2020-06-19

PREDICTORS OF PSYCHOSOCIAL AND PHYSIOLOGICAL DISTRESS IN COLORECTAL CANCER PATIENTS

Hyrum Eddington

Honors Thesis

PREDICTORS OF PSYCHOSOCIAL AND PHYSIOLOGICAL DISTRESS IN COLORECTAL CANCER PATIENTS

by
Hyrum Surya Eddington

Submitted to Brigham Young University in partial fulfillment of graduation requirements for University Honors

Biology Department
Brigham Young University
June 2020

Advisor: Dr. Arden M. Morris

Honors Coordinator: Dr. Steven L. Peck

ABSTRACT

PREDICTORS OF PSYCHOSOCIAL AND PHYSIOLOGICAL DISTRESS IN COLORECTAL CANCER PATIENTS

Hyrum Surya Eddington
Biology Department
Bachelor of Sciences

Distress among cancer patients has been broadly accepted as an important indicator of patient well-being. However, questions remain such as what patient characteristics are associated with high distress and whether patient-reported distress is correlated with distress biomarkers. To answer these questions, we performed a survey study of 238 colorectal patients in which we assessed patient-reported distress, possible contributors to that distress, and patient anxiety and depression. We also abstracted demographic and clinical information from patient charts and collected measures for salivary cortisol and sarcopenia. We conducted bivariate statistical analyses between patient demographics, clinical factors, and psychosocial measures with our three outcome variables patient-reported distress, cortisol, and sarcopenia, and also performed pair-wise bivariate analyses between each of our outcome variables. We found that patient-reported distress is associated with gender, partnered status, and cancer type and that these effects

vary with patient age, in some cases disproportionately affecting younger patients. We also show that cortisol only displays positive correlations with emotional problems, anxiety, and depression in young patient groups (15-49 yrs, 50-65 yrs) and that sarcopenia is non-associated with psychosocial measures. We found no significant associations between patient-reported distress, salivary cortisol, and sarcopenia.

Our results suggest that young, single patients experience high levels of distress compared to other patient groups, and that salivary cortisol is only effective as a distress biomarker in younger patients. We suggest that despite often being considered less biased, distress biomarkers are not more useful than patient-reported measures in helping clinicians understand distress in colorectal cancer patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Cancer-related distress, defined as "a multifactorial unpleasant experience of a psychological, social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment" [1], has been termed the "sixth vital sign" due to its prevalence and association with adverse clinical outcomes [2]. In fact, the American College of Surgeons Commission on Cancer now requires documentation of distress as part of Comprehensive Cancer Center accreditation [3]. A causal mechanism to explain the association between psychosocial distress, physiologic stress, and clinical outcomes is incomplete, however, and requires further study before it can provide a basis for improved patient care. Identification of patient characteristics associated with or even predictive of high levels of distress could clarify both the nature of distress in cancer patients and guide development of appropriate interventions to minimize distress-related adverse outcomes. Benefits of understanding and ameliorating distress among patients with cancer may apply not only to patients, but to healthcare systems as well, as distressed patients often experience longer hospital stays and incur higher healthcare costs [4-6].

Previous studies of the relationship between distress and poor outcomes among cancer patients have been limited to mixed cancer populations and may miss concerns related to cancer sub-types [7]. Specifically, the role that distress plays in colorectal cancer patient outcomes has not been explored despite the fact that colorectal cancer is the third most common and second most lethal cancer in the United States [8] and is associated with specific socially stigmatized challenges.

In this study, we examined the relationship between patient-reported psychosocial distress and two physiologic biomarkers of stress, salivary cortisol and sarcopenia. Additionally, we analyzed the associations of each indicator with demographic, clinical, and psychosocial variables. We focused on two questions: 1) How are demographic, clinical, and psychosocial factors associated with higher levels of psychosocial distress and physiologic stress? 2) What is the correlation between psychosocial distress and physiologic stress? By narrowing our sample to patients taken from the colorectal cancer population, we provide results that are both enlightening and specific to physicians and patients who interact with and treat colorectal cancer.

