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LOYOLA UNIVERSITY CHICAGO

THE SYMPTOM EXPERIENCE OF PATIENTS RECEIVING EPIDERMAL
GROWTH FACTOR RECEPTOR INHIBITORS

A DISSERTATION SUBMITTED TO
THE FACULTY OF THE GRADUATE SCHOOL
IN CANDIDACY FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

PROGRAM IN NURSING

BY

JOSIE HOWARD-RUBEN

CHICAGO, ILLINOIS

DECEMBER 2014

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Success consists of going from failure to failure without loss of enthusiasm.

--Winston Churchill

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LIST OF ABBREVIATIONS

<i>ALK</i>	anaplastic lymphoma receptor tyrosine kinase
Bcr-ABL	fusion gene associated with chronic myelogenous leukemia
ECOG	Eastern Cooperative Oncology Group
<i>EGFR</i>	epidermal growth factor receptor
EGFRI	epidermal growth factor receptor inhibitor
ErbB1	tyrosine kinase receptor member of EGFR family, HER1
ErbB2	tyrosine kinase receptor member of EGFR family, HER2
ErbB3	tyrosine kinase receptor member of EGFR family, HER3
ErbB4	tyrosine kinase receptor member of EGFR family, HER4
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-EGFRI-18	Functional Assessment of Cancer Therapy-EGFRI
GDI	Global Distress Index
HCA	hierarchical cluster analysis
HER1	human epidermal growth factor receptor 1, also EGFR
HER 2/neu	human epidermal growth factor receptor 2
HER3	human epidermal growth factor receptor 3
HER4	human epidermal growth factor receptor 4
KMO	Kaiser-Meyer-Olkin statistic
MHI-5	Mental Health Index-5

MOAB	monoclonal antibody
MSAS	Memorial Symptom Assessment Scale
MSAS-SF	Memorial Symptom Assessment Scale-Short Form
ONS	Oncology Nursing Society
PAF	principal axis factoring
PS-VAS	Performance Status-Visual Analog Scale
SPSS	Statistical Package for the Social Sciences
TKI	tyrosine kinase inhibitor
TOUS	theory of unpleasant symptoms

ABSTRACT

This study explored the symptom experience of patients receiving epidermal growth factor receptor inhibitors (EGFRIs) for breast, colon, head and neck, and colon cancer. EGFRIs are targeted therapies used at various points along the treatment continuum for these solid tumors, and may be first, second or third-line agents which can be used as single agents or in combination with other therapies. The most common side effect of these agents include dermatologic effects, such as rashes, hair, and nail changes, but they can also contribute to other side effects such as fatigue, anxiety and diarrhea. Most previous work has addressed the dermatologic side effects and has not addressed the holistic patient experience. A descriptive, correlational design, guided by the theory of unpleasant symptoms, explored the overall symptom experience, including dermatologic and other symptoms, in patients receiving these treatments. The relationship of key variables (age, diagnosis, gender, EGFRi therapy, and symptom clusters) to the outcomes of quality of life, psychological status, and functional status was also explored. Co-occurring symptoms (symptom clusters) were identified by factor analysis procedures. Three symptom clusters were identified: a psychological-cognitive cluster; a treatment-related dermatologic cluster that has not been previously identified as a symptom cluster; and, a mucocutaneous and fatigue cluster. These symptom clusters had differing impacts on outcomes, so knowledge of the effects of these symptom clusters can guide nursing practice in the care of patients receiving these targeted therapies.

Keywords: Symptom experience, factor analysis, theory of unpleasant symptoms, epidermal growth factor receptor inhibitor, quality of life, functional performance, psychological status, symptom cluster.

CHAPTER ONE

INTRODUCTION

Significance of the Problem

People living with cancer must cope not only with the threat of serious illness, but also with bothersome and disruptive symptoms brought on by rigorous cancer therapies. Chemotherapy and radiation therapy are associated with well-known symptoms, such as hair loss, nausea and vomiting, and myelosuppression, as well as symptoms resulting from organ toxicities, and an array of long-term side effects. The symptom experiences of patients receiving these traditional modalities of treatment have been extensively studied and are well understood by health care providers. In recent years, however, targeted and biologic therapies have outpaced traditional chemotherapy for new drug approvals in oncology, and much remains to be discovered about the symptom experience associated with these agents.

The newer targeted therapies exert their therapeutic effects differently than cytotoxic chemotherapies. Rather than killing both healthy and cancer cells, targeted therapies aim to more precisely alter cellular function. Some focus on cell signaling pathways, others induce apoptosis (programmed cell death), some influence the immune system, while others deliver radiation or other substances to cancer cells (Targeted Cancer Therapies, 2014). Treatment with targeted therapies, such as the epidermal growth factor receptor inhibitors (EGFRIs), may result in a challenging symptom

experience that features novel dermatologic symptoms that patients may not expect to be associated with cancer treatment.

The present study explored the symptom experience of patients receiving epidermal growth factor receptor inhibitors (EGFRIs), also called anti-*EGFR* therapies or signal transduction inhibitors. Rather than exerting their mechanism of action through the cytotoxic effects characteristic of conventional chemotherapy, targeting rapidly dividing cells at various points in the cell cycle, EGFRIs work by influencing human epidermal growth factor receptor (*EGFR*) signaling pathways. The human epidermal growth factor family comprises four tyrosine kinase receptors, including *ErbB1* or *HER1* (*EGFR*), *ErbB2* (*HER 2/neu*), *ErbB3* or *HER3*, and *ErbB4* or *HER4* (Mahipal, Kothari, & Gupta, 2014), but for this research study, the focus is on EGFRIs.

EGFRIs are currently indicated for selected patients diagnosed with advanced non-small cell lung cancer, breast cancer, colon cancer, pancreatic cancer, head and neck cancers, and other solid tumors of epithelial origin where epidermal growth factor receptors (*EGFR*) are overexpressed.

New Targets for Cancer Therapy

The unstable genome of the cancer cell has been described as its Achilles' heel (Levitzki & Klein, 2010), highlighting the genome as a susceptible target. Abnormal and overactive cell signaling pathways result from chromosomal mutations, mutations of oncogenes and tumor suppressor genes, and other epigenetic changes. Most readers will be familiar with an early and newsworthy application of a targeted therapy, using the drug imatinib (Gleevec®), for a chronic form of leukemia associated with the *Bcr-Abl*

tyrosine kinase oncogene. Patients treated with this agent demonstrate a remarkably improved remission rate of greater than 90% (Balagula, Rosen, & Lacouture, 2011), offering a glimpse of the potential of targeted therapies in cancer. As molecular profiling of tumors continues to be refined, subtype characteristics of tumors will influence the type of targeted therapy prescribed, as in the case of EGFRIs.

Science is just beginning to identify these molecular changes that lead to the development of cancer, and as they are discovered, future therapies will target these genetic aberrations. One such mutation affects the *EGFR* protein on the surface of cancer cells, contributing to the development of various solid tumors. The *EGFR* gene encodes a type of protein kinase which serves as a receptor for the epidermal growth factors family. In normal cells, epidermal growth factor binds to *EGFRs* and spurs activation of signaling pathways, which in turn, help to govern cell growth, proliferation, and migration. Activation of overexpressed or mutated *EGFRs* requires a process of binding, dimerization and phosphorylation. When a mutation creates an excess number of receptors, the result is pathway dysregulation and subsequent abnormal cell growth, cell proliferation, avoidance of apoptosis (programmed cell death), cell migration and neovascularization of tumors.

EGFRs include an extracellular ligand-binding domain, a transmembrane region, and an intracellular tyrosine kinase domain. Both the extracellular and intracellular domains of these proteins are treatment targets. EGFRIs include both monoclonal antibodies (MOABs), cetuximab and panitumumab, which are given by infusion, and tyrosine kinase inhibitors (TKIs), afatinib, erlotinib, gefitinib, and lapatinib, which are

oral agents. MOABs target tyrosine kinase receptors outside of the cell, while TKIs are small molecules that target the intracellular domain.

Lung cancer has a projected incidence in the United States of 224,210 (Siegel, Ma, Zou, & Jemal, 2014), and is the most common cause of cancer death globally, contributing to more than a million deaths (Network, 2014). Activated oncogenes such as *EGFR* or other mutations (e.g. *ALK*) occur to varying degrees in various patient populations, but the impact of EGFRi therapy on the patient symptom experience will be significant, primarily because of the prevalence of lung cancer. In lung cancer, approximately 10-15% of Caucasian, and 40% of Asian non-small cell lung cancer patients carry the *EGFR* mutation (Cooper, Lam, O'Toole, & Minna, 2013), making treatment with EGFRIs a first treatment option over chemotherapy. Genetic signposts, such as this mutation and others, now influence treatment selection, allowing providers to tailor therapy, when possible, for each patient.

Activating *EGFR* mutations occur most commonly in patients in lung cancer patients with no prior history of smoking, in adenocarcinoma, in females, and in Asians, and occur in a small area of the *EGFR* gene. Because EGFRIs have a different mechanism of action than traditional chemotherapy, their symptom profile is different and less familiar to practitioners and patients alike. The impact of these agents on the symptom experience is just beginning to be understood, and this study will add to the evidence on this topic.

Overview of EGFR-Related Symptoms

The on-target effects of EGFRIs result in a high incidence of dermatologic toxicities, such as skin, hair and nail changes, because EGFR is essential for the normal physiology of the skin. *EGFR* is expressed in the basal cell layer of the epidermis, in the outer layers of the hair follicles, as well as in the sebaceous epithelium (Lacouture, 2006; Lynch et al., 2007; Andreis et al., 2010; Lacouture, Maitland, et al., 2010; Chan & Tan, 2011; Chanprapaph, Vachiramon, & Rattanakaemakorn, 2014). Normal epidermal growth and development depends upon *EGFR* signaling, and its absence or disruption, such as occurs in a mutation, has been illustrated in an animal model. Mice lacking normal *EGFR* expression and signaling displayed skin defects like those experienced by patients on EGFRIs (Mascia et al., 2013).

Dermatologic changes resulting from EGFR therapy include primarily rash and xerosis (dry skin), but also erythema, telangiectasia, hyperpigmentation, and nail and hair changes. These are the most commonly reported side effects associated with the EGFRIs, with an incidence of all grade skin toxicity ranging from 47 to over 90%, depending on the specific agent (Ocvirk, Heeger, McCloud, & Hofheinz, 2013). With a protracted treatment course, most patients will develop one or more of these dermatologic symptoms. For example, a study of 16 patients treated with the EGFRIs cetuximab, panitumumab, or erlotinib for more than six months reported that 100% developed some form of cutaneous symptom (Osio et al., 2009); however, more severe Grade 3 or 4 skin toxicities occur in only about one of five patients (Peuvrel et al., 2012 ; Brodell, Hepper, Lind, Gru, & Anadkat, 2013). With the advent of prophylactic skin care protocols, the

severity of dry skin, itching and rash can be ameliorated in some patients, but a solid evidence base for many treatments is currently lacking. Specific symptoms will be addressed more fully in chapter two.

Other Factors Affecting the Symptom Experience

The symptom experience of patients receiving EGFR therapy may also be exacerbated by other concurrent treatment modalities, such as chemotherapy and radiotherapy (e.g. concurrent cetuximab and radiation in head and neck cancer) (Pryor, Burmeister, Burmesiter, Poulsen, & Porceddu, 2011), as well as by other symptoms common in the oncology population, such as fatigue or lack of energy. In addition, many patients receiving these therapies may also have advanced disease and may be experiencing a greater symptom burden, both physical and psychological, as a result of their disease status (Wong et al., 2010). As a result, the overall symptom experience of patients treated with EGFRIs may be much more complex and multifaceted than the widely-reported profile depicting primarily dermatologic toxicities.

Impact on Outcomes

Collectively, both a cancer diagnosis and the side effects of treatment significantly impact quality of life (Fox & Lyon, 2006, 2007; So et al., 2009; Joshi et al., 2010; Deshields, Potter, Olsen, Liu, & Dye, 2011; Dodd et al., 2011; Husain, Myers, Selby, Thomson, & Chow, 2011; Roiland & Heidrich, 2011), functional status (Dodd, Miaskowski, & Paul, 2001; Given, Given, Azzouz, Kozachik, & Stommel, 2001; Chen & Tseng, 2006; Miaskowski et al., 2006; Cheng & Lee, 2011; Dodd et al., 2011), and psychological status (Adler & Page, 2008; Breen et al., 2009). Due to their unique side

effect profile, EGFRIs carry a significant symptom burden (Wu, Balagula, Lacouture, & Anadkat, 2011), and may exert a negative psychological and physical effect on health-related quality of life (Joshi et al., 2010; Rosen et al., 2013), and can even lead to treatment interruption (Boucher, Olson, & Piperdi, 2011). All of the TKIs are self-administered oral medications, so adherence to treatment amidst a difficult symptom experience is also a concern (Mancini, McBride, & Kruczynski, 2013; Matthews & Caprera, 2014). A better understanding the overall symptom experience associated with EGFRIs will provide actionable knowledge that can proactively address patient symptoms so that treatment adherence concerns are minimized.

Most research addressing symptoms associated with EGFRIs has explored the obvious rash and other dermatologic symptoms, while a broader focus on the overall symptom experience has been limited (Osio et al., 2009; Andreis et al., 2010; Joshi et al., 2010; Rosen et al., 2013). Joshi et al. (2010) found EGFRi-related skin toxicities affected emotional well-being, while Wagner and Lacouture (2007) reported physical symptoms like pain, itching and stinging had an impact on quality of life. One study did not find a correlation between skin rash and psychological distress, but did find highly significant relationships between perceived quality of life and psychological distress and social avoidance (Romito et al., 2010). Despite the fact that there is some evidence that quality of life and psychological status are affected by patients receiving EGFRIs, most clinical and research literature suggests that patients are most bothered by the esthetic complications of the rash (Wu et al., 2011). This misconception suggests that there is a need for a greater understanding of the symptom experience so that providers fully

appreciate how patients are impacted by EGFR treatment. As there are only a few published studies exploring these relationships, with none in the nursing literature, the interplay between EGFR-related symptoms and the overall symptom experience has not been fully explored, so this study is a first step in this direction.

Purpose of the Study

EGFR treatment-related symptoms constitute a significant burden for patients undergoing treatment for cancer. To date, there is a paucity of research on the overall symptom experience associated with these therapies, and there is no nursing research that addresses this topic. Most research exploring side effects of EGFRs has been conducted in the context of clinical trials, and focuses on dermatologic symptoms, but not on the overall symptom experience of the patient receiving these therapies. Along with uncomfortable and visible dermatologic symptoms, patients can also experience other symptoms such as dry mouth, fatigue, and psychological distress.

Significance to Nursing

This study was a descriptive, correlational survey designed to explore the symptom experience, including discovery of any co-occurring symptoms (symptom clusters), associated with EGFR therapy. In addition to describing the full range of symptoms associated with EGFR therapies, this study explored the impact of these symptoms on key outcomes. Co-occurring symptoms, or symptom clusters, were identified by factor analysis procedures and supported by hierarchical cluster analysis. The relationship of key variables (age, diagnosis, gender, EGFR therapy, and symptom clusters) to outcomes was explored.

The study of the symptom experience, including any identified symptom clusters, in patients receiving EGFRIs contributes to the nursing literature by: a) fully describing the symptom experience of patients receiving EGFRIs; b) providing data to support the co-occurrence of symptoms in patients receiving EGFRIs; c) providing preliminary information about the relationship of symptoms or identified symptom clusters and key outcomes; and, d) providing preliminary data to help generate hypotheses for interventional research to improve symptom control, as well as symptom management interventions for symptom clusters. Specific applications to nursing practice, education and research are outlined below.

Relevance to nursing practice. The American Cancer Society estimates that 1,665,540 new cancer cases will be diagnosed, and 585,720 Americans are expected to die of cancer, in 2014 (Siegel et al., 2014). Lung and colorectal cancers are projected to be among the most common cancers in men (exceeded only by prostate cancer), and breast, lung and colorectal cancers will be the top three cancer diagnoses in women in 2014. If even 10% of these newly diagnosed patients with lung, breast, or colon cancer were eventually treated with an EGFRi, this would amount to a considerable number of patients who could potentially benefit from the new knowledge generated by this study.

Overall, the number of cancer survivors has more than quadrupled since 1971, when 3 million people were identified as survivors. In 2007, 11.7 million people in the United States were described as cancer survivors (Rowland et al., 2011). By 2012, the number of U.S. cancer survivors had risen to 13.4 million people in 2012, or just under 5% of the population, according to a recent report from the Centers for Disease Control

(Ekwueme et al., 2014). About 68% of cancer survivors were still alive five or more years after their diagnosis (Siegel et al., 2012), and nearly 60% of those individuals were older than 65. Many cancer diagnoses can now be considered to be more like chronic diseases which require a series of treatments over time. An improved understanding of the symptom experience of patients receiving EGFRIs may benefit a significant number of patients who may be treated with these drugs, whether they are among the newly diagnosed with advanced disease, or are receiving EGFRIs later in the treatment continuum.

An essential role of the health care team is to help each patient to manage their symptom experience, allaying its impact on important outcomes. Since patients perceive their illness and its treatment through their collective symptom experience, optimal patient care should address the occurrence of all symptoms in order to tailor symptom management strategies (Brown, Cooley, Chernecky, & Sarna, 2011), many of which will require multiple interventions. Describing dermatologic symptoms along with other symptoms that co-occur, and exploring their relationship to important outcomes will create a better understanding of what patients experience and lead to enhanced patient care. In addition, the majority of oncology patient care has shifted to the outpatient arena away from the infusion suite (Neuss et al., 2013), where patients may have less in-person contact with oncology nurses. Some EGFRi agents, such as cetuximab and panitumumab, are given as infusions, but other agents, such as the TKIs in this study, are taken orally. When patients receive oral agents, patient teaching strategies in the practice setting must

be highly focused, delivered in new formats, or via new technologies due to limited interaction with oncology nurses.

The EGFRi symptom experience is illustrated by this case example. A 65 year-old retired woman taking erlotinib for advanced lung cancer develops an itchy facial rash after six weeks of therapy. The rash causes her anxiety and discomfort, and although she has been advised that its presence may be indicative of a therapeutic response, it still causes psychological distress. The rash, as well as her severe dry skin and dry eyes, cause her to be irritable. Upon waking, her eyelashes are covered with crusts, causing inconvenience and irritation. Everyday tasks like housekeeping are more difficult due to changes in her nail beds and sore fingers, and she isn't sure how her grandchildren will react when they come to visit, as she looks different and is unable to prepare their favorite foods for them. A holistic plan of care could not only preemptively manage her dry skin, but could help her identify other interventions such as caring for her eyes, soaking her nails, and using relaxation techniques or meditation to help her cope with any distress symptoms may cause.

