (testosterone, etc…) - Pittsburgh Sleep Quality Index - Semmes Weinstein monofilament test - Trail-making - Bells-test Every visit: - ESAS - aPG-SGA - Hand grip – 1 year pilot End-evaluation: - ESAS - DT - a-PG-SGA - 6 min walk - Sit to stand - SLS - Modified CHAMPS - MOCA if previously completed, for comparison - **Hand grip – 1 year pilot** - **FSI - 1 year pilot**	 RN MD RN MD NUT PT PT PT OT MD NUT MD OT OT MD RN,OT OT OT OT RN NUT NUT RN MD RN MD NUT PT PT PT OT OT NUT OT
Timeline	2 – 4 Months	

SUPPORTIVE REHABILITATION		
Prognosis	6 months or greater, patients with active disease	
Patient Population	- Patient is experiencing problems secondary to cancer and/or its treatments such as deconditioning, fatigue, weakness, nutritional and digestive problems or cognitive loss requiring an interdisciplinary approach (Physician, Nurse, Occupational Therapist, Physical Therapist, Dietitian) - Patients with active disease undergoing treatment or not	
Goals	- Optimize physical, nutritional and functional status - Minimize impact of cognitive dysfunction in daily living - Educate and empower patients to make healthy life choices	
Tools	First visit (all patients): - ESAS - DT - a-PG-SGA - 6 min walk - Sit to stand - SLS (Single Leg Stand) - Blood work (SMA-10, CRP, albumin, CBC,) - **Hand grip – 1 year pilot** - **Mini-Cog – 1 year pilot** - **FSI** - 1 year pilot As needed: - MOCA - Blood work (testosterone, etc…) - Pittsburgh Sleep Quality Index - Semmes Weinstein monofilament test - Trail-making - Bells-test Every visit: - ESAS - a-PG-SGA - Hand grip – 1 year pilot End-evaluation: - ESAS - DT - a-PG-SGA - 6 min walk - Sit to stand - SLS - Modified CHAMPS - MOCA if previously completed, for comparison - **Hand grip – 1 year pilot** - **FSI - 1 year pilot**	 RN MD RN MD NUT PT PT PT MD NUT MD OT OT MD RN,OT OT OT OT RN NUT NUT RN MD RN MD NUT PT PT PT OT OT NUT OT
Timeline	2 – 4 months	

CACHEXIA		
Prognosis	Non-curative intent / Greater than 3 months	
Patient Population	- Patients with inoperable/incurable/metastatic cancer presenting with weight loss, anorexia and indicators of abnormal metabolism (anemia, CRP, hypoalbuminemia, increased tumor markers, etc…) - Eastern Cooperative Oncology Group (ECOG) 1 or 2 - Pain control is not primary concern	
Goals	- To optimize nutritional and functional status - Identify and minimize metabolic abnormalities associated with cachexia - Inform and empower the patient to act on their nutritional status.	
Tools	First visit (all patients): - ESAS - DT - a-PG-SGA - Blood work (SMA-10, CRP, albumin, CBC, TSH, LFTs) - Vital signs - Hand grip – 1 year pilot - Mini-Cog – 1 year pilot - FSI if fatigue is $\geq$ 4 on ESAS – 1 year pilot As needed/feasible - Additional blood work (bioavailable testosterone) - OT/PT referral - Referral to MNUPAL (McGill Nutrition and Performance Laboratory) Every visit: - ESAS - a-PG-SGA - Hand grip - Blood work (to be done on a monthly basis prior to clinic appointment) - Vital signs End-evaluation: - FSI if was done at the first visit – 1 year pilot - When appropriate, transition to Cancer Rehab or Day Hospital	 MD,RN MD,RN NUT MD RN NUT MD OT MD MD MD MD,RN NUT NUT MD RN OT
Timeline	- Until return to normal nutritional status or referral to the day hospital.	

LEGEND:
RN: Registered Nurse
MD: Medical Doctor
OT: Occupational Therapist
PT: Physical Therapist
NUT: Nutritionist

Appendix 2: Palliative and supportive care referral form



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☐ HME MCH ☒ HGM MGH ☒ HRV RVH
☒ HNM MNH ☒ ITM MCI ☒ CL LC

* F M U – 1 0 4 0 *

Mission des soins de cancer
Cancer Care Mission

Référence au programme de soutien en oncologie
Douleur reliée au cancer, soins palliatifs, réadaptation, cachexie, lymphoedème

Supportive Care Program Referral
Cancer Pain, Palliative Care, Cancer Rehabilitation, Cachexia, Lymphedema

Numéro de dossier / Unit Number / Nom du patient / Patient's Name

Téléphone / *Telephone* **:514-934-1934 ext 48412** **Télécopieur** / *Fax* **:514-934-8415**

Date (AAYY/MM/JD) :

Nom du référant / *Referral from:*

Diagnostic / *Diagnosis :* **ECOG**_____

Maladie métastatique / *Metastatic Disease :* ☐ **Non**/*No* ☐ **Oui**/*Yes*_____

Traitements / *Treatments*

☐ **Chirurgie** / *Surgery* **Radiothérapie**/ *Radiotherapy* ☐ **En cours** /*Ongoing* ☐ **Terminée** /*Completed* **Chimiothérapie** / *Chemotherapy* ☐ **En cours**/*Ongoing* ☐ **Terminée**/*Completed*

Plan de soins / *Goals of care:* ☐ **Curatif** / *Cure* ☐ **Palliatif** / *Palliative* ☐ **Incertain** / *Uncertain*

Imagerie récente/ *Recent Imaging*

☐ **Radiographie** *X-ray*	☐ **IRM** *MRI*	☐ **Échographie** *Ultrasound*	☐ **Aucune imagerie** *No imaging done*
☐ **TDM** *CT Scan*	☐ **TEP** *PET*	☐ **Scintigraphie osseuse** *Bone Scan*	☐ **Oui**/Yes ☐ **Non**/No **Les images sont-elles dans Oacis?** *Is imaging in Oacis?*

☐**Autres (spécifiez)** / *Other (specify) :*_____

Si l'imagerie a été effectuée à l'extérieur du CUSM, assurez-vous que le rapport soit envoyé par télécopieur au numéro suivant 514-934-8415 **ou apporté par le patient lui-même** / *If imaging done outside of MUHC ensure the report is faxed to 514-934-8415 or brought with the patient*

Urgence de la référence / *Referral Urgency*

☐ **HAUTE PRIORITÉ** / *HIGH PRIORITY* **Rendez-vous le plus tôt possible 24-48 heures** *Appointment as soon as possible 24-48 hours*	☐ **MODÉRÉE** / *MODERATE* **Rendez-vous dans une semaine** *Appointment within 1 week*	☐ **FAIBLE** / *LOW* **Rendez-vous dans les 2 semaines** *Appointment within 2 weeks*

Raison de la demande / *Reason for the Referral*

☐ **Douleur reliée au cancer** / *Pain related to cancer*

☐ **Gestion de symptômes autre que la douleur** / *Symptom management other than pain (précisez / specify)* _____

_____

☐ **Soins palliatifs** / *Palliative care*

☐ **Réadaptation** / *Rehabilitation (précisez / specify)* _____

☐ **Perte de poids** / *Weight loss*

☐ **Lymphoedème** / *Lymphedema*

☐ **Autre**/ *Other* _____

Nom du médecin en lettres moulées / *Print name of referring physician*

Signature du médecin / *Referring physicians' signature*

Original- Dossier médical/ Medical Record **Copie jaune**/ Yellow copy- **Service**

DM-2331 (REV 2011/08/15) projet pilot *CUSM Repro MUHC*