METHODS

Study population

After study approval by the University of Michigan Institutional Review Board, we approached sequential patients referred for consultation at a tertiary multidisciplinary colon and rectal cancer (CRC) clinic over a two-year period and invited them to participate in the current study. Simultaneously, we created a prospective clinical registry of patients seen at the multidisciplinary clinic including information from in-person surveys and chart review. Data were abstracted by research assistants and validated by clinician members of the research team. The clinical registry was reviewed regularly to ensure that each patient's record was updated until they reached surveillance, at which time the record was designated as complete. For the current study, patients were included if they had a new diagnosis of colon or rectal adenocarcinoma, were able to read, write, and speak English, and provided informed consent. Patients with other diagnoses such as anal squamous cell carcinoma, gastrointestinal stromal tumors (GIST), carcinoid, melanoma, or appendiceal cancer were excluded from the study. Patients who were prescribed medications that affect salivary cortisol levels (i.e. estrogens, synthetic glucocorticoids, androgens, and phenytoin) were also excluded for analyses involving cortisol as a distress indicator.

Clinical and psychosocial measures

Demographic and clinical data for each eligible patient were abstracted from the electronic medical record. Abstracted demographic data included age, sex, race, and whether patients listed Medicare, Medicaid, Other, or None/Self-Pay as their primary

insurance. Abstracted clinical data include cancer type, cancer stage, as well as physical and mental health comorbidities derived from patient charts.

Patient-reported distress and psychosocial variables including social, emotional, and physical needs were collected via a survey administered during the first clinical visit. Patient-reported distress and psychosocial variables were assessed using survey tools including the Distress Thermometer [9] and Impact Thermometer [10] (collectively DIT), the Problem List (PL), [11] and the Hospital Anxiety and Depression Scale (HADS) [12]. Both the DIT and the PL are tools developed by the National Comprehensive Cancer Network (NCCN). The DIT includes two measures which patients rate on a 1-10 scale: first, the distress they are experiencing, and second, the impact that distress has on their day-to-day life. The PL allows patients to indicate unmet needs contributing to their distress, classified as emotional, physical, spiritual, social, and practical needs. For the purpose of this study, we added problems particularly relevant for CRC patients to the standard PL (stoma bag, flatulence, strength). The previously validated HADS instrument classifies each patient as normal, borderline, or abnormal for separate domains of depression and anxiety.

Salivary Cortisol

In order to measure salivary cortisol, eligible patients were provided with a saliva collection kit (Sarstedt Inc., Nümbrecht, Germany) and were instructed to chew a cotton roll at 3 pm any day during the week following their appointment and received one reminder phone call. Given the diurnal variation in cortisol levels, the time 3 pm was chosen because it has the highest likelihood of producing an unaffected, undistorted

cortisol measurement [13]. Saliva samples were mailed in the accompanying envelope for laboratory assessment of cortisol content.

Sarcopenia

Patient frailty was assessed by psoas density abstracted from computed tomography (CT) scans collected as part of the initial clinical evaluation. We calculated two morphometric indicators of sarcopenia, total psoas muscle area and mean psoas muscle density [14], from CT scans using algorithms programmed in the Analytic Morphomics Lab at the UM [15, 16].

Patient CT images in closest temporal proximity to date of study consent were loaded. CT imaging technique including dose parameters and contrast administration varied with patient and institution, but 5 mm sections were used for all study measurements. At the level of the superior endplate of L4, bilateral psoas muscles were manually contoured and the sum of their areas recorded. This value was normalized by patient height for subsequent comparisons. Regions of interest were created and CT density (HU with SD) recorded including full manual contour of bilateral psoas muscles as above. All measurements were performed by a single abdominal radiologist with 7 years of post-residency experience on a dedicated workstation (GE Advantage Workstation, v. 4.6, Waukesha, WI).

Statistical Analysis

The primary outcomes were patient-reported distress (1-10 scale), and the two biomarkers salivary cortisol (ng/mL) and sarcopenia (measured as total and mean psoas density) To test for associations between these primary outcomes and patient

demographics (i.e. gender, race, partnered status, cancer type, and cancer stage), we performed Wilcoxon rank-sum tests. In addition to patient demographics, we evaluated the relationship between primary outcomes with HADS anxiety and depression, and with PL measures (i.e. emotional, social, physical and total problems) using Spearman rank correlations. Analyses for each of these variable sets were performed for the entire study population and then stratified by age categories: 15-49 years, 50-65 years, and 66+ years. Statistical analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria) [17].