Despite experiencing multiple symptoms, it is possible that patients such as the woman described above may prioritize and receive advice only for the most pressing or overt (e.g. dermatologic) symptoms during their brief encounter with health care providers. But other associated symptoms, such as dry eyes, or feeling sad or nervous, could remain untreated. Evidence suggests that patients may underreport their symptoms for a variety of reasons, such as thinking a symptom is too minor to mention, blaming a symptom on aging or comorbidity, prior minimization by the provider, failure to receive

helpful information upon previous reporting, and lack of time in the patient-provider interaction (Royer, Phelan, & Heidrich, 2009). Further, patients may assign symptom priorities “based on the meanings they ascribe to them” (Maguire, Stoddart, Flowers, McPhelim, & Kearney, 2014). For example, about half of all patients who experienced fatigue in one study did not report it to their physician, perhaps due to resignation over its inevitability, its relative unimportance, or because they perceived a lack of treatment options to address it (Stone et al., 2000; Passik et al., 2002), so it is possible that some EGFR-related symptoms could be viewed by patients as unavoidable discomforts. Further, clinicians tend to “underestimate the incidence, severity, or distress of symptoms experienced by cancer patients” (Xiao, Polomano, & Bruner, 2014). Thorough assessment is the first step in addressing all of the EGFR-related symptoms, and for some symptoms, use of a questionnaire may result in an increase in the symptom prevalence reported by patients, as patients may feel less encumbered by time restraints, and may feel more able to surface symptoms not part of routine clinical assessments (Teunissen et al., 2007).

Treating all symptoms, rather than individual symptoms, could prove beneficial to both providers and patients (Chan, Richardson, & Richardson, 2011) by anticipating possible problems, preventing symptoms from worsening, reducing the number of medications used, decreasing medication side-effects, averting unplanned visits to a health care provider, reducing costs, and enhancing patient well-being and satisfaction (Walsh & Rybicki, 2006; Berger, Yennu, & Million, 2013). Patients experiencing poor symptom management incur unnecessary health care costs for hospitalizations and

emergency consultations to manage toxicities and out-of-control symptoms (Fortner, Okon, & Portenoy, 2002). Reduced direct and indirect costs of health care are a potential benefit of optimal and novel symptom management, a model which has been explored in patients receiving chemotherapy (Given, Bradley, You, Sikorskii, & Given, 2010). In addition, treatments used for one symptom could affect other symptoms (Kapella, Larson, Patel, Covey, & Berry, 2006) and offer a “crossover” benefit, as in the examples of cognitive-behavioral therapies used for both pain management and amelioration of fatigue (Fleishman, 2004). At present, these benefits are largely theoretical, and need to be explored in future research, as very few intervention studies have investigated treatment protocols for multiple symptoms.

Relevance to oncology nursing education. Although oncology nurses have always assessed symptoms using a whole person approach, nursing education about symptom management traditionally has focused on single, high-incidence symptoms, such as fatigue, pain, and nausea and vomiting. As a result, both nurses and nursing students are oriented to the management of those symptoms as they occur individually, a situation which contributes to a reductionist approach to patient care. Studies of the symptom experience related to specific treatments create a more realistic picture of what patients face, and nursing education content can be based on this new knowledge.

Symptom clusters can be viewed as correlates of quality of life and other outcomes in chronic conditions, and addressing interventions that target them can impact outcomes (Motl & McAuley, 2009). Nursing education could emphasize an awareness of symptoms that cluster together in various cancer diagnoses or in relation to specific

treatments. In turn, oncology nurses will have a heightened awareness of symptoms likely to co-occur, and can proactively teach patients relevant self-care skills, such as symptom management strategies that might offer the “crossover” effect as described above. Nursing education on symptom assessment and management strategies must continually evolve to address the symptom experience associated with new therapies as they are introduced.

Relevance to oncology nursing research. The Oncology Nursing Society (ONS) conducts a research priorities survey and produces a research agenda every few years, and for 2013, *symptom management: self-management symptom control* was rated as the fourth highest priority. *Fatigue, pain, nausea, psychological distress, and neuropathy* were ranked by all respondents as the top five symptoms causing patient distress, and two of these (fatigue and psychological distress) have been addressed in the current study (Lobiondo-Wood et al., 2014).

The 2013 ONS research survey also ranked research priorities separately by the educational degrees of respondents. For nurses with advanced degrees, *self-management interventions to improve symptom control, symptom management interventions and management interventions of symptom clusters* were ranked as the top three priorities. These topics were also ranked in the top 20 for nurses with basic nursing degrees, but at lower priorities. The present research provides a foundation for addressing all three of these priorities as well as for two of the prioritized symptoms, fatigue and psychological distress, in patients receiving EGFRIs (Lobiondo-Wood et al., 2014).

Oncology nurses continue to prioritize symptom management as a topic worthy of research, with a greater focus on self-management, multiple concurrent symptoms, and technology, with each of these elements included in the current work. Nursing research in the area of concurrent symptoms or symptom clusters has proliferated over the last decade; however, symptom clusters in patients receiving EGFRIs have not been systematically studied to date, and the preponderance of research on EGFRIs has focused on the dermatologic symptoms. The present study included a more comprehensive assessment of symptoms than in previously published work because 38 possible symptoms were included, and data were collected on symptoms beyond skin, hair and nail changes, with the intent of discovering the existence of symptom clusters in this patient population.

Nursing research studies featuring interventions for symptom clusters are limited (Xiao, 2010) and have only recently increased, and none related to EGFRi therapy have been published at this writing. A recent review described 24 studies that included interventions for patients experiencing symptom clusters, with eighteen focused on early cancer and six on advanced disease (Berger et al., 2013), but none included patients receiving EGFRIs. This study is a first step toward the identification of symptom clusters in these patients so that interventions can be developed.

Purpose of the Study

The current study was designed to describe the symptom experience, including any symptom clusters, in patients receiving EGFRIs, and to explore the relationships between symptoms, any identified symptom clusters, and key outcome variables of

quality of life, performance status, and psychological functioning. The intent is to develop a more comprehensive understanding of the symptom experience of patients receiving these therapies, and to provide a foundation for the development of hypotheses for interventions aimed at helping these patients to better self-manage their symptoms.

Specific Study Aims

The specific study aims were to:

1. Describe the symptom experience (symptom frequency and distress) of patients receiving EGFRi therapy.
2. Describe the quality of life, functional performance and psychological status of patients receiving EGFRi therapy.
3. Identify any co-occurring symptoms or symptom clusters in patients receiving epidermal growth factor receptor inhibitors.
4. Explore the relationships between any identified symptom clusters and key variables, including gender, age, primary cancer, EGFRi, and the outcome variables of quality of life, functional performance and psychological status.

CHAPTER TWO

LITERATURE REVIEW

Even as cancer care evolves to a paradigm of personalized medicine based on molecular profiles and targeted therapies, newer treatments continue to create symptom management challenges. Oncology nurses help patients to navigate their treatment course, assisting them to manage the unpleasant symptoms they confront, regardless of modality of therapy. Underpinning this continually evolving clinical practice is nursing research, such as the present study, designed to address the gaps in knowledge about how patients experience symptoms.

In this chapter, the theoretical framework used to guide this study will be presented. The concepts of symptoms, the symptom experience, and symptom clusters will be briefly reviewed as they relate to this theoretical framework. The available literature on the symptom experience of patients receiving EGFRIs will be summarized, and the relationship between EGFRi-related symptoms and key variables, such as age, gender, primary diagnosis, and type of agent, as well as performance outcomes of interest, including functional status, quality of life and psychological functioning, will be presented. Finally, the current knowledge about EGFRi symptoms and gaps in knowledge will be summarized.

Conceptual Framework: The Theory of Unpleasant Symptoms

The revised theory of unpleasant symptoms (Revised Theory of Unpleasant Symptoms, Figure 1) is the model selected to guide this research study (Lenz & Pugh, 2003). The TOUS has been described by its authors as a middle-range theory (Lenz & Pugh, 2008) “designed to integrate knowledge about a variety of symptoms” (p. 159). As Lenz and Pugh (2008) noted, symptom management is a central component of nursing clinical practice. The TOUS is valuable as a general tool to address the “multivariate assessment of the symptom experience itself and of possible influencing factors, and provides a rationale and framework for applying a biopsychosocial approach....suggesting that multiple management strategies may need to be applied simultaneously” (p. 85).

The TOUS has served as the theoretical scaffold for a number of discussion papers and nursing research studies in oncology (Redeker, Lev, & Ruggiero, 2000; Carpenter et al., 2004; Lee, 2005; Fox & Lyon, 2006; Fox, Lyon, & Farace, 2007; Fox & Lyon, 2007; Myers, 2009; So et al., 2013; Hsu & Tu, 2014); and in studies of patients with Alzheimer’s disease, cardiac disease and heart failure, cirrhosis, domestic violence, fatigue, renal failure, stroke, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, Parkinson’s disease, and in pregnant, postpartum and breastfeeding women (Hutchinson & Wilson, 1998; McCann & Boore, 2000; Corwin, Klein, & Rickelman, 2002; Gift, Stommel, Jablonski, & Given, 2003; Gift, Jablonski, Stommel, & Given, 2004; Crane, 2005; Reishtein, 2005; Kapella et al., 2006; Liu, 2006; Rychnovsky, 2007; Jurgens et al., 2009; Motl & McAuley, 2009; Song, Moser, & Lennie,

2009; Farrell & Savage, 2010; Woods, Kozachik, & Hall, 2010; Robinson et al., 2013; Eckhardt, Devon, Piano, Ryan, & Zerwic, 2014).

Model Components

The TOUS comprises three major concepts: the symptom or symptoms, influencing factors (physiological, psychological, and situational), and performance outcomes (Lenz, Suppe, Gift, Pugh, & Milligan, 1995; Lenz, Pugh, Milligan, Gift, & Suppe, 1997; Lenz & Pugh, 2003, 2008). In the present study, in an effort to operationalize all three major concepts, the symptoms or symptom clusters align with the symptom element of the model; the influencing factors are the primary cancer diagnosis, EGFR therapy, gender, and age; and the performance element (cognitive, physical and social functioning) includes the outcome measures of quality of life, performance status and psychological functioning. For the purpose of this study, all of these elements make up the patient's symptom experience, as represented in Figure 2.

All three components of the model—symptoms, influencing factors and performance outcomes—can affect the symptom experience. When the original TOUS model was published (Lenz et al., 1995), a single symptom was represented in the model schematic since the original work was derived from the study of single symptoms. A major revision to the model (Lenz, Pugh, Milligan, Gift, & Suppe, 1997) added the concurrent measurement of more than one symptom, including interaction and multiplicity between and among multiple symptoms (Myers, 2009). The revised model is a more realistic foundation for research on symptoms, particularly in patients with advanced cancer when patients are likely to experience multiple concurrent symptoms

(Vainio & Auvinen, 1996; Walsh & Rybicki, 2006; Kirkova, Aktas, Walsh, Rybicki, & Davis, 2010).

The TOUS model is not without limitations. For example, the distinct attributes of the three categories of influencing factors are somewhat hazy. The theorists have wrestled with how to categorize social support and similar constructs as either situational factors or psychological factors. For example, social support and level of education would be considered as situational factors, while level of trust and self-efficacy might be described as psychologic factors, so the classification seems somewhat arbitrary. Further, the distinction between psychologic and physiologic factors is blurry. According to the theorists, “Psychologic factors represent one of the more complex and controversial components of the model....As psychobiological research underscores the physiological basis for mood, the psychologic and physiologic factors impacting the symptom experience become difficult to separate” (Lenz and Pugh, 2001, pp. 77-78).

Lenz and Pugh concede that “the complex relationships among the three categories of influencing factors and between these factors and the symptom experience need much fuller elaboration, and the categories themselves need continuing clarification” (p. 87). Additionally, the theorists recognize the need for additional development of the performance or outcomes aspect of the theory, including the addition of more inclusive outcomes beyond performance that “that may be important consequences of the symptom experience” (p.88). The “meaning” of the symptom experience is also not included in the model (Armstrong, 2003), and might be considered a significant omission, although it could be argued that the distress component of

symptom measurement and the cognitive element of performance could address symptom meaning. However, Lenz and Pugh (2008) state that the concept of meaning is distinct from distress.

Further, by characterizing psychological constructs as influencing factors, perceived symptoms such as anxiety and worry are not addressed by the model. The model has been critiqued for an overemphasis on physical symptoms since there is not a clear distinction between psychological symptoms and the psychological influencing factors, so these concepts overlap (Xiao, 2010). Although TOUS is not a perfect model (Brant, Beck, & Miaskowski, 2009), it fits with the current study by embracing the multiplicity and synergy inherent in the symptom experience, and allowing for the incorporation of other performance-related constructs as part of the overall symptom experience.

Symptoms Component of the Model

The Oxford American Dictionary defines *symptom* as “a physical or mental feature that is regarded as indicating a condition of disease, particularly such a feature that is apparent to the patient: a sign of the existence of something, especially of an undesirable situation” (Mc Kean, 2005). *Symptom* is derived from the, late Middle English *synthoma*, symptom of a disease, from Medieval Latin based on the Greek *sumptoma*, a happening. Symptoms, defined as “the perceived indicators of change in normal function as experienced by patients” (Rhodes & Watson, 1987), and as “subjective experiences reflecting changes in a person’s biopsychosocial function, sensation, or cognition” (Larson et al., 1994), are the subjective heart of the human illness

experience. Symptoms can also include deviations in sensation and appearance (Tse, 2003).

The TOUS model accounts not only for the presence of symptoms, but reflects the multidimensionality of symptoms by including the dimensions of distress, timing, intensity, and quality as part of the model. The distress dimension captures the bothersome nature of the symptom, or its affective impact. The dimension of quality describes the unique characteristics of a symptom, such as burning or stinging. The dimension of intensity refers to the degree, strength, or severity of a symptom. Finally, the dimension of timing refers to the duration and/or frequency of a symptom, and/or its temporal relationship to any precipitating factor or situation. Lenz and Pugh (2008) note that while measuring all of these dimensions would be ideal when conducting symptom research, selection of “one, two, or three characteristics is still valid and informative for health care providers in managing symptoms” (p.167), and is the approach used in the current study.

Symptom clusters. Despite the fact that oncology patients often experience multiple symptoms, until recently, much symptom research has focused on single symptoms. Researchers at the University of California at San Francisco (Dodd, Janson, et al., 2001; Dodd, Miaskowski, et al., 2001) were the first to discuss the concept of symptom clusters in oncology. The definition of symptom clusters used in the current study is derived from this early work on symptom clusters and then later refined. Symptom clusters are defined as a set of two (Chow, Fan, Hadi & Filipczak, 2007; Kim, McGuire, Tulman & Barsevick, 2005) or perhaps three (Dodd, Janson, et al., 2001;

Miaskowski, Aouizerat, Dodd, & Cooper, 2007) or more symptoms that occur together and appear to be related to each other, such as nausea, vomiting and anorexia, but which are not required to share causation (Dodd, Miaskowski & Lee, 2004. p. 77).

Kim et al. defined a symptom cluster as:

...2 or more symptoms that are related to each other and that occur together. Symptom clusters are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters. Symptoms in a cluster may or may not share etiology. (p. 278)

Symptom clusters have also been described as a “group of concurrent symptoms that may have a synergistic effect as a predictor of patient outcome” (Ferreira et al., 2008) and morbidity (Fan, Filipczak, & Chow, 2007). Synergy among symptoms is consistent with the definition used for symptom clusters in this study and is supported by the theory of unpleasant symptoms. Although there is agreement that concurrency of symptoms is necessary, there is no consensus on temporal aspects of each symptom, or how long symptoms must be present to be considered as part of a symptom cluster (Dodd, Miaskowski, & Paul, 2001). In addition, there is no consensus on the interactivity and the strength of relationship required between and among symptoms, despite suggestions that symptom clusters are characterized as the “degree to which symptoms are inextricably interactive, where any single symptom is largely codependent on changes in other symptoms” (Tilden, Tolle, Drach & Hickman, 2002, p. 74).

Symptom experience. Patients do not experience symptoms as isolated events, but rather through the totality of their symptoms. The term symptom experience embraces the multidimensional aspects of having symptoms, including the “individual’s

perception of a symptom, evaluation of the meaning of a symptom and response to a symptom” (Dodd, Janson, et al., 2001). The concept of the *symptom experience* was first characterized as an individual’s perception and response to both the occurrence of symptoms and the resulting distress (Watson, Rhodes, & Germino, 1987), and later described as the manifestation of symptom occurrence and symptom distress (Rhodes, McDaniel, Homan, Johnson, & Madsen, 2000). The symptom (Dodd, Janson, et al., 2001) or symptoms experience (Armstrong, 2003) is particularly complex and multidimensional in oncology patients, who rarely experience single symptoms, depending on their treatment and physiologic status.

Armstrong (2003), in a concept analysis of the *symptoms experience*, noted that while the phrase is commonly used in the oncology literature, the concept has not been well-defined. For the purposes of her analysis, Armstrong referred to the “experience of multiple symptoms as the ‘*symptoms experience*’” (p. 601), defined as “the perception of the frequency, intensity, distress, and meaning occurring as symptoms are produced and expressed” (p. 602), and subsequently developed the Symptoms Experience Model to address how patients perceive symptoms.

The symptom experience component of TOUS is implied, rather than directly stated. However, through utilization of valid instrumentation, the symptom experience can be adequately measured. All of the major TOUS concepts, including influencing factors (operationalized in this study as age, disease, specific EGFR, and gender), outcomes (operationalized as quality of life, performance, and psychological status) and symptoms (e.g. symptom assessment instruments), can be empirically measured with

good reliability and validity, and serve as a basis for describing the symptom experience in patients receiving EGFRIs.

Operationalization of the symptoms component. In the present study, the symptoms were measured on the dimensions of timing and distress. As noted by the model developers, measurement of one or more dimensions of each symptom is acceptable, so timing and distress were included as they are measured by the symptom instrument. Timing of symptoms was addressed through assessment of symptoms over the past week, which is the time frame employed by the symptom assessment instruments. Distress was measured by directly asking how much each symptom distressed or bothered the respondent. Intensity was not included in this study, nor was quality. Asking participants to evaluate four dimensions of their reported symptoms would have proven daunting and may have led to incomplete surveys, so response burden was considered when choosing the MSAS-SF over the original version.