RESULTS

Out of 315 patients approached for participation in our study, 268 (85%) consented to participate and 238 (76%) completed both the survey and the salivary cortisol sample. Among our participants, 59% were male, 86% were of white race (Table 1). Twenty-one percent were ≤ age 49 years, 44% were 50-65 years, and 35% were ≥ 66 years. Thirty-seven percent of participants reported Medicare as their primary insurance, 8% reported Medicaid, and 54% reported "Other". Sixty-three percent of participants were diagnosed with colon cancer, while 37% were diagnosed with rectal cancer. Cancer stage was derived from the electronic health record and included 9% Stage I, 16% Stage II, 39% Stage III, and 36% Stage IV.

		Age Group (years)		
Factor	Overall, n=238	15-49, n=50	50-65, n=104	66+, n=84
Sex				
Male	59%	50%	59%	64%
Female	41%	50%	41%	36%
Race				
White	86%	80%	85%	91%
Non-white	14%	20%	15%	9.5%
Relationship Status				
Single	32%	28%	24%	43%
Partnered	69%	72%	76%	57%
Insurance				
Medicare	37%	6.0%	11%	89
Medicaid	8.0%	8.0%	14%	0%
None/Self-Pay	0.4%	2.0%	0%	0%
Other	54%	84%	75%	11%
Cancer Type				
Colon	63%	58%	61%	69%
Rectal	37%	42%	39%	31%
Cancer Stage				
I	9.3%	6.0%	6.9%	14%
II	16%	20%	17%	13%
III	39%	36%	41%	38%
IV	36%	38%	35%	35%

Table 1: Demographic and clinical characteristics of the patient cohort

We found significant associations between sociodemographic and clinical characteristics and patient-reported psychosocial distress (Table 2). Men had higher median patient-reported distress than women (M: 3.0, F: 5.0, $p < .001$), single patients had higher median patient-reported distress than partnered patients (S: 5.0, P: 4.0, $p = .018$), and patients diagnosed with rectal cancer had higher median patient-reported distress than those diagnosed with colon cancer (C: 4.0, R: 5.0, $p = .026$). When stratified by age group, the effects of gender and partnered status were driven primarily by differences in median patient-reported distress among the youngest and oldest age groups. Specifically, the increase in distress among women relative to men was significant only among the 50-65 and 66+ age groups (50-65; F: 5.0, M: 4.0, $p = .015$, 66+; F: 5.0, M: 2.0, $p = .015$). Similarly, the differences in median distress by partnered status were observed only among the youngest age group (mean patient-reported distress: S: 7, P: 3.5, $p = .005$). Conversely, while there was an overall significant difference in median distress between colon and rectal cancer (C: 4.0, R: 5.0, $p = .026$), there were no significant differences in any individual age group, although median rectal distress was consistently higher than median colon distress.

Every Problem List category at almost every age group as well as HADS-based anxiety was positively correlated with patient-reported distress. In contrast, depression was only correlated with patient-reported distress in the youngest age group (Table 2).

We found no overall association between sociodemographic factors, anxiety and depression scores, or PL values and the physiologic stress biomarkers, cortisol and sarcopenia, with the exception of a significant difference in total psoas area between men and women (M: 2998.7, 1832.3). Nor did we find any correlation between patient-

reported psychosocial distress and the physiologic stress biomarkers, salivary cortisol and sarcopenia.

Patient Factors and Patient-reported Psychosocial Distress, Stratified by Age Group.	**Median Distress (range 1-10) by Age Group (years)**			
Sociodemographic and clinical	Overall	15-49	50-65	66+
Sex				
Female	5.0**	5.0	5.0**	5.0**
Male	3.0	4.5	4.0	2.0
Race				
White	4.0	4.0	5.0	4.0
Non-White	4.5	5.5	3.5	3.0
Relationship status				
Single	5.0**	7.0**	5.0	5.0*
Partnered	4.0	3.5	4.0	3.0
Cancer site				
Colon	4.0**	4.0	4.0*	2.0
Rectal	5.0	6.0	5.0	4.0
	Correlation by Age Group (years)			
HADS/PL Measures	Overall	15-49	50-65	66+
Anxiety	0.55**	0.62**	0.59**	0.44**
Depression	0.19**	0.22**	0.13*	0.22*
Physical Problems	0.42**	0.41**	0.42**	0.43**
Emotional Problems	0.61**	0.57**	0.61**	0.62**
Social Problems	0.28**	0.26**	0.30**	0.27**
Total Problems	0.57**	0.54**	0.58**	0.55**

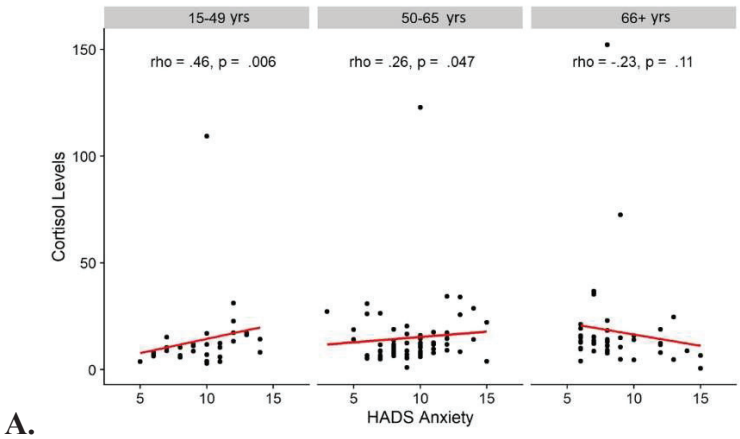
Table 2: Table shows effects and p-values of tests of association between pt-reported distress and demographic and psychosocial variables. For categorical demographic variables, the group medians are shown along with the p-value of the corresponding Mann-Whitney U test. For psychosocial numeric variables, Spearman rank correlation (Spearman's rho) is

Within specific age group stratifications, however, anxiety, depression, Emotional Problems, and Social Problems were correlated with cortisol levels (Table 3). Anxiety and cortisol levels were positively correlated in younger patients (15-49 and 50-65 age groups) but showed no significant pattern in the oldest age group (15-49; rho: .046, p = .006, 50-65: rho: .026, p = .047) (Figure 1). Depression was also positively correlated with cortisol in the 15-49 age group (rho: .54, p = .001), but was negatively correlated with cortisol in the oldest 66+ age group (rho: -.37, p = .010). Patient-reported Emotional

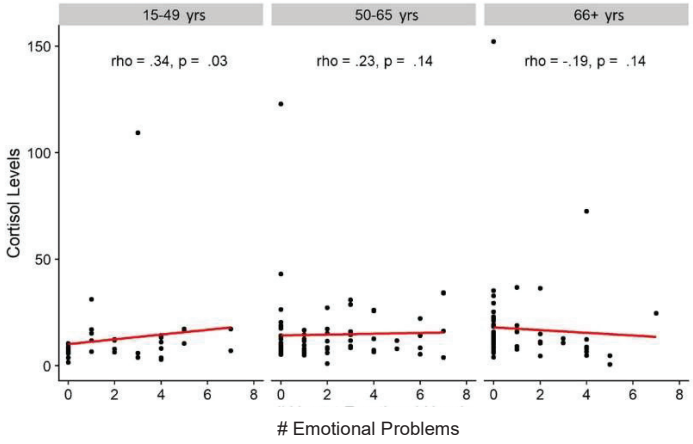
Problems were significantly correlated with cortisol levels in the youngest age group (rho: .34, p =.030) but showed no correlation with cortisol in the 50-65 and 66+ age group. Social Problems were positively correlated with cortisol only in the 50-65 age group (rho: .32, p = .007).