Influencing Factors Component of Model

In the TOUS model, influencing factors are classified as physiological, psychological and situational factors. Physiologic factors can include disease status and severity, such as cancer diagnosis and stage of illness, as well as comorbidities. Psychological factors address mood, response to illness, understanding of disease, and other mental and emotional aspects. Situational factors may include socioeconomic factors, family and social support, and lifestyle behaviors (Gift, 2009). Application of the TOUS model places the patient in the context of family, community and environment, and considers how these factors can contribute to the symptom experience, and in turn

can affect performance (Lenz & Pugh, 2008). In the TOUS model, these influencing factors can also interact, synergize and impact each other.

Critiques of the model have asserted that there is a lack of clarity with regard to influencing factors (or antecedents), symptoms and outcomes (Brant et al., 2009) in that they are sometimes overlapping (Hutchinson & Wilson, 1998), with the authors responding that the “components of the TOUS ...are better conceptualized as fluid and possibly interchangeable depending on context” (Lenz & Pugh, 2003, p. 84). This remark is relevant to the present study, as psychological symptoms, such as worrying, feeling sad, feeling irritable, and feeling nervous are viewed as symptoms and overall psychological status is an element of performance and is measured as an outcome.

Operationalization of the influencing factors. As noted above, the influencing factors included in the present study are primarily physiologic and include age, gender, primary cancer diagnosis, and specific EGFR, and were included as part of the demographic questionnaire.

Performance Component of the Model

Performance, including cognitive, physical and social functioning, represents how the patient lives with their health issues, and encompasses activities of daily living, social interaction, ability to problem solve, ability to concentrate, role performance and quality of life (Gift, 2009). Lenz and Pugh (2008) acknowledge that the performance component of the model should be further refined, and specifically note that one of the limitations of the model is the omission of quality of life as an element of the performance outcome, which has also been noted in other critiques of the model (Myers, 2009).

Operationalization of the performance factors. In this study, outcome measures serve as a proxy for performance, and include measures of quality of life, performance status, and psychological functioning.

Review of the Literature on the Symptom Experience of Patients Receiving EGFRIs

Because the original conception of this study included the concept of symptom clusters, multiple literature searches were conducted to determine the state of the science on symptoms, symptom experience, symptom clusters, and EGFRIs, using the following databases: Academic Search Premier; CINAHL Plus; Health Source: Nursing/Academic Edition; PsychInfo; MEDLINE via OvidSP; and ProQuest Dissertations. No studies reporting on “symptom clusters” associated with EGFRIs were found.

Separate searches using the same databases for each EGFR drug (afatinib, cetuximab, erlotinib, gefitinib, lapatinib, panitumumab) using the “AND” operator with the term “symptom clusters” and “symptom experience” yielded few relevant studies. Publications related to the outcomes of interest using MeSH terms skin diseases/psychology AND epidermal growth factor receptor inhibitor as well as psychology AND epidermal growth factor receptor inhibitor resulted in several relevant citations, although none included a discussion of symptom clusters (Wagner, 2007; Wagner & Lacouture, 2007; Coleman, Kovtun, Nguyen, Pittelkow, & Jatoi, 2010; Joshi et al., 2010; White, Roydhouse, & Scott, 2011; Boers-Doets et al., 2013).

No research exploring the symptom clusters associated with EGFRIs and their impact on the outcome of quality of life, while explicitly addressing functional performance and psychological status was found. Quality of life (Jatoi, Green, Rowland,

Sargent, & Alberts, 2009; Andreis et al., 2010; Joshi et al., 2010; Ensslin, Rosen, Wu, & Lacouture, 2013) associated with EGFRIs has been explored, and four studies using a qualitative approach exploring the symptom experience of patients receiving EGFRIs have been published (Wagner & Lacouture, 2007; Coleman, Kovtun, Nguyen, Pittelkow, & Jatoi, 2011), including three focused on instrument development (Wagner & Lacouture, 2007; Boers-Doets et al., 2013; Wagner et al., 2013).

Qualitative Research Related to EGFR Therapy

Four qualitative papers, primarily using structured interviews and content analysis (although this was not always explicitly stated), have explored the symptom experience of EGFR therapy. In a brief report, Wagner and Lacouture (2007) reported on interviews of 20 patients about their experiences with an EGFR-related rash, generating new information about the overall EGFR-related symptom experience beyond dermatologic symptoms, but also confirming the distressing nature of the dermatologic effects of these therapies.

This was the first outward physical appearance of the disease...it's a pretty significant burden to carry around...people look at you and say, 'What is wrong with that woman?' Where before they did not know... before, you could choose who you told about your cancer...and that puts a burden on you, it creates a dynamic that did not exist before...when before you could keep your privacy. (Wagner & Lacouture, 2007, Discussion Section, para. 5)

The above comment illustrated that the facial rash caused by cetuximab became a sign of cancer made visible, with the impact of violating the privacy of the patient (Boers-Doets et al., 2013). This outward sign might require an explanation of the rash to others with consequences to psychological status.

The distress caused by physical symptoms associated with EGFRIs was emphasized, as noted by a participant.

I could not get away from the dryness. The dry, cracking...It felt like I had been sitting in the Arctic in the elements, the rawest elements—the salt, the wind, the abrasion, and the cold. And there was no sense of humidity for like months. It had basically torn away the entire skin and it felt this way...so I would say it was the dryness, the sensitivity and the burning, and the inflammation of the actual pustule. (Wagner & Lacouture, 2007, Results Section, para. 3)

The authors also described other physical symptoms associated with EGFRIs, as illustrated in the following quote:

It was difficult to sleep because it hurt. And the burn. I had to lay sitting up so the skin would not move because it hurt so much. It was hard to wash. You could not put on any makeup, combing my hair hurt like hell because I have had a lot of hair loss. (Wagner & Lacouture, 2007, Results Section, para.4)

In an extension of this work, the authors reported on additional interviews with patients that reinforced the premise that physical symptoms are most relevant to quality of life. Items highly endorsed by patients reflected skin hurting, burning or stinging, skin irritation, concern about hair loss or change in texture, and pain in fingers and toes (Wagner et al., 2013).

Another qualitative study of 15 patients who had developed an EGFRi-induced rash focused on the dermatologic toxicities and associated co-morbidities of EGFRIs (Coleman et al., 2011). Four themes emerged from structured interview content: actual physical discomfort, concerns about physical appearance, social isolation, and what the authors termed high medical morbidity (Coleman et al., 2011, p.1248), which consisted of bleeding or pain that required hospitalization for a morphine drip. The findings

associated with the high medical morbidity theme are novel findings not previously reported.

A paper exploring the utility of the FACT-EGFR-18 in a native-speaking population in The Netherlands included a structured interview survey to learn more about participant responses. Boers-Doets et al. (2013) anecdotally reported that physical symptoms recorded by the FACT-EGFR-18 influenced quality of life adversely, with the most distressing symptoms having the greatest impact on quality of life, although no statistical analysis of items was performed.

Overall, the impact of EGFRIs on quality of life was considerable, as exemplified by the following comments (Boers-Doets et al., 2013).

Do you see how I look? I even (sic) no longer have a face; I look stupid; that makes me sad...I get grumpy; easily irritated. I don't allow the grandchildren to kiss me. I find it unpalatable...I have very much difficulty with sitting and lay down because of pimples between my buttocks... (p. 1922-1924)

In summary, these papers offer important insights into the symptom experience of patients receiving EGFRIs, but have several limitations. Each of the studies included a small sample size, ranging from 10 to 20 participants. Two of the papers reported on the same sample (Wagner, 2007; Wagner et al., 2013), so the findings discussed above are based on the responses of 45 participants in total. Two of these papers were actually focused on instrument development and one on linguistic evaluation, but researchers did ask about the most bothersome aspects of dermatologic toxicity associated with EGFRIs and their impact on quality of life. Three of the studies were conducted at a single site, which in all cases was a tertiary care center in the Midwest, so findings may not be

applicable in other settings; the last was conducted at three hospitals in the Netherlands, so the findings may not be generalizable to patients in the United States.

Quantitative Research Related to EGFR Therapy

Studies exploring the impact of EGFRIs on the performance outcomes of quality of life, functional performance and psychological status are summarized here. In addition, a review of symptoms associated with EGFRIs, largely derived from clinical trials work, will also be presented in order to help characterize the physical symptoms associated with EGFRIs.

EGFRIs and quality of life. Several papers have explored quality of life as an outcome measure using dermatology-specific quality of life instruments (Osio et al., 2009; Andreis et al., 2010; Jatoi et al., 2010; Joshi et al., 2010) with some evidence of a negative impact of these treatments on quality of life. Osio expressed concern that because of this impact on quality of life, treatment interruption or dose reduction could be required. Andreis et al. (2010) reported on the impact on quality of life in advanced colon cancer patients receiving EGFRIs (presumed to be cetuximab and panitumumab). Women between the ages of 55-65, as well as patients who experienced a partial remission (as opposed to those with no response to treatment), and those with most severe symptoms, demonstrated the greatest declines in quality of life as measured by the Skindex-29. Joshi et al. (2010) also reported on the impact of EGFR toxicity (rash, xerosis, paronychia, and pruritus) on QOL, using the Skindex-16, and found no difference with respect to cancer type, gender, or treatment type with regard to symptoms, emotions, function or overall score. In the Joshi study, about half the patients

were treated with erlotinib (49.3%), so this variation in treatment and primary cancer site (i.e. lung cancer) may have contributed to an inconsistent impact on quality of life.

In another group of patients receiving a variety of EGFRIs (described as erlotinib or other small molecule inhibitors and cetuximab or other monoclonal antibody), skin symptoms, including itching, burning and stinging, and psychological symptoms, such as worry and embarrassment, were reported. These symptoms accompanied the occurrence of rash, and negatively impacted self-reported quality of life as measured by the Skindex-16 (Jatoi et al., 2010, p. 1021), but results by age and gender were not reported, so how these findings relate to the above studies is not clear.

A recent study comparing quality of life as measured by the Skindex-16 in patients receiving targeted therapy vs. non-targeted therapies revealed that quality of life in patients on targeted therapies was worse, and that rash and pruritus had the greatest adverse impact on quality of life (Rosen et al., 2013). In addition, these patients had more adverse events than patients on non-targeted therapies. Both the total Skindex-16 score and the emotion subdomain were significantly different between the two groups.

Despite the general agreement by the above studies that these therapies impact quality of life adversely, it is possible that effective treatment with EGFRIs may also ameliorate symptoms and result in improved quality of life, as has been documented repeatedly in clinical trials. A study reporting quality of life outcomes in a sample of Chinese patients with *EGFR* mutation-positive advanced NSCLC receiving erlotinib or chemotherapy found that the erlotinib arm compared favorably with the chemotherapy

group on several measures (Chen et al., 2013), but a different quality of life instrument, not specific to dermatologic therapy, was used in this study.

Another trial that added afatinib to best supportive care reflected improvement of several symptoms (cough, dyspnea, pain, fatigue) as well as in physical functioning and health-related quality of life (Hirsh, 2011; Hirsh et al., 2013). Gefitinib therapy was also associated with improvement in health-related quality of life when compared with combination chemotherapy, although symptom improvement varied by *EGFR* mutation status, showing greater improvement in *EGFR*-mutated tumors, as would be expected (Thongprasert et al., 2011). Similarly, another study documented improvements in global quality of life, functioning, cough, pain and dyspnea in patients with *EGFR* mutations (Di Maio et al., 2012).

To summarize, although there is evidence of an adverse impact on quality of life with EGFR therapy, improvement in quality of life has also been documented, possibly reflecting changes in health status and relief of disease-related symptoms resulting from successful treatment. In addition, the various targeted therapies may exert differing impacts on quality of life (Joshi et al., 2010), and variations in the measurement strategy, such as the specific quality of life instrument used in each study, may also play a role in these inconsistent results. However, it can be concluded that quality of life is among the most important patient-reported outcomes. A large study exploring content validity of a quality of life in lung cancer patients revealed that quality of life, independence and performance, rather than physical symptoms, were ranked as most concerning by patients (Gralla, Hollen, Msaouel, Davis, & Petersen, 2014).

EGFRIs and functional status. Functional status, or performance status, has been described as the ability to engage in the performance of normal daily activities required to address basic needs, to engage in role performance, and to maintain health and well-being (Leidy, 1994; Wilson & Cleary, 1995). The capacities to ambulate, to function in chosen roles, and to work are all activities that fall within the realm of functional status.

In symptom cluster research, the available evidence suggests that the more numerous and severe symptoms are, the greater the impact on functional status (Dodd, Miaskowski, et al., 2001; Given et al., 2001; Gift et al., 2004; Barsevick, Dudley, & Beck, 2006; Chen & Tseng, 2006; Fox & Lyon, 2006; Chen & Lin, 2007; Chow, Fan, Hadi, & Filipczak, 2007; Fox et al., 2007; Fox & Lyon, 2007; Ferreira et al., 2008; Hadi et al., 2008; Dodd, Cho, Cooper, & Miaskowski, 2010; Ryu et al., 2010; Tsai, Wu, Chiu, & Chen, 2010; Dodd et al., 2011; Roiland & Heidrich, 2011; Kim, Barsevick, Beck, & Dudley, 2012). Although functional status has not been studied extensively with EGFRIs, several authors reported that activities of daily living and social activity were affected by EGFRi treatment (Joshi et al., 2010; Boers-Doets et al., 2013).

EGFRIs and psychological status. While most people treated for cancer have normal psychological functioning (Kornblith, 1998), a significant number of patients can experience distress and other disruptions of psychological status, with estimates of 29 to 43 percent of patients experiencing such distress (Zabora, Brintzenhofe Szoc, Curbow, Hooker, & Piantadosi, 2001). A cancer diagnosis, cancer treatment, and living with the associated life changes can both generate distress and exacerbate existing psychological

issues (Adler & Page, 2008). In general, patients undergoing cancer therapy are at risk for distress and disruption of psychological well-being (Fox & Lyon, 2006, 2007), and patients with severe symptoms are at risk for concurrent psychoneurologic symptoms (Kim, Barsevick, Beck, et al., 2012).

The logically consistent conclusion relating rash to psychological distress may not be so clear cut. Paradoxically, development of rash was perceived by some patients as a sign of hope and effectiveness of therapy, reflecting the suggested correlation of the rash occurrence to treatment effectiveness. In fact, in patients receiving erlotinib, there is evidence to suggest that skin rash is associated with improved response and survival time (Pérez-Soler et al., 2004; Wacker et al., 2007); similar findings have been reported with cetuximab, panitumumab, and gefitinib (Lacouture, et al., 2011).

In patients receiving EGFR therapy, psychologic distress was reported in 41% of Italian patients receiving cetuximab for advanced colon cancer (Romito et al., 2010), but when compared to an instrument validation sample, there were no significant differences found ($p = 0.583$). While the impact of EGFR-related symptoms on psychological well-being is presumed, patients did not rate items related to social function as highly important to quality of life as often as clinical experts did in instrument development work for the EGFR-18 (Wagner, 2007); rather, patients ranked social well-being items as less distressing than items affecting physical and functional well-being. However, in open-ended interviews, items reflecting an impact on social well-being were identified by patients as being somewhat important. The ambiguity around patient ratings of items that impact quality of life related to EGFR therapy, as well as the lack of congruence

between the ratings of patients and professionals, warrants further exploration (Boers-Doets et al., 2013).

Research Related to Influencing Factors and EGFR Therapy

The following discussion summarizes available research related to the influencing factors of age and gender, both with respect to symptoms in general, as well as to symptoms associated with EGFR therapy.

Age. It has been suggested that in patients with advanced cancer, symptom severity for common symptoms decreases with age (Kirkova, Rybicki, Walsh, & Aktas, 2012), and older patients had lower occurrence rates for many symptoms, as well as lower severity, frequency, and distress ratings for some symptoms when compared to younger patients (Cataldo et al., 2013). However, a recent study comparing cancer patients in various older age groups (60-69, 70-79, and 80-89) with regard to psychological and somatic symptoms suggests that the impact of age on the symptom experience may not be linear, with the 70-79 year old group reporting the lowest scores for depressive, anxiety and somatic symptoms, while those 80 and older reported the highest (Cohen, 2014), suggesting that comorbidities may be related to symptom severity in older patients. The relationship between age and the symptom experience demands further study as findings have also varied with specific symptoms, with fatigue and drowsiness more common in younger patients (Cheung, Le, Gagliese, & Zimmerman, 2011).

The overall impact of age on EGFR-related symptoms in oncology patients also requires further study, but the literature seems to suggest possible, but inconsistent

relationships. For example, rash related to erlotinib is more likely to be associated with age older than 70 (as well as nonsmokers and people with fair skin), while cetuximab rash is associated with age younger than 70 (Lacouture et al., 2011). In another study, Jatoi et al. found that men, and those under 70, receiving cetuximab, were more likely to develop a Grade 3 or 4 rash. Age was further explored by treating it as a continuous variable, with the subsequent discovery of an inverse relationship between severity of rash and age. The risk factors of male sex and younger age were described as additive, with age less than 70 and male sex resulting in an 8% risk of rash (Jatoi et al., 2009, p. 122). However, two studies specifically designed to explore the impact of age on cetuximab- and erlotinib-related rash did not find it to be a predictor of appearance, duration and grade of the rash (Giuliani & Marzola, 2013a, 2013b), although the age cut-off was 65 (as opposed to 70 in other studies), and the sample sizes were small.

Jatoi et al. (2009) suggested that the purported less dramatic dermatologic toxicity in the older patient may be a function of fewer epidermal growth factor receptors and therefore fewer targets for EGFRIs, but it is unclear whether this is true across different therapies. In fact, no relationship between rash development and various risk factors, including age and type of therapy, was found in a subsequent retrospective analysis of over 4,000 patients with a variety of cancer diagnoses (Solomon & Jatoi, 2011). Inconclusive evidence linking age to rash severity for cetuximab and erlotinib has also been reported, so much remains to be discovered about this potential relationship (Giuliani & Marzola, 2013a, 2013b).

As noted earlier in the discussion of quality of life, age may be a factor with respect to perceived quality of life. An interaction between age and quality of life has been reported with the EGFRIs, with patients younger than 50 reporting a greater impact on QOL than older participants with similar symptom profiles (Jatoi, et al., 2009; Joshi, et al., 2010).