Patient Factors and Salivary Cortisol, Stratified by Age Group.	**Median Cortisol (ng/mL) by Age Group (years)**			
Sociodemographic and clinical	Overall	15-49	50-65	66+
Sex				
Female	11	8	11.7	12.1
Male	10.6	10.4	10.1	12.6
Race				
White	11.1	8.6	11.7	12.3
Non-White	8.2	6.5	7.6	14.9
Relationship status				
Single	11.7	9.1	10.4	12.8
Partnered	10.4	8.6	10.6	11.8
Cancer site				
Colon	10.5	8.1	10.1	12.9
Rectal	11	9.6	11	11.2
	Correlation by Age Group (years)			
HADS/PL Measures	Overall	15-49	50-65	66+
Anxiety	0.08	.46**	.26**	-0.23
Depression	-0.06	.54**	-0.22	-.37**
Physical Problems	.13*	0.20	0.10	0.10
Emotional Problems	0.03	.34**	0.14	-0.19
Social Problems	.19**	0.19	.32**	0.04
Total Problems	.13*	.30*	0.19	-0.01

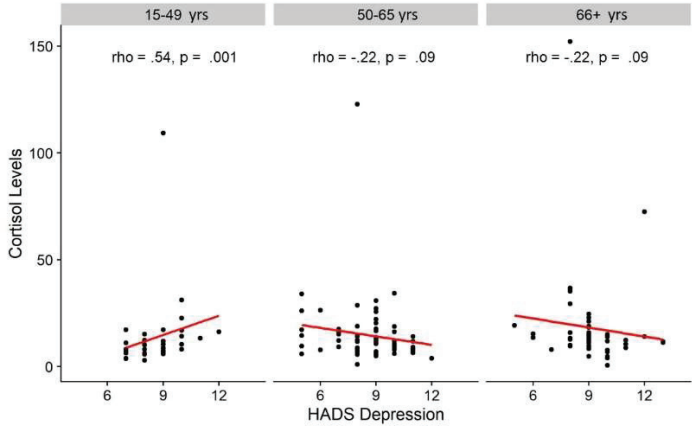
Table 3: Table shows effects and p-values of tests of association between cortisol and demographic and psychosocial variables. For categorical, demographic variables, the group medians are shown along with the p-value of the corresponding Mann-Whitney U test. For psychosocial, numeric variables, Spearman's rank rho is reported along with corresponding p-value. P-value keys are as follows: ** -> p <.05, * -> p < .1



A.



B.



C.

Figure 1: Scatterplots fitted with linear models show positive correlations between cortisol and anxiety, depression, and unmet needs in age group 15-49, and between cortisol and emotional needs in age group 50-65. Depression is negatively correlated with cortisol in the 66+ age group. Test statistics and p-values were calculated using Spearman rank correlations.

DISCUSSION

Our study aimed to examine correlations between patient-reported psychosocial distress as well as two biomarkers of physiologic stress, cortisol and sarcopenia, among colon and rectal cancer patients to determine the most sensitive indicator among this patient population. We found that patient-reported distress was significantly associated with patient demographic and clinical characteristics and was, with the exception of depression, positively correlated with all HADS and PL measures among all age groups. Gender, partnered status, and cancer type also were associated with patient-reported distress, but not race.

In our analysis of patient demographics associated with patient-reported distress, we found that the gap in distress between single and partnered individuals was driven by the large disparity of median distress in the 15-49 age group (S: 7, P: 3.5), suggesting that the distress associated with cancer as a single individual is exacerbated in younger cancer populations. While literature consistently suggests that youth and singleness are each separately associated with high distress levels compared to other cancer populations [18-20], our study additionally implies that the experience of distress in young and single cancer patients may be even more acute than either of these life circumstances alone.

Although gender effects related to psychosocial distress have not previously been studied among patients with colorectal cancer, our finding that median distress was higher among women is consistent with the breast cancer literature [21, 22], which supports a hypothesis that women report more distress related to body-image and other social effects [23] [24]. This gender difference in median distress was largest in the oldest 66+ age group. Women also had lower median psoas density, which would normally

indicate higher levels of sarcopenia but may have been due to innate gender differences in muscle composition [25]. A slight increase in median distress was observed among patients with rectal vs. colon cancer. These findings are consistent with previous literature indicating distress related to radical surgery, body image, social stigma, and the bother of caring for a potentially permanent stoma [26, 27].