Gender. The role of gender in the cancer symptom experience is not clear. In early work in this area, research in lung cancer patients suggested that there was no effect of gender on symptom scores (Kurtz, Kurtz, Stommel, Given, & Given, 2000); this finding was similar to the conclusions of other studies (Cooley, Short, & Moriarty, 2003; Gift et al., 2004; Hoffman, Given, von Eye, Gift, & Given, 2007). However, gender was found to contribute to distress scores in patients with metastatic cancer, where women had worse scores for anxiety and appetite (Zimmermann, Burman, & Follwell, 2010), and to a higher incidence of depression in female patients with colon cancer (Kurtz, Kurtz, Stommel, Given, & Given, 2002).

Recent work on symptom clusters in advanced cancer has not yielded consistent findings with respect to gender, most likely because of disparate patient populations and cancer diagnoses. An increased prevalence of a gastrointestinal symptom cluster in women has been reported in one study (Jiménez et al., 2011); in another study, women reported worse nausea scores than men (Cheung et al., 2011). Gender may play a role in the severity of rash associated with the EGFRIs, as suggested by a preliminary secondary analysis of 933 stage III colon cancer patients treated with surgery and cetuximab, where more men than women developed a Grade 3 rash, odds ratio 2.0, 95% CI [1.14–3.88]

(Jatoi et al., 2009), so the authors speculated about a hormonal influence on rash development.

Symptoms Experienced by Patients on EGFR Inhibitor Therapy

In order to provide a basis for understanding the overall symptom experience of patients who receive EGFR inhibitor therapy, which is the major aim of this study, a review of symptoms caused by these agents is included here. As noted in chapter one, the most common dermatologic symptoms related to EGFR inhibitor therapy include changes in skin such as rash, xerosis (dry skin), erythema, telangiectasia, hyperpigmentation, and nail and hair changes.

Rash. The EGFR-inhibitor-related skin toxicity most frequently reported in the literature is a papulopustular rash occurring from two to eight weeks after the start of treatment, with a peak intensity occurring at about four weeks, although there is variability in patients, among agents, and with respect to dosage and treatment schedule. Often incorrectly described as acneiform, but more correctly characterized as a folliculitis, the rash generally appears on the scalp, face (forehead, cheeks, nose and chin), chest, upper back, shoulders, and behind the ears, all areas replete with sebaceous glands (Segaert et al., 2009).

The genesis of EGFR-inhibitor-related rash is not completely understood, but has been described as inflammation of the pilo-sebaceous follicle (Peuvrel et al., 2012) and as a superficial, predominantly neutrophilic, suppurative folliculitis with disruption of the epithelial lining (Brodell et al., 2013). The pathophysiology of these changes is related to disruption of the normal hair cycle and the disruption of normal *EGFR* activity in the

basal keratinocytes, with a resultant proliferation of pro-inflammatory cytokines and an attendant inflammatory response. Although not yet definitive, preliminary evidence suggests that skin phototype correlates to some extent with rash severity in patients receiving erlotinib, wherein lower phototypes (i.e. lighter skin that burns more easily when exposed to sunlight) tend to be more likely to exhibit severe rash (Luu, Lai, Patel, Guitart, & Lacouture, 2007; Lacouture et al., 2011). However, more research is required as others have found no correlation with skin phenotype (Joshi et al., 2010). Genetic changes to the EGFRs may contribute to the occurrence of rash in patients receiving EGFRIs (Parmar et al., 2013), but other factors may also play a role, with nonsmokers, as well as patients over the age of 70 more commonly exhibiting rash in patients treated with erlotinib (Rosen et al., 2013; Balagula & Lacouture, 2014). Conversely, age younger than 70 has been associated with rash in male patients receiving cetuximab.

Rash is a symptom prevalent across all EGFRIs, with reviews citing an incidence of 83% in patients receiving TKIs (Curry et al., 2013), and 85-93% in patients on cetuximab or panitumumab (Molinari, De Quatrebarbes, Andre, & Aractingi, 2005; Curry et al., 2013). In general, a higher grade rash occurs with greater frequency in patients treated with monoclonal antibodies (10-17%) in comparison to the small molecule tyrosine-kinase inhibitors (5-9%) (Lacouture et al., 2011), but studies have included patients on a variety of therapies, so the impact of each agent is not entirely understood. Regardless of grade, these adverse effects constitute far more than a nuisance, causing dose reductions, treatment interruptions, poor adherence, and even infections, all of which can impact treatment outcomes (Boone et al., 2007).

In one series, 96 of 138 individuals (69%) who received cetuximab, panitumumab (MOABs) or erlotinib (a TKI) developed a rash (Solomon & Jatoi, 2011), consistent with findings in another study where 65% experienced papulopustular rash (Chan & Tan, 2011). This trend was confirmed by a subsequent meta-analysis of 13 studies reporting EGFR-related rash that revealed an overall risk difference of 74% for all rashes, and 12% for Grade 3 and 4 rashes in patients receiving cetuximab and panitumumab when compared with those on non-EGFR therapy (Mittman, 2011).

A literature review assessing severe (Grade 3-4) folliculitis, when focused on an analysis of lung cancer patients, demonstrated a greater incidence with cetuximab (9%) and erlotinib (8%) in comparison to gefitinib (2%) ($p < .0001$) (Bachet et al., 2012), suggesting a comparable rate of rash between a TKI and a MOAB, as well as a differential impact between two TKIs. These findings confirm earlier work documenting that in the small molecule kinase inhibitors, rash was reported in 44% of patients receiving gefitinib, with an expected higher incidence of 49-75% in patients receiving erlotinib (Lacouture, Mitchell, et al., 2010). Mild rash and acneiform lesions were reported in 73% of patients on afatinib, with a grade 3 rash seen in about 13% (Lacouture et al., 2013). In addition, palmar-plantar erythrodysesthesia was reported in 7% of patients on afatinib, and bullous, blistering lesions have also been reported.

Xerosis. Dry skin, or xerosis, develops after several weeks in some patients taking EGFRIs, and virtually all patients receiving these therapies for six months will develop this cutaneous manifestation, which can evolve into a chronic form of eczema. A further complication associated with xerosis is infection and inflammation, as the

barrier protection of the skin is compromised. Painful fissures of the fingertips and on the feet have been described (Osio et al., 2009; Segaeert et al., 2009).

Nail changes. Nail changes occurred in approximately 10-15% of patients treated with EGFRIs after four to eight or more weeks of treatment (Osio et al., 2009; Becker, van Wijk, Smit, & Postmus, 2010; Lacouture, Maitland, et al., 2010). In a meta-analysis ($n = 2107$) of EGFRIs and nail toxicity, the overall incidence reported was 17.2%, 95% CI [13.8%, 21.3%], with a risk of high grade nail toxicity suggested to be relatively small at 1.4%, 95 CI [0.9%, 2.1%] (Garden, Wu, & Lacouture, 2011). No statistically significant difference in nail changes were noted among the EGFRIs included in the meta-analysis, suggesting a general effect of EGFRi inhibitors on keratinocytes in the vicinity of the nail (Garden et al., 2011).

Nail fold inflammation (paronychia) often involves the great toe, although other toes, as well as fingernails, are often affected. Granuloma-like lesions may result in nail bed inflammation and onycholysis (described as a loosening or separation of the nail plate from its supporting structures), although this occurs rarely (Stevenson & El-Modir, 2011). Onychodystrophy, or nail malformation, as well as slower nail growth and nail brittleness, have also been described.

Hair changes. EGFRi treatment that spans from seven to ten weeks or longer has been linked with an array of hair growth changes. Trichomegaly, which describes curly, long, and rigid eyelashes, and trichiasis, or misdirected eyelashes, as well as eyebrow overgrowth, can develop following long-term treatment with EGFRIs. Interestingly, scalp alopecia also may occur, and both frontal and total alopecia, as well as scarring alopecia

have been reported (Pongpudpunth, Demierre, & Goldberg, 2009). Other hair abnormalities, such as facial hypertrichosis in women, reduced facial hair growth in men, loss of hair on arms and legs, and changes in texture, color, and overall manageability of hair have been documented (Segaert & Van Cutsem, 2005; Osio et al., 2009; Pongpudpunth et al., 2009; Segaert et al., 2009; Balagula, Lacouture, & Cotliar, 2010).

Ocular toxicities. About one third of patients receiving EGFRIs experience ocular reactions (Basti, 2007), most commonly blepharitis and dysfunctional tear syndrome (i.e. dry eye) (Borkar, Lacouture, & Basti, 2013), but also including iridocyclitis, and corneal epithelial defect, as well as conjunctivitis, meibomitis and periocular skin changes (Fraunfelder & Fraunfelder, 2012).

Pruritus. A meta-analysis of studies including many different targeted therapies found an incidence of 17.4% all-grade pruritus (Ensslin et al., 2013). An early theory accounting for the pathophysiology of pruritus or itching is the accumulation of mast cells in the skin tissue, as demonstrated in a small sample of patients treated with erlotinib (Gerber et al., 2010).

Associated mucocutaneous symptoms. Depending on the specific agent, EGFRIs may also cause mucocutaneous symptoms such as erythema, flushing, radiation dermatitis, balanitis, hyposalivation, mucositis and taste changes (Osio et al., 2009; Lacouture, Maitland, et al., 2010; Katakami et al., 2013).

Other symptoms. Other symptoms reported to occur with EGFRIs include anorexia, fatigue, nausea (Ross et al., 2010), insomnia, anxiety (Wagner & Lacouture, 2007), electrolyte imbalances and diarrhea (e.g. erlotinib and afatinib) (Hirsh, 2011;

Katakami et al., 2013), infusion reactions (e.g. cetuximab) (Ouwkerk & Boers-Doets, 2010), interstitial lung disease and associated pulmonary symptoms, (Nguyen & Neal, 2012; Katakami et al., 2013), and pain (Wong et al., 2010).

Gaps in the Literature

The purpose of the current study was to describe the symptom experience of patients receiving EGFRIs and to explore their impact on performance, including quality of life, functional status and psychological status. The symptom experience of the patient undergoing EGFRi therapy has not been fully described, and concurrent symptoms or co-occurring symptoms associated with these targeted therapies have not yet been systematically explicated in the nursing literature. Most of the EGFRi symptom-oriented literature published to date focuses on specific aspects of EGFRi therapy, such as the dermatologic effects of these agents (Garden et al., 2011; Wu et al., 2011; Ensslin et al., 2013; Urban & Anadkat, 2013); hypersensitivity or infusion reactions (Lenz, 2007); or reflects the grading of toxicities as in clinical trials. No nursing studies exploring symptoms or symptom clusters associated with EGFRIs have been published at this writing, and none explore the impact of EGFRIs on outcomes.

The symptom experience resulting from treatment with these agents, as well as from a diagnosis of cancer, includes an array of symptoms that go beyond skin, hair and nails changes, and may affect quality of life, functional performance and psychological status, so gaps in knowledge on this topic remain. The current health care environment requires that care be delivered as cost-effectively as possible. Proactive identification and treatment of high incidence symptoms should be implemented whenever possible in order

to enhance the effectiveness and efficiency of care processes, but even more importantly, to help maintain and improve every patient's quality of life, psychological status and functional performance.

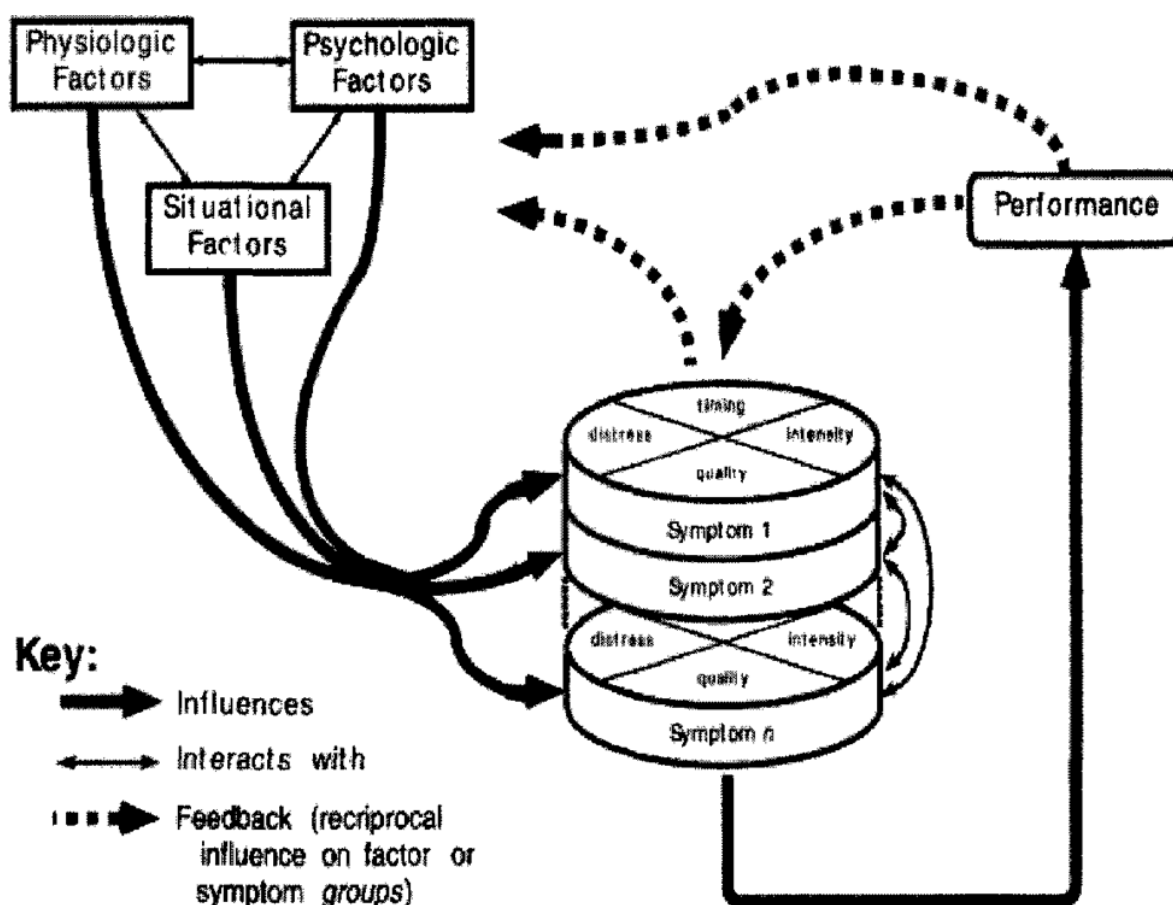


Figure 1. Revised Theory of Unpleasant Symptoms Model
 Reprinted with permission. Lenz, E. R., Pugh L.C., Milligan, R. A., Gift A. & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: an update. *Advances in Nursing Science*, 19(3): 14-27.

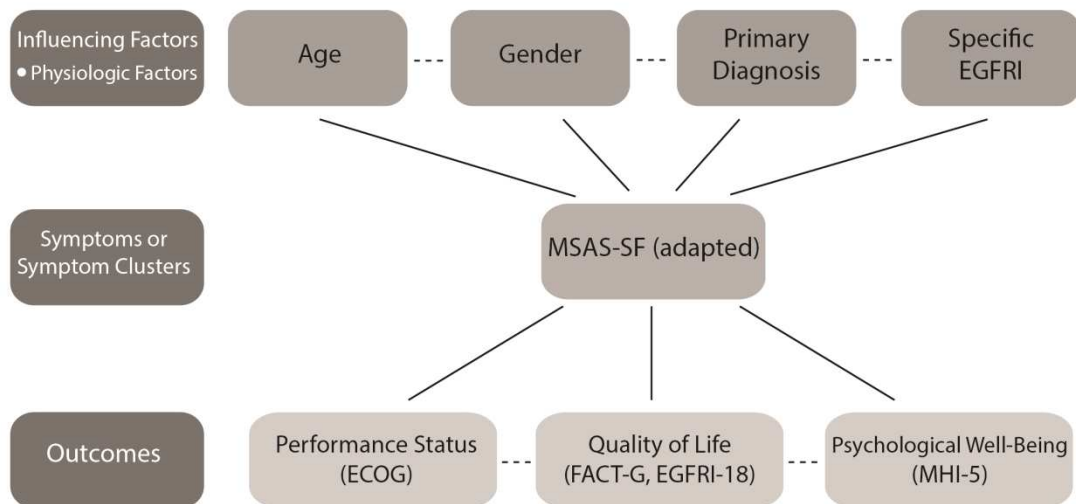


Figure 2. Application of the Theory of Unpleasant Symptoms

CHAPTER THREE

METHODS

The purpose of this cross-sectional descriptive study was to describe the symptom experience of patients receiving any currently available FDA-approved epidermal growth factor receptor inhibitors (EGFRIs) (such as erlotinib, gefitinib [continuing patients], afatinib, lapatinib, cetuximab and panitumumab) as part of their cancer therapy, which could include those diagnosed with breast, colorectal, head and neck, lung, and pancreatic cancers.

Specific Aims

The specific study aims were to:

1. Describe the symptom experience (symptom frequency and distress) of patients receiving EGFRi therapy.
2. Describe the quality of life, functional performance and psychological status of patients receiving EGFRi therapy.
3. Identify any co-occurring symptoms or symptom clusters in patients receiving epidermal growth factor receptor inhibitors.
4. Explore the relationships between any identified symptom clusters and key variables, including gender, age, primary cancer, EGFRi, and the outcome variables of quality of life, functional performance and psychological status.

Design and Setting

A cross-sectional, descriptive, correlational design using primarily a web-based format (with an option for paper format) has been used for this study. Because EGFR therapy is appropriate for only a small percentage of patients with breast, colorectal, head and neck, lung, and pancreatic cancers, recruitment for this study included several strategies designed to reach a large potential volunteer pool. See Figure 3 for a graphical depiction of recruitment strategies. In order to achieve an optimal sample size, direct recruitment of participants from online support sites and patient support communities, as well as indirect recruitment of participants through health care providers, was implemented. The goal was to achieve a sample size of 100.

Recruitment Procedures

1. Indirect recruitment.

Letters describing the study were sent to health care providers, including oncologists and oncology nurses, from Illinois, Wisconsin and Indiana. Descriptive flyers providing information about study participation and eligibility criteria were included in the mailing for distribution to potential participants. Mailing lists were purchased for this purpose, and approximately 3000 first-class mailings were sent to members of these lists.

2. Direct recruitment through health care settings.

Following initial Institutional Review Board (IRB) approval at Loyola University Health System, additional IRB permission was sought at another health care system and at Northwestern University (NU). The Northwestern

IRB reviewed the Loyola IRB determination and the study protocol and did not require a separate submission to the NU IRB. Clinicians at NU agreed to share the flyers with patients who might be eligible, so flyers were supplied for this purpose.

3. Direct recruitment through patient support settings.

Participants were also recruited from patient support organizations in the Midwest. Flyers were posted at patient support centers in The Cancer Health Alliance, including Wellness Place (Palatine), Wellness House (Hinsdale), Cancer Wellness Center (Northbrook), The Cancer Support Center (Homewood and Mokena), Living Well Cancer Resource Center (Geneva), and also at Gilda's Club (Chicago) and at the Rush University Medical Center Gilda's Club site. Flyers were made available at a Breathe Deep LUNGeivity community event.

4. Direct recruitment through online support groups.

Informational flyers, web site links, or study descriptions (depending on what was allowed by site administrators) were posted on the web sites of a variety of online patient support groups. Information was posted on the Cancer Support Community, Colon Cancer Alliance, Inspire.com, Lung Cancer Alliance, LUNGeivity Foundation, Metavivor.org, Pink-Link.org, National Lung Cancer Partnership, Navigating Cancer and Blood Disorders, and the Pancreatic Cancer Action Network Survivors Network. Postings were also shared via social media to reach a broader audience. Despite positive

responses to initial queries about posting these announcements, many other sites ultimately opted not to post study announcements, citing their own research agenda, changes in policy about posting third party requests, inability to evaluate research requests, and their desire not to inundate participants with such requests. Many site administrators simply never responded to repeated email requests. Using a similar strategy, one researcher reported receiving 300 responses and 135 usable data sets from participants who responded to a study announcement on an online support group web site (e.g. LUNGeivity) (J. Cataldo, personal communication). In another study, a mailed survey about symptoms and quality of life sent to 140 members of an online support group of brain tumor patients generated a 52% response rate (Fox et al., 2007), but specific mailing lists such as this were not available for this study.

5. Direct recruitment through study web site.

For all potential volunteers, an informational web site was available, and participants originally were able to contact the researcher by phone or email if they had questions about the study.

The original procedure required potential participants to contact the researcher to be screened for eligibility. However, the procedure requiring contact with the investigator was in place only for the first few months of recruitment. After several months of recruitment activities with a low accrual rate (8 participants), and in order to facilitate more rapid recruitment, a direct link to the study and screening questions was

provided on a study web site and was updated at patient support communities after consultation with the IRB and the doctoral advising committee.

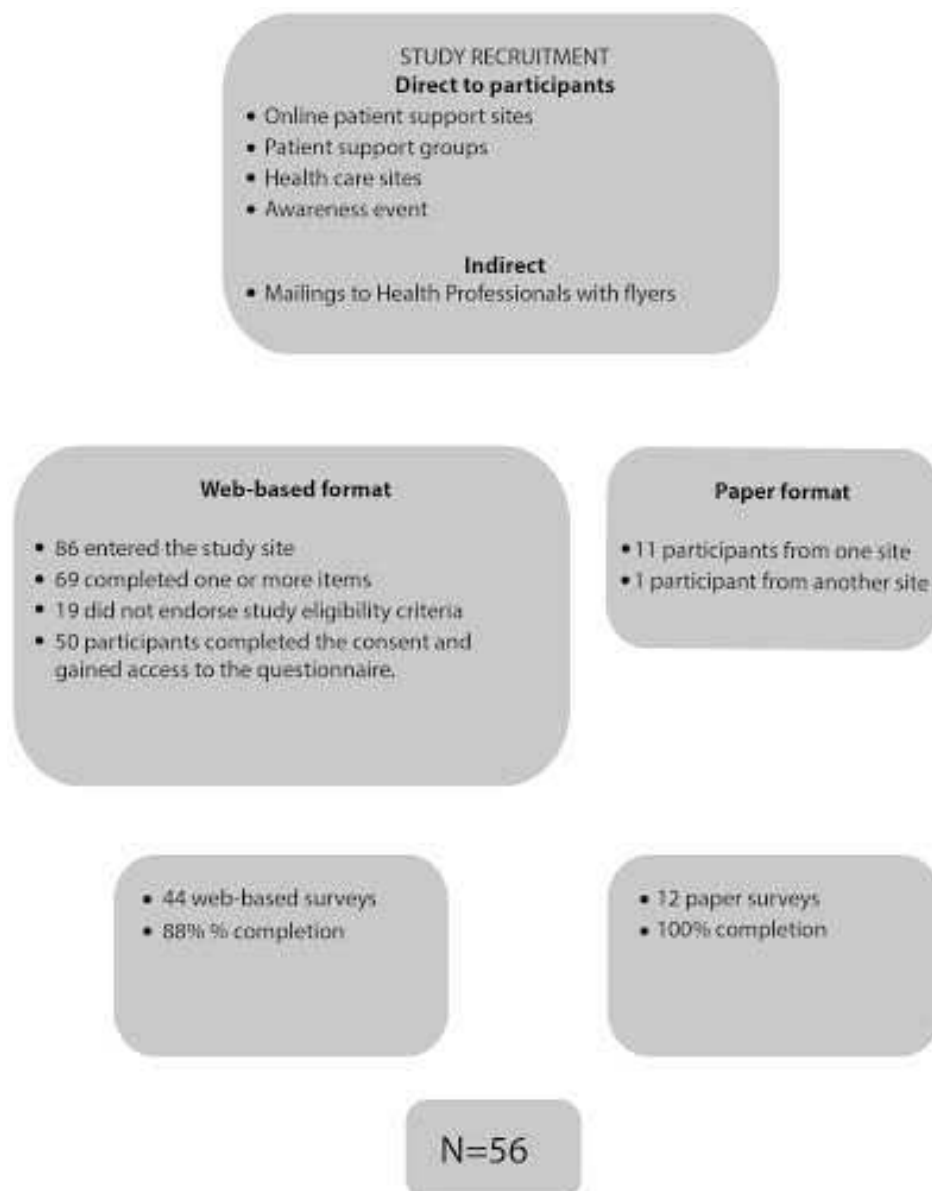


Figure 3. Direct and Indirect Study Recruitment

Sample

The sample for this study included participants receiving EGFRIs who responded to online or other posted announcements at support sites, or who were told about the study by their health care provider.

Inclusion criteria were as follows:

1. Treatment with an EGFRi (either a MOAB or a TKI) *for at least four weeks.*

These agents include afatinib (Gilotrif®), erlotinib (Tarceva®), gefinitib (Iressa®) (continuing patients), lapatinib (Tykerb®), and the monoclonal antibodies cetuximab (Erbix®) and panitumumab (Vectibix.)

2. Ability to speak, read, write and understand English.
3. Age 18 years or over.
4. Ability and willingness to consent to participate in the study.
5. Ability and willingness to complete study activities, including completion of required questionnaires online, or by completion of paper instruments.

Exclusion criteria were as follows:

1. Patients who self-reported significant dermatologic disease unrelated to cancer treatment, such as severe acne vulgaris, erythema multiforme, psoriasis or rosacea.
2. Patients with a poor performance status unable to complete the survey instruments, which required 20-30 minutes to finish.

Participants responded to the following item which included the first exclusion criteria: “I do not have one of the following skin conditions: acne vulgaris, erythema

multiforme, psoriasis or rosacea.” The second exclusion criteria would have resulted in patients not completing the survey, so submission of the survey assumes adequate performance status.

Sample Size Calculation

Aims 1 and 2 were descriptive and did not require sample size calculation. Aim 3 required factor analyses for identification of symptom clusters or co-occurring symptoms, and will be discussed further below. Sample size calculation for Aim 4, assuming a medium effect size and a power of 0.8 at a 0.05 level of significance, ranged from 85-92 with 5 variables included in the model. If an additional two variables were entered, to total 7, required sample size would increase to 103-104 (Newton & Rudestam, 1999), so the initial proposed sample size was 100.

Sample Size for Factor Analysis

Sample size for this study, however, was primarily driven by the use of exploratory factor analysis for deriving symptom clusters as described in Aim 3. Power analysis is not used to generate a sample size for factor analysis, and there is no standard method for calculation of an appropriate sample size.

Factor analysis procedures traditionally have been thought to require a large sample size, but opinions vary regarding ideal sample sizes for factor analytic procedures. Although several rules of thumb governing sample size for factor analysis appear in the literature, stringency in their application has diminished. Traditional practice has suggested that in order for factor analysis results to be reliable, they must be generated from very large samples (i.e. at least several hundred up to 1000), or that sample size

should range from 2-10 times the number of variables (Kline, 2002; Costello & Osborne, 2005; Mundfrom, Shaw, & Tian, 2005). Kline (1994) argued that the ratio of subjects to factors should be a consideration when determining sampling adequacy, with a goal of accruing more than 20 subjects for each factor. Ideally, a larger sample size is preferred, but an efficient solution can result from more modest sample sizes.

The actual characteristics of the data have emerged as an important influence on sample size (MacCallum, Widaman, Zhang, & Hong, 1999; Costello & Osborne, 2005). The number of variables and their associated loadings constitute one important element when considering results of a factor analysis. Stevens (2002) suggested that a factor is reliable when one of the following conditions are met: 3 or more variables, with any n and loadings of 0.8; 4 or more variables, with any n , and loadings of 0.6; 10 or more variables with loadings of 0.4 and n larger than 150; factors with only a few loadings require a sample size greater than 300 (p.395).

Other characteristics of the data, including high communalities (greater than 0.6), overdetermination, and simple, non-overlapping factor structures, are more relevant to the determination of an adequate sample size than just the number of variables (MacCallum et al., 1999). Communality (h^2) reflects the percent of variance for a given variable that is accounted for by all identified factors, and is the sum of squared loadings across factors for that variable. When communalities are greater than 0.6, a sample size of less than 100 may be adequate. When communalities are lower, a sample size of at least 100 is preferred. Overdetermination, which occurs when each factor has several high loadings, also may mitigate the need for a larger sample size. In research designed

to test the stability of factor solutions, samples meeting the characteristics of high communalities and a desirable level of overdetermination maintained factor structures with a sample size as low as 60 (MacCallum et al., 1999). Mundfrom et al. (2005) extended this work with similar samples and found adequate factor solutions with sample sizes of 35-75. With a fairly simple factor structure, such as the one derived in the current study, it has been noted that a sample size of 50-100 would be acceptable (Darlington, n.d.).

Large sample sizes have generally been recommended as a strategy to overcome measurement error. In the clinical setting, however, it has been argued that patients symptom reports may so accurate that larger samples are not necessary (Olson, Hayduk, & Thomas, 2014).

Statistical Analysis

Descriptive statistics, correlations, exploratory factor analysis, cluster analysis and multiple regressions were used in this study. Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS Version 22). Descriptive statistics were generated for the following variables: age, educational level, gender, marital status, primary cancer diagnosis, stage of disease, and tobacco use. Descriptive statistics for symptom frequency, symptom distress, quality of life, EGFRI-related quality of life, MSAS-SF (adapted), performance status and psychological status are reported.

A variety of statistical approaches have been employed to generate symptom clusters, such as correlations, structural equation modeling, factor analysis, principal component analysis and cluster analysis. Factor analysis based on Pearson correlation has

demonstrated stability in the identification of symptom clusters from different measurement tools (Miaskowski et al., 2007; Henoch, Ploner, & Tishelman, 2009), so exploratory factor analysis was selected as the primary method to identify symptom clusters in the present study. A scree plot, eigenvalues, the Kaiser-Meyer-Olkin test and Bartlett's test of sphericity were examined to determine the adequacy of the factor structure.

Factor analysis explores a given set of variables to determine if they possess an underlying latent structure which can be used to explain correlations among the variables. Kline describes a factor as a "dimension or construct which is a condensed statement of the relationships between a set of variables" (Kline, p. 5). Royce (1963), as quoted by Kline, stated that "a factor is a construct operationally defined by its factor loading" (Kline, p. 5). Factor loadings are described as the relationships or correlations of a variable with a factor (Kline, 1994). Correlation coefficients for factor loadings can range from -1 to 1.0 (Johnson & Wichern, 2002).

Hierarchical cluster analysis was also used to confirm the symptom clusters. Hierarchical cluster analysis procedures do not require a specific sample size as they are an exploratory approach "without an inferential test" (Kim, Barsevick, Beck, et al., 2012). Hierarchical cluster analysis has been used in other studies on symptom clusters, so reexamining symptoms with this approach provides some additional support for the clusters identified via factor analysis with the relatively small sample available in this study (Hockenberry, Hooke, McCarthy, & Gregurich, 2011; Chen, Nguyen, Cramarossa, et al., 2012; Chen, Nguyen, Khan, et al., 2012).

Correlations and multivariate procedures were employed to explore the relationships between the symptoms, the derived symptom clusters and the dependent variables of performance status, psychological functioning and quality of life, as well as any differences by age, gender, treatment or disease.

Instruments

The instruments selected for data collection include are listed in Table 1 and are discussed below.

Table 1. Model Components, Variables and Measures

Model Component	Variable	Measures
Influencing Variables	Age Gender Primary Diagnosis Specific EGFR	Demographic tool
Symptoms	Symptoms Symptom clusters	MSAS-SF (ADAPTED)
Performance	Functional performance Psychological status Quality of life Dermatologic QOL	ECOG PS MHI-5 FACT-G FACT-EGFR-18

Note. EGFR: epidermal growth factor receptor inhibitor; MSAS-SF (adapted): Memorial Symptom Assessment Scale- Short Form; ECOG PS: Eastern Cooperative Oncology Group; MHI-5: Mental Health Index-5; FACT-G: Functional Assessment of Cancer Therapy-General; FACT-EGFR-18: Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18 Subscale; QOL: Quality of Life.

Memorial Symptom Assessment Scale (MSAS-SF) (adapted)

The Memorial Symptom Assessment Scale-SF (MSAS-SF) was selected for this study because it offers the most comprehensive cancer symptom inventory available, measures symptoms along several dimensions, and has established psychometric properties (Kim et al., 2009b). The original long form MSAS was developed to measure the frequency, severity and distress of 32 symptoms associated with a cancer diagnosis, and has established psychometric properties (Portenoy et al., 1994a; Portenoy et al., 1994b; Portenoy et al., 1994c). The MSAS-SF is a modified version of the instrument which also measures 32 symptoms; distress and frequency are measured for 28 physical symptoms while frequency is measured for four psychological symptoms (Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000). The MSAS-SF was used in this study instead of the longer original version in order to reduce response burden. Both versions of the instrument contain blank spaces to allow for the addition of symptoms not included on the tools, so the MSAS-SF has been adapted for this study to include additional symptoms prevalent in this patient population. Items added to the scale included *changes in my fingernails or toenails, other changes to my fingers and toes, dry skin, changes in hair growth on my face, changes to my eyelashes, and other changes to scalp hair.*

Scoring. The scoring of the MSAS-SF is different than the original MSAS scoring. Physical symptoms are rated with regard to the degree of distress they cause. Participants select from the following descriptors for every physical symptom they endorse: “no distress,” “a little bit of distress,” “somewhat distressing,” “quite a bit of distress,” and “very much distress.” These descriptors are then coded and scored as

follows. If a symptom is not present, it is scored as a 0. If it is present, and causes no distress, it is scored as a 0.8., if it causes a little bit of distress, the score is 1.6, if it is somewhat distressing, the score is 2.4, if there is quite a bit of distress, it is scored at 3.2, and if a symptom is associated with very much distress, the score is 4.0

Psychological symptoms are rated in terms of prevalence: “rarely,” “occasionally,” “frequently,” and “almost constantly.” Participants select one of those descriptors for every psychologic symptom they endorse. When symptoms are present, the scoring is as follows: 1 if the symptom is present but occurs rarely; 2 if the symptom is present and occurs occasionally; 3 if the symptom is present and occurs frequently; and 4 if the symptom is present and occurs almost constantly. The two scoring methods reflect the distress associated with the symptom for physical symptoms and the prevalence of the symptom for psychological symptoms. Subscales for physical (PHYS) and psychological (PSYCH) symptoms, as well as a global distress index (GDI), can be generated from the MSAS but were not included in this study because additional items were included as symptoms. Future work could explore this aspect of the scoring.

Reliability and validity. The original, condensed, and short forms of the MSAS have been used to measure symptoms in multiple studies in oncology (Chang et al., 2000; Kris & Dodd, 2004; Gwede, Small, Munster, Andrykowski, & Jacobsen, 2008 ; Kim et al., 2009b; Kim et al., 2009a; Molassiotis, Wengstrom, & Kearney, 2010; Webber & Davies, 2011; Cataldo et al., 2013; Oksholm et al., 2013; Kenne Sarenmalm, Browall, & Gaston-Johansson, 2014; Miaskowski et al., 2014; Ritchie et al., 2014). MSAS tools have also been used to measure symptom clusters in in other patient populations, despite the

original purpose as an oncology symptom inventory. Representative studies of non-oncology patients include nonalcoholic fatty liver disease (Houghton-Rahrig et al., 2013), heart and lung disease (Blinderman, Homel, Billings, Portenoy, & Tennstedt, 2008; Song, Moser, Rayens, & Lennie, 2010; Strada, Homel, Tennstedt, Billings, & Portenoy, 2013), and HIV (Aouizerat et al., 2010).

MSAS-SF psychometrics. In a sample of 299 cancer patients, the Cronbach alpha coefficient, assessing internal reliability, ranged from 0.76 to 0.87 in repeated administration of the MSAS-Short Form (Chang et al., 2000). Subscales of the FACT-G, the Karnofsky Performance Status, and extent of disease served to establish criterion validity and convergent validity for the MSAS-SF. Repeatability was evaluated by a test-retest measurement at one day (0.86 to 0.94) and one week (0.40 to 0.84).

Correlation coefficients were reported to be in the appropriate direction for the subscales of the MSAS-SF and for the FACT-G: $r = -0.74$ ($p < 0.001$) for the PHYS and FACT-G physical well-being subscales; $r = -0.68$ ($p < 0.001$) for the PSYCH and FACT emotional well-being subscales, and $r = -0.70$ ($p < 0.001$) for the GDI and FACT total QOL subscales. MSAS scores reflecting a higher symptom burden would be larger, while FACT-G scores reflecting a good quality of life would also be higher, explaining the negative correlation.

FACT-G

In the present study, the FACT-G was used as a global measure of quality of life. The FACT-G (Functional Assessment of Cancer Therapy-General) Version 4 is 27-item questionnaire with well-established reliability and validity that measures quality of life

across four domains: physical well-being (PWB), social and family well-being (SWB), emotional well-being (EWB) and functional well-being (FWB) (Cella et al., 1993; Webster, Odom, Peterman, Lent, & Cella, 1999). The FACT-G can be self-administered or scored by an interviewer and can be completed in 5-10 minutes (Danahauer et al., 2007). An item related to sexuality was not included in the present study as a similar question about problems related to sexuality was asked on the MSAS-SF. Two participants did not complete all items on the FACT-G Social Well-Being (SWB) subscale, and one did not complete all items on the Functional Well-Being (FWB) subscale, so these were scored in accordance with the procedure outlined for missing data.