The finding that salivary cortisol was only positively correlated with depression, anxiety, and emotional problems among younger age groups suggests that cortisol may be an ineffective biomarker of cancer-related distress for older patients. Age results in a decrease in activity within the hypothalamic-pituitary-adrenal (HPA) axis [28]. This decrease in sensitivity may explain why anxiety and emotional problems show no correlation with salivary cortisol in the 66+ age group. Notably, depression is negatively correlated with salivary cortisol in the 66+ age group, which seems to be inconsistent with an HPA axis reduction explanation. However, recent literature suggests that high cortisol levels in elderly individuals along with reduced axis sensitivity are associated with adverse neurological outcomes including depression [28]. Why this pattern is only seen then in depression and not in anxiety as well in our study is currently unclear.

We found no correlation between patient-reported distress and sarcopenia or salivary cortisol, but did find a significant positive correlation between HADS and PL measures, suggesting that biomarkers are not superior to patient-reported measures for distress. Similar to salivary cortisol, sarcopenia may be influenced by confounding variables such as age. Additionally, there were no significant pairwise correlations among the three distress measures, suggesting that these three measures are not equivalent in

assessing patient distress, though biomarkers may demonstrate usefulness in determining likelihood of other clinical outcomes.

Our study was subject to several limitations which should be noted. Our sample population was of limited racial/ethnic diversity and therefore for analytical purposes we collapsed all non-white race categories into one variable to provide additional statistical power. In addition, we noted 4 subjects with high outlier cortisol levels. Although we repeated testing to confirm these results and searched for exogenous sources, it is possible that these data resulted from undocumented medications such as SSRI's. While we excluded patients with medications that may affect cortisol levels, the remaining presence of some extreme outliers suggests some relevant medications might not have been captured. Despite these limitations, we are confident in our results and expect that future studies with additional medication exclusion parameters would find similar results, and we recommend a more diverse sample population in order to draw race-related conclusions.

Our study found that gender, age, partnered status, and cancer type are all important patient characteristics to consider when evaluating a patient's risk for psychosocial distress. Additionally, our study found an overall lack of concordance between patient-reported psychosocial distress and biomarkers of physiologic stress. While it might be expected that biomarkers are more unbiased therefore more reliable indicators of patient distress, we found few associations between cortisol and sarcopenia with patient characteristics and HADS and PL measures. In conclusion, our data suggest that given the difficulty of reliably measuring patient distress from biomarkers, measures

of patient-reported psychosocial distress are more useful than biomarkers for clinicians to understand and respond to the cancer patient experience.

WORKS CITED

1. National Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology: Distress Management, version 3.2012*. 2012, National Comprehensive Cancer Network: Fort Washington, PA.
2. Allen, J.O., et al., *Expanding the NCCN guidelines for distress management: a model of barriers to the use of coping resources.* J Community Support Oncol, 2014. **12**(8): p. 271-7.
3. American College of Surgeons, C.o.C., *Cancer Program Standards 2012: Ensuring Patient-Centered Care, v 1.1*. 2012, American College of Surgeons: Chicago, IL.
4. Hamer, M., Y. Chida, and G.J. Molloy, *Psychological distress and cancer mortality.* Journal of Psychosomatic Research, 2009. **66**(3): p. 255-8.
5. Faller, H., et al., *Coping, distress, and survival among patients with lung cancer.* Archives of General Psychiatry, 1999. **56**(8): p. 756-62.
6. Brown, K.W., et al., *Psychological Distress and Cancer Survival: A Follow-Up 10 Years After Diagnosis.* Psychosomatic Medicine, 2003. **65**(4): p. 636-643.
7. Carlson, L.E., A. Waller, and A.J. Mitchell, *Screening for distress and unmet needs in patients with cancer: review and recommendations.* Journal of Clinical Oncology, 2012. **30**(11): p. 1160-77.
8. Jemal, A., et al., *Annual Report to the Nation on the Status of Cancer, 1975–2009, Featuring the Burden and Trends in Human Papillomavirus (HPV)–Associated Cancers and HPV Vaccination Coverage Levels.* Journal of the National Cancer Institute, 2013.
9. Roth, A.J., et al., *Rapid screening for psychologic distress in men with prostate carcinoma.* Cancer, 1998. **82**(10): p. 1904-1908.
10. Akizuki, N., et al., *Development of an Impact Thermometer for use in combination with the Distress Thermometer as a brief screening tool for adjustment disorders and/or major depression in cancer patients.* Journal of Pain and Symptom Management, 2005. **29**(1): p. 91-99.
11. *Distress Management Clinical Practice Guidelines in Oncology.* 2003. **1**(3): p. 344.
12. Zigmond, A.S. and R.P. Snaith, *The Hospital Anxiety and Depression Scale.* Acta Psychiatrica Scandinavica, 1983. **67**(6): p. 361-370.
13. Hsiao, C.-P., et al., *High perceived stress is linked to afternoon cortisol levels and greater symptom distress in patients with localized prostate cancer.* Cancer Nursing, 2011. **34**(6): p. 470-8.
14. Ma, X., et al., *Imaging-based quantification of hepatic fat: methods and clinical applications.* Radiographics, 2009. **29**(5): p. 1253-77.
15. Poterucha, T., B. Burnette, and A. Jatoi, *A decline in weight and attrition of muscle in colorectal cancer patients receiving chemotherapy with bevacizumab.* Medical Oncology, 2012. **29**(2): p. 1005-9.
16. Caram, M., et al., *The Impact of Sarcopenia On Transplant-Related Outcomes in Patients with Non-Hodgkin's and Hodgkin's Lymphoma*, in *American Society for Blood and Marrow Transplantation and Center for International Blood and Marrow Transplant Research, BMT Tandem Meetings*. 2013: Salt Lake City, UT.
17. Team, R.C., *R: A language and environment for statistical computing.* 2013.
18. Kwak, M., et al., *Trajectories of psychological distress in adolescent and young adult patients with cancer: a 1-year longitudinal study.* Journal of clinical oncology, 2013. **31**(17): p. 2160-2166.

19. Rosen, A., K.A. Rodriguez-Wallberg, and L. Rosenzweig, *Psychosocial Distress in Young Cancer Survivors.* Seminars in Oncology Nursing, 2009. **25**(4): p. 268-277.
20. Tuinman, M.A., et al., *Distress, problems and referral wish of cancer patients: differences according to relationship status and life phase.* Psycho-Oncology, 2015. **24**(6): p. 699-704.
21. Faller, H., et al., *Perceived need for psychosocial support depending on emotional distress and mental comorbidity in men and women with cancer.* Journal of Psychosomatic Research, 2016. **81**: p. 24-30.
22. Hagedoorn, M., et al., *Couples dealing with cancer: role and gender differences regarding psychological distress and quality of life.* Psychooncology, 2000. **9**(3): p. 232-42.
23. Koyama, A., et al., *Gender differences in cancer-related distress in Japan: a retrospective observation study.* BioPsychoSocial Medicine, 2016. **10**(1): p. 10.
24. Choi, E.K., et al., *Impact of chemotherapy-induced alopecia distress on body image, psychosocial well-being, and depression in breast cancer patients.* Psychooncology, 2014. **23**(10): p. 1103-10.
25. Cooper, R.G., S. Holli, and M.I. Jayson, *Gender variation of human spinal and paraspinal structures.* Clin Biomech (Bristol, Avon), 1992. **7**(2): p. 120-4.
26. Ho, M.Y., et al., *A qualitative focus group study to identify the needs of survivors of stage II and III colorectal cancer.* Psychooncology, 2016. **25**(12): p. 1470-1476.
27. Sprangers, M.A., et al., *Quality of life in colorectal cancer. Stoma vs. nonstoma patients.* Dis Colon Rectum, 1995. **38**(4): p. 361-9.
28. Yiallouris, A., et al., *Adrenal Aging and Its Implications on Stress Responsiveness in Humans.* Frontiers in endocrinology, 2019. **10**: p. 54-54.