The FACT instruments have been widely used in the oncology population, and are applicable across various cancer diagnoses. The FACT-G correlated well with most subscales of the SF-36, and it discriminated between patients with cancer and community dwelling elders ($p < 0.002$) (Overcash, Extermann, Parr, Perry, & Balducci, 2001).

Scoring. All items are scored from 0-4, anchored at “not at all,” with a score of zero, “a little bit,” “somewhat,” “quite a bit,” to “very much.” Some items are scored straightforwardly, but negatively worded items are reverse scored, and all items are then summed to obtain a subscale or total score. Higher scores indicate a better quality of life. A total score is calculated as the sum of all four subscales, given that 80% of items have been completed, resulting in a total score for all items that can range from 0-108 points.

FACT-EGFRI 18

In order to more fully characterize the quality of life of patients receiving EGFRIs, the Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor (known as the FAST-EGFRI-18 or FACT-EGFRI 18) was also used in the present study. The EGFRI-18 is a self-report tool that was recently developed to describe the impact of 18 EGFRI-related skin, nail and hair toxicities on the four dimensions of quality of life incorporated in the Functional Assessment of Cancer Therapy (FACT) instruments. This instrument provides additional condition-specific quality of life assessment and is a companion module to the core FACT-G items.

As is customary with the construction of these additional modules, the developers used a triangulation method, including literature review, qualitative data collection via patient ($n=20$) and expert panels ($n=12$), and quantitative surveys, on candidate items in order to generate the items for the EGFRI-18 (Wagner & Lacouture, 2007; Wagner et al., 2010; Wagner et al., 2013). The initial version of the EGFRI-18 incorporates 18 items assessing the effect of skin, nail and hair treatment-related symptoms on quality of life. Although there are other dermatology quality of life instruments (e.g. Skindex instruments) (Chren, Lasek, Quinn, & Covinsky, 1997), they were not specifically designed to address the dermatologic toxicities associated with EGFRI therapy. The authors developed this tool in response to a lack of EGFRI standardized patient-reported outcome measures (Wagner et al., 2013), so for this reason it was selected for the present study.

As this is a newer tool, psychometric properties have not yet been published, and a large cooperative group study is currently underway to validate this questionnaire in patients with colorectal or lung cancer receiving cetuximab, panitumumab, or erlotinib (S1013: Validation of Cancer Questionnaire for Skin Toxicities in Patients With Colorectal Cancer or Lung Cancer Receiving Cetuximab, Panitumumab, or Erlotinib Hydrochloride, 2013), but no data has been reported yet.

Mental Health Inventory-5 (MHI-5)

Psychological functioning was operationalized by the mental health subscale (also known as the MHI-5, and referred to as such in this study), which is a 5-item questionnaire designed to assess for mental health concerns. The Mental Health Inventory (MHI-5) has been validated as a simple tool for as a measure of general mental health and for detecting depressive symptoms and anxiety in both a healthy population and in those with a variety of chronic illnesses, including cancer (Ganz et al., 2003).

Respondents answer questions about their psychological well-being selecting responses of “all of the time,” “most of the time,” “some of the time,” “a little bit of the time,” and “none of the time.” The MHI-5 was recently evaluated in oncology patients and was found to be brief, simple to administer, and easy for patients with a sixth to ninth grade reading level to understand (Johns et al., 2013). The items were scored and transformed to a scale ranging from 0 to 100, with a higher score indicating a more optimal level of functioning. Evaluation of the MHI-5 as a screen for psychological function revealed areas under the curve of 0.739 for anxiety disorders to 0.892 for major

depression (Berwick et al., 1991), and 0.73 for some anxiety disorders, such as generalized anxiety disorder (Cuijpers, Smits, Donker, ten Have, & de Graaf, 2009).

Eastern Cooperative Oncology Group Performance Status (ECOG PS)

In this study, functional status is measured by the ECOG Performance Status scale. Performance status scales such as the ECOG PS assess the impact of illness on the activities of daily living and overall functional well-being. The ECOG PS quantifies a continuum of self-care and activity, ranging from fully active and able to perform all normal activities, to unable to perform self-care and completely disabled. In the clinical trials and treatment setting, functional or performance status is typically scored by the clinician. However, self-rating using the one-item ECOG PS scale has been explored, and has been described as reasonable since patients are more attuned to their physical condition than others may be (Ando et al., 2001). The descriptors used for each level of the ECOG PS are self-explanatory and easily completed by patients. For example, patients in the process of being diagnosed with lung cancer produced reliable ratings of performance status, so the researchers concluded that patients could viably assess their own performance status (Blagden, Charman, Sharples, Magee, & Gilligan, 2003).

In a study exploring whether performance status could be described by patients using the Performance Status Visual Analog Scale (PS-VAS), which is a different instrument, Gralla confirmed that patients were able to rate their own performance status, and demonstrated adequate correlation between the scale and both the ECOG ($r = .43$) and Karnofsky ($r = .46$) Performance Scales, suggesting that reasonably equivalent information could be gained from any of these instruments (Gralla et al., 2005).

The value of patient-reported performance or functional status is highlighted by studies revealing variations in these scores between patient ratings and health care provider ratings. One study examined ratings between patients and a variety of clinicians, reporting that the correlations between patient- and provider-reported ECOG PS scores varied from 0.51 (patients and registered nurses) to 0.64 (patients and radiation therapy students as well as physicians), providing evidence of only moderate agreement (de Borja, Chow, Bovett, Davis, & Gillies, 2004); another also found a lack of congruence in over half of patient and physician ratings at diagnosis, with patients rating their functional status as lower than physicians (Dajczman et al., 2008).

Ethical Considerations

Protection of Human Subjects

The Loyola University Medical Center Institutional Review Board (IRB) classified this study as exempt as no identifiable information was collected. Anonymity for all study participants was protected. Any study related data, including data input for analysis, has been maintained in password-protected files managed by the investigator. Potential risks to participants were minimal, but could include heightened stress due a greater awareness of potential symptoms attributable to their therapies.

The web-based survey was housed by the software vendor on the secure Qualtrics web site and all data was time-stamped and encrypted in transmission. Network security on Qualtrics includes a Transport Layer Security (TLS) encryption connection, firewall protection, intrusion detection and prevention, and security scans. The vendor is prevented through confidentiality agreements from accessing or disclosing information in

the database. Servers are located in a data center with security and environmental controls and are backed up nightly. All data at rest are encrypted and all deprecated hard drives where data is stored are destroyed by the United States Department of Defense methods and delivered to a third-party destruction service (Qualtrics, 2014). A unique identifier for each response masked each survey response, and no identifying information, including IP address, was recorded. Survey responses are viewable to the researcher only via a username and password.

Participants could complete the survey using the device of their choice as the survey was optimized for mobile formats, and could be viewed on tablets, smartphones or personal computers. In addition, completion of the instruments took approximately 20 minutes (most completed the online version in approximately 8-15 minutes, although longer time frames were recorded), and may have taken more time if there were connectivity or other technical issues. Participants were allowed to start the web-based survey and return later to complete it if necessary.

For participants completing the web-based survey, eligibility requirements were presented and then a consent form appeared prior to the study instruments. Participants reviewed it and checked a statement indicating that they agreed to participate in the study (“I agree to participate in this study”). Volunteers who agreed to the consent and affirmed that they met the inclusion criteria advanced to the study questionnaire. Participants who did not meet the study criteria or who did not agree to participate in the study received a message thanking them for their time, but indicating that they were not

eligible to participate. The survey software recorded the consent as part of the questionnaire.

Participants completing paper surveys checked off the same eligibility and informed consent prior to study enrollment. In addition, their completion of the survey return by mail was evidence of their consent. All participants who completed the paper survey were provided stamped, pre-addressed envelopes for return of the survey to the investigator. The investigator's return address was pre-printed on the return envelopes, and in no case did any participant include their own address or any other identifying information in the returned surveys. Data from the paper surveys was entered into the Qualtrics' site and paper copies were destroyed by the investigator.

CHAPTER FOUR

RESULTS

The present study was designed to explore the symptom experience of patients receiving EGFRIs, including the identification of symptom clusters, and the impact of any identified symptom clusters on patient outcomes. The theory of unpleasant symptoms (TOUS) provided a useful framework from which to explore the symptom experience in study participants. The TOUS model allowed for the measurement of distress and frequency of symptoms, and also for evaluation of the impact of symptoms on patient-reported outcomes, including performance, quality of life, and psychological status. Findings from the current study can inform future work in this area and can be replicated in larger and more purposeful samples.

Data Analysis

Statistical procedures included descriptive methods (frequencies, percentages, and measures of central tendency), Pearson correlations, one-way ANOVA, nonparametric Mann-Whitney U, independent t-tests, exploratory factor analysis, hierarchical cluster analysis procedures and regressions. The demographic characteristics of participants are presented as percentages for age range, gender, educational level, living arrangements and relationship status. Clinical characteristics, including primary cancer diagnosis, stage of disease, duration of EGFRi therapy and tobacco use are also reported. ECOG

Performance Status scores are reported by percentage and frequency. For all scales and the selected subscales, measures of central tendency were used for analysis. Data collected using the FACT-G, EGFRI-18, MHI-5, and ECOG Performance Scale were assessed for normality by examining skewness and kurtosis values, visual inspection of the Kolmogorov-Smirnov (Ghasemi & Zahediasl, 2012) or Shapiro-Wilk tests of normality, and deviations from normality are reported. The internal consistency reliability of each instrument and relevant subscales for the FACT-G were confirmed using Cronbach's alpha.

Exploratory factor analysis, using principal axis factoring with an oblique rotation was used to identify co-occurring symptoms, or symptom clusters. Multiple factor analyses were run, using various methods and rotations, in order to find the best solutions. The Kaiser-Meyer-Olkin measure of sampling adequacy, communalities, Bartlett's test of sphericity, diagonals on the anti-image correlation matrix, and inter-item correlation coefficients were examined to determine the appropriateness of the data for factor analysis.

Because of the small sample size, an alternative approach to deriving symptom clusters was also implemented. Hierarchical cluster analysis was used as a comparison to factor analysis, as HCA can be used with small samples. This additional procedure allowed for comparison of symptom clusters identified using different statistical approaches.

Independent t-tests, one-way ANOVAs, and non-parametric tests were used to assess the differences on outcome variables between the identified symptom clusters.

Variables with statistically significant Pearson correlations with the outcome variables of quality of life, functional performance and psychological status were included in a forced entry linear regression model to explore their effect on outcomes. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS Version 22).

Sample Characteristics

A total of 56 participants were eligible for inclusion in the study during the recruitment period and are included in this analysis. Participants were able to complete the study online or on paper; 44 participants completed online surveys and 12 completed surveys on paper.

For the online version, a total of 86 participants entered the study site over a ten month period from June, 2013 to May, 2014, after being directed to the survey site by the investigator or after directly responding to survey recruitment materials that were posted on online support groups, on the survey web site, at support group settings or at health care sites. Of this group, 69 participants completed one or more items. However, 19 failed to respond affirmatively to the study eligibility criteria, and were redirected out of the study site. In total, 50 participants completed the consent and gained access to the questionnaire. Six of this group started the survey, but stopped after answering a few questions, so responses for those participants were largely incomplete and are not included in the analysis, resulting in a completion rate for the online version of 88% (44/50 who accessed the questionnaire and were eligible to complete it).

Most participants who completed paper copies had received information about the study from a nurse (n =11) who had received a study recruitment letter directed to health

care professionals. One received the paper survey from the investigator after responding to postings about the survey. Paper copies of the surveys were supplied to participants, and all of the distributed paper surveys were returned by pre-addressed stamped envelope, with a completion rate of 100%. The completed surveys were anonymous, and no identifying information was collected. All paper surveys were completed by December, 2013.

These procedures resulted in a total of 56 participants who completed most survey instruments and are included in the data analysis, with a total of 55 who completed all instruments. One participant did not complete the EGFRI-18, so data is presented for the participants who did complete these instruments. Overall, a total of 55 participants completed all measures as procedures for missing data could be applied for the FACT-G. As the participants were anonymous, there was no follow-up procedure for missing data.

Demographic Characteristics

Demographic characteristics of the sample are presented in Table 2. Nearly two-thirds of the participants included in this sample are female. About 10% reported that they were younger than 50 years of age, with about one-third of patients between 50-59, and another third between 60-69 years of age. This sample, as might be anticipated in a study conducted primarily online, appears to be well-educated, with 82% reporting that they have received a college or graduate degree. The majority of participants (75%) are married, and a corresponding number of participants live with a spouse (60%) or a spouse and children (16%). Relationship status and living arrangements for participants in this sample suggest a significant amount of social and psychological support.

Table 2. Participant Characteristics (N=56)

Characteristic	Age	Percentage
Characteristic	N	Percentage
Gender		
Male	20	35.7
Female	36	64.3
Age		
30-39	1	1.8
40-49	5	8.9
50-59	18	32.1
60-69	17	30.4
70-79	2	21.4
>80	3	5.4
Educational Level		
Elementary	0	0
High School	10	7.9
College	29	51.8
Graduate School	17	30.4
Relationship Status		
Married	42	75.0
Single	1	1.8
Divorced	10	17.9
Widowed	3	0.4
Living Arrangements		
Live with spouse	33	58.9
Live with spouse and children	9	16.1
Live with children	3	5.4
Live alone	10	17.9
Live with others not listed	1	1.8

Clinical Characteristics

Clinical characteristics are reported in Table 3. Only two participants (3.6%) reported receiving radiation therapy concurrent with the study, but 18 of 59 (30%) indicated that they were receiving other treatments, including various chemotherapy agents and other drugs, including trastuzumab, carboplatin, 5-fluorouracil, 5-fluorouracil and carboplatin, cabozantinib, paclitaxel protein-bound and carboplatin, paclitaxel and carboplatin, capecitabine, zoledronic acid, irinotecan, denosumab, letrozole, exemestane, and experimental drug MK-2206. A total of nine participants were receiving cytotoxic chemotherapy, including concurrent carboplatin as a single agent reported by five participants, trastuzumab reported by four participants, and 5-FU reported by three participants. The remaining agents listed above were reported by one or two participants, and several participants were taking multiple agents.

Co-morbidities were reported as follows: eight participants reported a diagnosis of diabetes; and two reported osteoporosis. A respiratory disorder, a gastrointestinal disorder, Graves' disease, Hashimoto's disease, an unspecified thyroid condition, hypertension, hemolytic anemia, and rheumatoid arthritis were each reported by one participant.

More than half of the participants (57%) reported applying a cream that their health care professional recommended. Sixteen reported using an oral medication, with seven reporting doxycycline and five reporting minocycline; others reported using an unspecified antibiotic, nystatin or Zyrtec.

Tobacco use (smoking) was reported by 7% (n=4) of participants; 0 reported using other tobacco products. The majority of participants (88%) (N=52) reported that they did not currently use tobacco products, and 5% (n=3) indicated that they quit using tobacco products on diagnosis.

Table 3. Clinical Characteristics

Characteristic	N	Percentage
Diagnosis		
Breast cancer	10	17.9
Colorectal cancer	7	12.5
Head and neck cancer	10	17.9
Lung cancer	29	51.8
Pancreatic cancer	0	0
Unknown	0	0
Stage of disease		
Stage I	1	1.8
Stage II	3	5.4
Stage III	2	3.6
Stage IV	50	89.3
Educational Level		
afatinib	2	3.6
erlotinib	24	42.9
lapatinib	10	17.9
cetuximab	16	28.6
panitumumab	4	7.1
Therapy duration		
At least four weeks	5	8.9
More than four weeks	9	16.1
More than eight weeks	42	75
Tobacco use		
I currently use tobacco products	0	0
I quit using tobacco at diagnosis	3	5
I do not currently use tobacco	52	88

Study Aim 1

The first aim of this study was to describe the symptom experience (symptom frequency and distress) of patients receiving EGFR therapy.

The following discussion will present information from the MSAS-SF in order to characterize the symptom experience of the participants. Additional information on identified symptom clusters will be presented in the discussion of Aim 3.

Memorial Symptom Assessment Scale-Short Form (Adapted)

A total of 38 symptoms were included in the MSAS-SF (adapted), including several not on the original instrument that are frequently experienced by patients taking EGFRs. As listed in Table 4, items added for this study included *changes in my fingernails or toenails, other changes to my fingers and toes, dry skin, changes in hair growth on my face, changes to my eyelashes, and other changes to scalp hair*. As expected, several of the symptoms added to the scale were retained through factor analysis, lending support to their inclusion in the adapted tool.

Symptom occurrence. Participants reported a mean of 11.71 symptoms (*SD*, 5.7; range, 1-28) over the previous week, which is consistent with other studies using the MSAS (Portenoy et al., 1994a; Chang et al., 2000; Deshields et al., 2011; Ritchie et al., 2014). Items marked in italics were added to the MSAS-SF for this study. The most common symptoms included *dry skin*, lack of energy, dry mouth, changes in skin, feeling sad, *changes to finger or toenails*, feeling worried, diarrhea, problems with sexual interest or activity, *changes in facial hair growth*, and difficulty sleeping. The most frequently occurring symptoms in a large heterogeneous sample of oncology patients reported

similar findings using the MSAS, with lack of energy, difficulty sleeping, problems with sexual interest or activity, pain, and feeling drowsy the most frequently endorsed symptoms in the overall sample (Deshields et al., 2011).

Table 4. Symptom Occurrence (N=56)

	Percentage	N
<i>Dry skin</i>	67.9	38
Lack of energy	65.5	36
Dry mouth	57.1	32
Changes in skin	55.4	31
Feeling sad	53.6	30
<i>Changes to my finger or toe nails</i>	53.6	30
Worrying	50	28
Diarrhea	48.2	27
Feeling drowsy	46.4	26
Problems with sexual interest or activity	44.6	25
<i>Changes in hair growth on my face</i>	44.6	25
Difficulty sleeping	44.6	25
Feeling nervous	42.9	24
Numbness/tingling in hands/feet	42.9	24
Feeling irritable	41.1	24
Changes in the way food tastes	39.3	22
<i>Other changes to the hair on my scalp</i>	39.3	22
<i>Changes in my eyelashes</i>	37.5	21
Hair loss	37.5	21
Difficulty concentrating	35.7	20
Itching	33.9	20
Cough	32.1	19
Weight loss	32.1	18
Pain	30.6	18
Lack of appetite	30.4	17
Nausea	28.6	16
Shortness of breath	26.8	15
<i>Other changes to my fingers or toes</i>	25	14
Mouth sores	25	14
Constipation	21.4	12
"I don't look like myself"	21.4	12
Difficulty swallowing	19.6	11
Dizziness	16.1	9
Sweats	16.1	9
Feeling bloated	10.7	6
Vomiting	8.9	5
Problems with urination	8.9	5
Swelling of arms and legs	8.9	5

Note. Items in italics were added to MSAS-SF for this study.

Symptom distress and prevalence. Using the MSAS-SF (adapted), physical symptoms were measured by the amount of distress caused, whereas psychological symptoms were measured by their prevalence. The overall distress and prevalence rankings are reported in Appendix A. When evaluated by the distress associated with physical symptoms, or prevalence of psychological symptoms, the symptoms of *dry skin*, lack of energy, worry, *changes to finger and toe nails*, problems with sexual interest and activity, changes in skin, dry mouth, feeling sad, and diarrhea, were ranked as most distressing or prevalent. While lack of energy and worry have long been considered very common and distressing symptoms in oncology, the emergence of dermatologic symptoms as major contributors to distress is remarkable when compared to previous work on cancer symptoms and symptom clusters.

Physical symptoms. The most distressing physical symptoms are highlighted in Table 5, and include five symptoms that can be described as dermatologic or mucocutaneous, three of which were added to the adapted version of the MSAS-SF for this study. Dry skin is the physical symptom causing the most distress in this study, followed by lack of energy. It is notable that nausea, vomiting, and lack of appetite, which long have been associated with cancer treatment, are less likely to be distressing in the setting of EGFR therapy.

Table 5. Most Distressing Physical Symptoms (N=56)

	Mean	S. D.
<i>Dry skin</i>	1.757	1.4902
Lack of energy	1.657	1.3802
<i>Changes to my finger or toe nails</i>	1.429	1.4925
Problems with sexual interest or activity	1.429	1.6552
Changes in skin	1.414	1.3814
Dry mouth	1.386	1.4269
Diarrhea	1.286	1.5077
<i>Changes in hair growth on my face</i>	1.100	1.3522
Difficulty sleeping	1.029	1.2646
Numbness/tingling in hands/feet	1.000	1.3495

Note: Items in *italics* were added to the MSAS-SF for this study.

Psychological symptoms. The prevalence of psychological symptoms is included in Table 6. Psychological symptoms are rated by prevalence, so that each of these symptoms occurred at least occasionally in the study sample. Worry was the item with the highest prevalence rating.

Table 6. Prevalence of Psychological Symptoms (N=56)

	Mean	S. D.
Worrying	1.60	1.2746
Feeling sad	1.35	1.1666
Feeling nervous	1.23	1.1907
Feeling irritable	1.19	1.1349

Relationship of symptom distress and prevalence to key demographic

variables. The independent variables of gender, diagnosis, specific EGFR therapy and age were examined to identify any significant differences in symptom distress and prevalence.

Gender. Overall, men reported more symptoms ($M = 13.95$, $SD = 5.24$) than women ($M = 10.75$, $SD = 5.74$), with significant differences in occurrence between genders for the symptoms lack of energy, dry mouth, problems with sexual interest or activity and dry skin. The most frequently reported symptoms were analyzed in terms of distress (for physical symptoms) and prevalence (for psychologic symptoms). Significant findings are reported in Table 7.

Table 7. Significant t-Tests of Symptoms by Gender with Descriptive Statistics

Symptom	Group						95% CI for Mean Difference	t	df
	Male			Female					
	M	SD	n	M	SD	n			
Dry skin	2.24	1.18	20	1.49	1.6	36	-1.5, -.003	-2.0**	49
Dry mouth	2.32	1.39	20	.867	1.17	36	-2.15, -.75	-4.16*	54
Worrying	.95	1.05	20	1.97	1.25	36	.36, 1.69	3.01**	54

Note: Only significant results are shown. * $p < .05$, ** $p < .01$

Diagnosis. Symptoms by prevalence and distress were examined for any significant variations by primary cancer diagnosis as illustrated in Table 8. Of the most frequently occurring symptoms, distress scores differed significantly across the diagnoses for three symptoms: worrying, diarrhea, and dry mouth. Worry caused the most distress in lung cancer patients. Breast cancer patients reported a higher incidence of diarrhea,

which is not an unexpected finding, as diarrhea is a known side effect of lapatinib and grade 1 or 2 diarrhea occurs in about 40% of patients (Moy & Goss, 2007). Similarly, there was considerable variation across the diagnoses for dry mouth, with head and neck cancer patients reporting a higher incidence of distress associated with this symptom. Head and neck cancer patients may have received radiation therapy, and xerostomia is a well-known effect of this treatment.

Table 8. Symptom Distress or Prevalence by Diagnosis

<i>Diagnosis</i>	<i>N</i>	Worrying		Symptom Diarrhea		Dry Mouth	
		<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>
Breast cancer	9	1.667	1.0000	2.844	1.3333	.533	1.1314
Colorectal cancer	7	.571	1.1339	1.143	1.1178	2.057	1.1178
Head and neck	10	1.400	1.4298	.640	1.3492	2.640	1.5572
Lung cancer	29	1.828	1.1973	1.103	1.4409	.966	1.1188

A one-way between groups ANOVA was conducted to compare the effect of diagnosis on symptom distress (physical symptoms) and prevalence (psychological symptom) are highlighted in Table 9.

Table 9. One-Way Analysis of Variance Symptoms by Diagnosis

		Sum of Squares	df	Mean Square	F	Sig.
Dry mouth	Between Groups	58.409	4	14.602	6.388	.000**
	Within Groups	116.573	51	2.286		
	Total	174.982	55			
Diarrhea	Between Groups	44.993	4	11.248	3.815	.009**
	Within Groups	150.364	51	2.948		
	Total	195.357	55			
Worrying	Between Groups	15.105	4	3.776	2.594	.047*
	Within Groups	74.252	51	1.456		
	Total	89.357	55			

Note: **p < 0.01, * p < .05

Specific EGFR. An independent t-test demonstrated a significant difference in symptom distress (physical symptoms) and prevalence (psychologic symptom) for several symptoms between participants taking small molecule tyrosine kinase inhibitors (TKIs) (lapatinib, afatinib, erlotinib) and those receiving monoclonal antibodies (MOABS) (panitumumab and cetuximab). Drugs were grouped together by a mechanism of action (TKIs: afatinib, erlotinib, lapatinib; MOABS: cetuximab and panitumumab) due to the small number of participants taking one option of each class of drug (afatinib, n = 2; panitumumab, n = 4). Of the symptoms most frequently reported, participants receiving MOABs experienced greater distress or prevalence with all of the symptoms, with the exception of worrying, which was more often prevalent in the TKI group.

Table 10. Descriptive Statistics and Independent t-Test Comparing Symptoms Distress and Prevalence by Type of EGFR Inhibitor

Symptom	Type of EGFR Inhibitor						t	df
	MOAB			TKI				
	M	SD	n	M	SD	n		
Lack of energy	2.44	1.11	20	1.22	1.33	36	-3.6**	45
Dry mouth	2.4	1.29	20	.822	1.17	36	-4.6**	54
Feeling drowsy	1.48	1.28	20	.6	1.00	36	-2.8**	54
Numbness/tingling in hands/feet	1.72	1.51	20	.6	1.07	36	-3.2**	54
Changes in skin	2.00	1.43	20	1.09	1.26	36	-2.5*	54
Worrying	1.15	1.27	20	1.86	1.22	36	2.06*	54

Note: **p < 0.01, * p < .05

In order to better understand the contribution of each specific agent to the distress associated with each symptom, distress and prevalence scores are reported in Table 11 for the three most frequently reported symptoms: dry skin, lack of energy and dry mouth.

For the symptom changes in skin, the distress scores are as follows: panitumumab ($M = 3.5$, $SD = .577$), cetuximab ($M = 2.25$, $SD = 1.9$), erlotinib ($M = 1.71$, $SD = 1.71$) and lapatinib ($M = .80$, $SD = 1.033$). Dry mouth, as noted in Table 10, caused greater distress in the MOAB group, with group means of cetuximab ($M = 3.06$, $SD = 1.61$),

panitumumab ($M = 2.75$, $SD = 1.61$), while less symptom distress was reported with lapatinib ($M = 1.1$, $SD = 1.9$) and erlotinib ($M = 1.08$, $SD = 1.3$).

Lack of energy also was reported with higher frequency in participants receiving MOAB therapy, with group means as follows: panitumumab ($M = 4.25$, $SD = .95$), cetuximab ($M = 2.75$, $SD = 1.3426$), lapatinib ($M = 2.3$, $SD = 1.7$), afatinib ($M = 1.5$, $SD = 2.12$), and erlotinib ($M = 1.21$, $SD = 1.58$). In addition, diarrhea appears to be associated with lapatinib therapy ($M = 3.2$, $SD = 1.93$), $F(1,3) = 2.978$, $p = .028$, with other group means reported as follows: panitumumab ($M = 2.0$, $SD = 1.41$), afatinib ($M = 1.5$, $SD = 2.12$), erlotinib ($M = 1.42$, $SD = 1.86$), and cetuximab ($M = 0.81$, $SD = 1.5$).

Table 11. Symptom Distress by Specific Agent

Specific Agent	N	Symptom					
		Dry Skin		Dry Mouth		Lack of Energy	
		Mean	SD	Mean	SD	Mean	SD
Cetuximab		2.25	1.9	3.06	1.61	4.25	.95
Panitumumab		3.5	.577	2.75	1.61	2.75	1.35
Afatinib		1.67	1.0			1.5	2.12
Erlotinib		1.71	1.71	1.08	1.3	1.21	1.58
Lapatinib		.80	1.03	1.1	1.9	2.3	1.7

Age. An analysis of variance demonstrated no significant difference in distress (physical) or prevalence (psychologic) with regard to the most frequently reported symptoms by age of participant.

Independent t-tests found no differences in the most frequently reported symptoms on distress or prevalence in those who completed the study online vs. on paper, but when all symptoms were compared, those who completed a paper survey reported greater distress associated with feeling drowsy. Analysis of variance found no significant differences by educational level for symptom distress or prevalence.

Comparisons between participants receiving therapies in addition to EGFRIs yielded several significant findings with regard to severity of reported symptoms, with the those patients reporting a greater lack of energy ($M = 2.73$, $SD = 1.609$), $t(54) = 2.384$, $p = .021$, diarrhea ($M = 2.32$, $SD = 2.102$), $t(36.4) = 2.230$, $p = .032$ and problems with sexual interest or activity ($M = 2.55$, $SD = 1.993$), $t(54) = 2.295$, $p = .026$ than those participants receiving EGFRIs alone. This finding is consistent with what would be expected in patients receiving multiple treatment modalities.

Other symptoms. Participants reported on any other symptoms they experienced that were not included in the items presented to them. Responses included the following: severe dry eye described as “very distressing;” dry eye that caused blurred vision, requiring the use of artificial tear drops and ophthalmic ointment at night; swollen eyelids oozing a “quasi liquid that hardens into a dry crust and is painful to remove;” excessive nasal mucous that hardens into a dry crust;” almost constant fatigue; problems with my fingernails “get so bad that I cannot use a knife and a fork;” swelling of lips; occasional long bone pain at night; uncertainty, “I don't know what I am supposed to be doing with my life;” sun avoidance that has “resulted in my giving up golf, biking and vacations at

beach. I run from the sun and must wear a hat at ALL times. I find this very confining;” changes to eyebrows; and foot pain.

Symptom clusters. Several procedures were used to generate factors (symptom clusters) of symptoms based on reported frequencies. These procedures included: exploratory factor analysis based on review of data characteristics with multiple iterations; exploratory factor analysis based solely on original communalities; and hierarchical cluster analysis as an alternative procedure to identify symptom clusters.

Factor analytic procedures resulted in the identification of three symptom clusters: Factor 1, a psychological-cognitive cluster; Factor 2, a dermatologic skin and hair cluster; and, Factor 3, a mucocutaneous and fatigue cluster. Factor 1 is very similar to clusters previously described, Factor 2 has not been previously described, and Factor 3 is similar to clusters previously described, but includes a treatment-related symptom. More information on these clusters will be presented in the section on Study Aim 3.

Study Aim 2

Describe the quality of life, functional performance and psychological status of patients receiving EGFRI therapy.

Quality of Life

Quality of life was measured in the present study by a general quality of life instrument, the FACT-G, and a treatment-specific scale, the EGFRI-18. The FACT-G family of instruments includes the basic core questionnaire and additional add-on panels specific to disease or treatment. When separate disease or treatment related panels are used, such as the EGFRI-18, the scores can be summed to yield a Total Quality of Live

(Total QOL) score. However, both FACT-G QOL and Total QOL scores are reported in the present study. Because the FACT-EGFRI-18 must still be refined, its sensitivity to variations in treatment-related dermatologic quality of life is not established.

Results for these two instruments are presented here.

FACT-G. The FACT-G measures quality of life across several domains, including Physical Well-Being (PWB, score range 0-28) with 7 items; Social/Family Well-Being (SWB, score range in original instrument 0-28) with 6 items in this version (score range 0-24), as a question about sexuality as not included for scoring, so this item was prorated; Emotional Well-Being (EWB) with 6 items (score range, 0-24); and, Functional Well-Being (FWB) with 7 items (score range 0-28). The FACT-G items includes a Likert scale with five responses from 0-4, (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very much). A total FACT-G score is derived by adding all of the subscales. Negatively worded items are reverse scaled, resulting in a higher score signifying a better quality of life for both the subscales and total scale. The overall FACT-G displayed a high level of internal consistency, as demonstrated by a Cronbach's alpha of 0.930.

Reliability statistics for the subscales are as follows: PWB subscale consisting of 7 items ($\alpha = .819$); SWB subscale consisting of 6 items ($\alpha = .904$); EWB consisting of 6 items ($\alpha = .847$); and FWB consisting of 7 items ($\alpha = .883$). As noted earlier, the current study, the item on sexuality was deleted as there was another variable that assessed problems with sexuality of sexual function as part of the MSAS-SF (adapted).

When more than 50% of the subscale items are answered, the subscale can be prorated by the following procedure: the sum of the subscale is multiplied by the number of items in the subscale, and then divided by the number of items that have been answered. The resulting subscale can be added to the other sub-scale scores to yield a total quality of life score. At least 22 of 27 FACT-G items must be completed, as well as at least 50% of the items of each subscale, in order for this procedure to be valid. All of the subscales are required to have a total subscale score (consistent with the above procedures) in order to calculate a total quality of life scale (Fairclough & Cella, 1996).

Results for the FACT-G are presented in Table 12, with the mean score suggesting minimal effect on quality of life in this sample.

Table 12. FACT-G Quality of Life Descriptive Statistics (N=56)

Subscale	Sample					General Norms	
	Range	Min	Max	Mean	SD	Mean	SD
Social Well-Being (SWB)	28	.00	28	21.68	6.59	<i>19.1</i>	<i>6.8</i>
Emotional Well-Being (EWB)	20	4	24	15.91	4.95	<i>19.9</i>	<i>4.8</i>
Physical Well-Being (PWB)	17	11	28	20.71	4.86	<i>22.7</i>	<i>5.4</i>
Functional Well-Being (FWB)	25	3	28	17.66	6.67	<i>18.5</i>	<i>6.8</i>
Total Quality of Life	77	29	106	75.96	18.59	<i>80.1</i>	<i>18.8</i>

Note: General population norms are shown in italics, and are from Brucker, P. S., Yost, K., Cashy, J., Webster, K., & Cella, D. (2005). General population and cancer patient norms for the Functional Assessment of Cancer Therapy-General (FACT-G) Evaluation & the Health Professions. 2005(28), 192–211.

For purposes of comparison, mean scores on the total FACT-G for the general population have been reported as 80.1 and 78.4 (Brucker, Yost, Cashy, Webster, & Cella, 2005) and 80.2 and 80 (Espie et al., 2008), 77.95 (15.16) (Yanez, Pearman, Lis, Beaumont, & Cella, 2013), and 78.4 (22.6) in patients with cancer (Danhauer et al., 2007). Yanez et al. reported subscale scores as follows: PWB ($M = 20.17$, $SD = 15.16$); SWB ($M = 22.67$, $SD = 4.76$); EWB ($M = 17.52$, $SD = 4.48$); FWB ($M = 17.6$, $SD = 5.86$). In this sample, it is interesting to note that SWB compares favorably with the general population means, suggesting that the participants, consistent with their relationship status and living arrangements, benefit from close relationships.

FACT-EGFRI-18. The FACT-EGFR-18 is a companion dermatologic quality of life instrument that addresses EGFRI treatment-related concerns. Statistics for the FACT-EGFRI-18 for this sample are presented in Table 12, including percentages of total score (where 100 percent would reflect the highest quality of life rating), in order to make the results easier to interpret. Complete results for each item in the FACT-EGFRI-18 are included in Table 13. Internal consistency using Cronbach's alpha for the overall FACT-EGFRI-18 was .886, with following reliability statistics for each of the subscales: physical (7 items, $\alpha = .757$); social-emotional (6 items, $\alpha = .772$); and functional (5 items, $\alpha = .750$). When the both the FACT-G and the EGFRI-18 scales are combined as they are in the current study to yield a total quality of life score, Cronbach's alpha for all 44 items is 0.915.

Despite similar subscales, there is discordance in the results of the two instruments. When used as part of a total quality of life score along with the FACT-G,

adding the EGFRI-18 effectively raised the quality of life score. As a result, the current original version of the EGFRI-18 should be explored further with regard to sensitivity to dermatologic quality of life in patients receiving EGFRI therapy. Participants had lower scores on emotional and functional well-being scores on the FACT-G than on the EGFRI, which may suggest declines in emotional and functional well-being globally, rather than specifically related to EGFRI therapy. Since the EGFRI-18 is a new instrument, there is no psychometric information available for comparison, but these discrepancies between the tools are areas for further inquiry.

Table 13. EGFRI-18 Dermatologic Quality of Life (N=56)

Sub-scale	Mean (SD)	Range	Percentage
Physical	17.9 (5.6)	4-28	89
Social-Emotional	19.4 (4.6)	6-24	81
Functional	17.6 (3.2)	5-20	87
Total	54.9 (12)	14-72	76

Note: No norms available.

Test of normality. Tests of normality for the total QOL score (FACT-G added to FACT-EGFRI-18) score were non-significant. A visual inspection of the histogram, Q-Q plots also showed that the scores were approximately normally distributed for the FACT-G and the combined FACT-G and FACT-EGFRI-18 scales (Total QOL). However, the

Kolmogorov-Smirnov test was significant for the FACT-EGFRI-18 scale alone. In addition, the FACT-EGFRI-18 demonstrated a negative skew, with skewness of $-.994$ ($SE = .322$) and kurtosis of 1.161 ($SE = .634$), indicating a long tail to the left (few lower scores) and many higher values, again calling into question the sensitivity of the instrument to impact of treatment on quality of life. However, since the outcome variable of quality of life is based on the mean sum scores of the FACT-G and FACT-EGFRI-18, described above as Total QOL, this variable will also be treated as a normal distribution.

Psychological Status

MHI-5. The MHI-5 is brief questionnaire that is used to assess mental health, including anxiety and depression, and was used to measure psychological status in the current study. There are several versions and available scoring procedures published, but for this study, a five-point scale was used, and the MHI-5 score was transformed to yield a total score of 0-100, with a higher score indicative of positive mental health (Hoeymans, Garssen, Westert, & P., 2004). The MHI-5 scale demonstrated a high level of internal consistency with a Cronbach's alpha of 0.906.

The MHI-5 has demonstrated good reliability (Rumpf, Meyer, & Hapke, 2001; Friedman, Heisel, & Delavan, 2005). No formal cut-off point for the MHI-5 has been agreed upon in the literature, with various studies citing scores from 72 (Hoeymans et al., 2004), to 76 to (Kelly, Dunstan, Lloyd, & Fone, 2008) to ≥ 80 as consistent with good general mental health (Clough-Gorr, Stuck, Thwin, & Silliman, 2010). An MHI-5 score of 52 or less has been cited as indicative of depressive symptoms (Kroenke et al., 2005;

Whang et al., 2009; Whang et al., 2012), and a score of ≤ 65 is suggestive of mood disorders (Rumpf, Meyer, Hapke, & John, 2001; Biddulph et al., 2014).

The MHI-5 score in the present study suggests a minimal impact on psychological status in this sample ($M=74.9$, $SD=16.3$, range 28-100), with a negative skew and a long tail to the left with more high scores (indicative of positive mental health). The MHI-5 is known to have a negative skew, but previous research suggests that response models are robust to departures from normality (Fone, Dunstan, John, & Lloyd, 2007). So although the mean score does not approach the levels described above associated with depression or mood disorders, the mean MHI-5 score in this sample suggests that assessment for psychological well-being would be advisable because there appears to be some effect of EGFR therapy. This score compares with the FACT-G Emotional Well-Being subscale score ($M=15.9$, $SD=4.95$, range 4-24), which suggests some impact on emotional dimension of quality of life.

Tests of normality. As noted above, the MHI-5 score is negatively skewed ($skewness = -.752$, $SE = .319$). Statistical tests for normality were not in agreement, with the Kolmogorov-Smirnov non-significant and the Shapiro-Wilk significant $W = (56)$. $.947$, $p = .016$. Inspection of the histogram, P-P and Q-Q plots indicated minor deviation from a normal distribution, so this outcome variable will be treated as normally distributed.

Functional performance/performance status. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) is widely accepted as a measure for assessment of functional status of patients. Descriptive statistics for the ECOG

Performance Scale are depicted in Table 14, indicating that almost 98% of participants reported a good or very good performance status overall. No participant reported being completely disabled and incapable of self-care.

Tests of normality. In advance of conducting inferential tests on this outcome variable, checks of normality were conducted and, results for this variable were non-normal with a skewness of .930 ($SE = .319$). Kurtosis was acceptable at .689 ($SE = .628$), but the Shapiro-Wilks test for normality of data was highly significant. Inspection of the histogram and the P-P and Q-Q plots indicated a significant deviation from the normal distribution. A log 10 transformation, including the addition of a constant due to the presence of zero values, improved the skewness, but the Shapiro-Wilks test was still highly significant, so the non-parametric Mann-Whitney U test was used on the original data to examine differences in this outcome variable between members of each cluster and non-members. In addition, the ECOG score is categorical variable and may not be appropriate for multiple regression.

Table 14. ECOG Performance Status

N=56	Score	N	Percentage
Fully active, able to carry on all pre-disease performance without restriction.	0	26	46.4
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.	1	24	42.9
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2	5	8.9
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3	1	1.8

Study Aim 3

Identify any co-occurring symptoms or symptom clusters in patients receiving EGFR therapy.

Symptom Clusters

Symptom clusters have been described as two or more symptoms that co-occur and that may or may not share the same etiology (Kim, McGuire, Tulman, & Barsevick, 2005). In oncology symptom cluster research, a basic concept is that there is a shared basis for a set of symptoms, whether caused by the treatment or the disease. This same premise is implicit in factor analysis, in that there is an underlying or latent dimension, possibly unobserved, that is shared by a set of variables.

Factor analysis. Factor analysis is a multivariate procedure that enables the researcher to reduce a set of variables into a smaller number of variables, known as factors. Factor analysis is based on correlation between items (e.g. symptoms).

Types of factor analysis

Clarification of the definition of factor analysis used in this context is essential. There are two types of factor analysis: confirmatory factor analysis and exploratory factor analysis. In exploratory factor analysis, the primary aim is to explore and discover key constructs in a set of data, while confirmatory factor analysis allows the researcher to test hypotheses (Kline, 2002). Confirmatory factor analysis provides an opportunity for hypothesis testing to determine if a proposed relationship between variables and constructs actually exists.

Exploratory factor analysis. The current research used exploratory factor analysis in order to discover symptom clusters in patients receiving EGFRIs. Exploratory factor analysis is a non-inferential statistical procedure, and can be understood as a heuristic technique, in that it allows the researcher to engage in a process of discovery of relationships among variables. No statistical confirmatory test for an appropriate factor analysis exists, and there is a significant amount of subjectivity that can come into play. Factors derived from the same data could conceivably vary, depending on decisions made by the researcher. However, the final factor solution is one that should be defensible. The goal of factor analysis should be to derive a parsimonious solution of factors that makes sense in the context of the data, while explaining variance in the data (Walker & Maddan, 2013).

Factor analysis resonates with some symptom cluster researchers because factors can be used to understand the relationship, and perhaps a shared biological cause, among various symptoms, and perhaps better inform their collective management. However, as noted, this statistical approach is based on a series of decisions that are inherently subjective (Kim & Abraham, 2008), and which should be based on an understanding of clinical scenarios. For this reason, the series of iterative decisions contributing to the final factor solution are described below.

Steps in exploratory factor analysis. A general series of steps should be undertaken in order to produce interpretable factors. First, a series of variables are selected and measured. Various characteristics of the variables, such as normality, skewness, and kurtosis, are observed. Inspection and evaluation of communalities is performed in order to identify possible variables to exclude, because items with low communalities will not contribute to the factor solution. Correlation coefficients are examined to determine which variables to retain, as items that do not correlate with others will not contribute to a factor solution. Along each step of the process, measures of sampling adequacy (Kaiser-Meyer-Olkin statistic and Bartlett's test of sphericity) are ascertained.

Various approaches to factor extraction and rotation (oblique vs. orthogonal) are evaluated in light of the purpose of the factor analysis, and all of these procedures are repeated on an iterative basis in order to identify a clear factor structure. Decisions about the number of factors to retain are made, using several rules of thumb, such as the scree

plot, eigenvalues greater than 1 (Kaiser criteria) and total variance explained. Finally, results must be interpreted in a meaningful way that has relevance to the application.

Measures of Sampling Adequacy

There are several measures to consider regarding the appropriateness of factor analysis for a set of data, including the Kaiser-Meyer-Olkin (KMO) Measure of Sampling Adequacy, Bartlett's test of sphericity, and the anti-image correlation matrix, which are all included the factor analysis procedures in SPSS.

The KMO statistic represents the amount of variance in a set of variables that may be resulting from underlying factors. KMO values, which are based on correlations and partial correlations, have been characterized by Kaiser (Zilmer & Vuz, 2010) in the following way: .90 or above "marvelous," .80 or above, "meritorious," .70 or above "middling," .60 or above, "mediocre," .50 or above "miserable," and below .50 as "unacceptable." As previously noted, a KMO for a set of variables of at least 0.6 is suggested for factor analysis (Tabachnik & Fidell, 2001), or the variables included in the solution should be reexamined or a larger sample generated (Field, 2009, p. 647). Individual variables with a KMO of less than 0.5 should be considered for elimination (Walker & Maddan, 2013). Elimination of variables with low KMO values is recommended, and will have the effect of raising the overall KMO statistic for the entire set of variables. As variables are removed, and factor analysis procedures are repeated, changes occur in the individual and overall KMO statistic.

Correlation provides the basis for factor analysis, so there must be some correlation among variables in order for them to "hang together" so that factors can be

identified. Bartlett's test of sphericity determines whether a correlation matrix is an identity matrix, where all diagonal values are 1 while off-diagonal values are 0. An identity matrix would be evidence of a lack of correlation among variables, and a set of such variables would not generate factors. In Bartlett's test of sphericity, if the p value is significant, the null hypothesis that the population matrix is an identity matrix would be rejected. Rejecting the null hypothesis is required for a set of data to be factor analyzed. However, Bartlett's test is often significant, and relying solely on this parameter to determine sampling adequacy is inadvisable.

Another step in determining sampling adequacy is inspection of the anti-image correlation matrix, which displays the negative of the partial correlations. Since this is an anti-image, desirable values should be low, closer to zero. Large values are problematic as such variables will have low correlations with other variables, and they should be considered for elimination from factor analysis if a theoretical or methodologic argument can be made for doing so (Walker & Maddan, 2013).

Decision-Based Factor Analysis Procedure

The first step in the process of generating a factor analysis in the current study was to examine the 38 symptoms included in the MSAS-SF (adapted) in order to determine which items should be retained and which could be removed due to low correlations with other symptoms. In a study with many variables, there may be thousands of correlations, and "without a simplifying procedure such a matrix would be incomprehensible" (Kline, 2002, p.4). With the original correlation that included all measured symptoms, the initial KMO measure of sampling adequacy was unacceptable at

.384, indicating that the current set of variables were not suitable for factor analysis, although Bartlett's test of sphericity was significant, providing an example of its frequent significance and lack of reliability as a measure of sampling adequacy. Additional examination of the data was required. Several approaches were used to identify which symptom variables to retain, including examination of inter-item correlations, consideration of symptom occurrence and prevalence as a criterion for retaining variables (symptoms), and iterative examination of the anti-image correlations.

Following the convention suggested by others, the criteria of symptom occurrence of at least 20% -25% was used as a first step for consideration of variables to include in the factor analysis (Gleason et al., 2007; Kim et al., 2009b; Baggott, Cooper, Marina, Matthay, & Miaskowski, 2012). Symptom severity or distress has also been used as a basis for deciding which symptoms to retain in factor analysis (Kim et al., 2009b), but there is not much difference between ranking the symptoms occurrence and severity, so frequency or prevalence was chosen as the approach here.

Using symptom frequency or prevalence as a criteria for exclusion, the following eight symptoms were removed, with their communalities shown in parentheses: problems with urination (.081), swelling of arms and legs (0.149), vomiting (0.142), feeling bloated (.095), dizziness (0.179), difficulty swallowing (0.232), and sweats (0.04). The communalities of all of the removed variables were low, which made them good candidates for removal from factor analysis. However, despite removing these symptoms, the KMO remained unacceptable at 0.436.

Inter-item correlations were then examined for all symptom variables, and those with correlations below .300, including the symptoms *changes in finger and toe nails*, *difficulty sleeping*, and *itching*, were removed from the factor analysis, which improved the KMO to 0.500, with Bartlett's test of sphericity remaining significant.

Communalities were again inspected, and variables deleted from the exploratory factor analysis due to low communalities were pain, diarrhea, changes in the way food tastes, nausea, numbness and tingling in fingers and toes, problems with sexual interest or activity and shortness of breath. Using this approach improved the KMO to 0.730, $\chi^2(105) = 301.994$, ($p = .000$).

The anti-image correlation matrix was then examined for measures of sampling adequacy. The anti-image correlation matrix includes the KMO values for each individual variable along the diagonal, and, as noted earlier, any values less than .500 suggest that the item should be removed from analysis (Field, 2009, p. 659). All of the remaining items had measures of sampling adequacy greater than 0.639. The off-diagonal elements should be close to zero, which was the case for many. The determinant for this set of factors was .002. In addition, each variable had at least one inter-item correlation at or near 0.400, and all communalities were above .300, ranging from .339 to .791.

As noted above, the goal of a factor analysis is to develop a solution that makes sense with regard to its application, is relatively easy to interpret, and possesses a simple structure with few or low cross-loadings. The iterative procedures described here resulted in such a factor structure. In the final solution, principal axis factoring using an oblique

rotation (Oblimin with Kaiser normalization) retained the following variables: difficulty concentrating, "I don't look like myself," *changes in my eyelashes, dry skin, feeling sad, worrying, feeling irritable, feeling nervous, other changes to scalp hair, hair loss, dry mouth, lack of energy, feeling drowsy, changes in hair growth on my face and other changes to my fingers or toes.* In this model, the three factors retained explained 48.03% of the total variance, and is shown in Tables 15 and 16.

Rationale for oblique rotation. As factor analysis is an exploratory procedure, multiple procedures were run through SPSS in order to identify the optimal factor structure and to explore the effect of various methods of rotation and extraction.

Principal components analysis was executed on the symptom variables in order to explore the data and to compare the results with iterations using other factor analysis procedures, including principal axis factoring (PAF), using both orthogonal (Varimax) and oblique (Oblimin and Promax) rotations. Maximum likelihood rotation and unweighted least squares methods, using both orthogonal and oblique rotation, were also performed, and each procedure yielded very similar results, but the above model best fit the data.

Selection of oblique rotation

Ideally, because the symptom variables in this study are derived from patient self-report, they would best be examined through an oblique rotation, which allows variables to load on several factors. Additionally, correlation coefficients in the factor structures were high, supporting the use of oblique rotation. In a real world setting, it is very likely that there would be variables that would cross-load on more than one factor, so oblique rotations, such as Oblimin with Kaiser normalization should be strongly considered. In

other applications, orthogonal solutions might be preferred due to the inherent simplification of their interpretation, so this type of rotation was also explored. However, in a clinical setting, a symptom in one factor might very likely also be present in another factor, and oblique rotation allows this redundancy to occur, and has been suggested as a reasonable approach in symptom cluster research (Skerman, Yates, & Battistutta, 2009).

Factor Solutions

As noted above, a three factor solution was derived: Factor 1: a psychological-cognitive cluster (feeling nervous, feeling sad, worrying, feeling irritable, difficulty concentrating, and “I don't look like myself”); Factor 2: a dermatologic skin and hair cluster (*changes in eyelashes, dry skin, hair loss, changes in facial hair growth and other changes in scalp hair*); and, Factor 3: a mucocutaneous-fatigue cluster of dry mouth, feeling drowsy, lack of energy, difficulty concentrating, and *other changes to fingers or toes*. Note that lack of energy and difficulty concentrating loaded on Factors 1 and 3, lending justification to an oblique solution. Difficulty concentrating is a common symptom in patients being treated for cancer, so cross-loading is not problematic.

Factor loadings are presented in Table 15 and 16 and include the structure (correlations between factors and variables) and pattern (factor loadings) matrices. With an oblique rotation, it is important to report both the structure and the pattern matrix (Pett, Lackey, & Sullivan, 2003; Thompson, 2004). Each factor had several excellent or very good loadings, and as previously described, high loadings of .600 or more with four or more variables can mitigate somewhat a small sample size (Stevens, 2002).

Cronbach's alpha for this set of symptoms (n=15) was .739. The factor loadings are

generally in the categories considered good to excellent ($> .70$ – excellent; $.63$ - very good; $> .55$ – good; $> .45$ – fair; $> .32$ – poor) (Comrey & Lee, 1992).

Eigenvalues for each factor are as follows: Factor 1 (psychological-cognitive), with an eigenvalue of 4.046 (23.96% of variance explained); Factor 2 (dermatologic skin and hair), with an eigenvalue of 2.497 (13 % of variance explained); and, Factor 3 (mucocutaneous and fatigue cluster), with an eigenvalue of 2.162 (11.07% of variance explained). A cumulative explained variance of 48.03 % resulted with this factor solution. In all iterations of factor analytic procedures, the scree plot (a graphic plot of eigenvalues) was examined. In the final solution, the scree plot suggested at least a three factor solution (Figure 4). Although a 4 factor solution was also generated, few items loaded on this fourth factor.

Table 15. Principal Axis Factor Analysis with Direct Oblimin Rotation
Structure Matrix Based on Iterative Process (N=56)

Symptom	Structure Matrix		
	Factor 1	Factor 2	Factor 3
Feeling nervous	.885		
Feeling sad	.805		
Worrying	.782		
Feeling irritable	.667		
“I don't look like myself”	.525		
Other changes scalp hair		.618	
Dry skin		.676	
Changes in eyelashes		.619	
Hair loss		.588	
Changes in facial hair growth		.549	
Other changes to fingers or toes			.633
Dry mouth			.620
Feeling drowsy			.579
Lack of energy			.584
Difficulty concentrating	.476		.533

Note: Factor loadings under .450 are suppressed.

Factor 1 Psychologic-Cognitive Eigenvalue of 4.046 (23.96% of variance explained)

Factor 2 Dermatologic Skin and Hair Eigenvalue of 2.497 (13.00 % of variance explained)

Factor 3 Mucocutaneous and Fatigue Eigenvalue of 2.162 (11.074% of variance explained)

Cumulative variance of 48.031% explained.

Table 16. Principal Axis Factor Analysis with Direct Oblimin Rotation Pattern Matrix Based on Iterative Process (N=56)

Symptom	Pattern Matrix Factor Loadings		
	Factor 1	Factor 2	Factor 3
Feeling nervous	.877		
Feeling sad	.827		
Worrying	.814		
Feeling irritable	.603		
“I don't look like myself”	.494		
Other changes scalp hair		.636	
Dry skin		.663	
Changes in eyelashes		.646	
Hair loss		.568	
Changes in facial hair growth		.531	
Other changes to fingers or toes			.716
Dry mouth			.629
Feeling drowsy			.543
Lack of energy			.561
Difficulty concentrating			.449

Note: Factor loadings under .40 are suppressed.

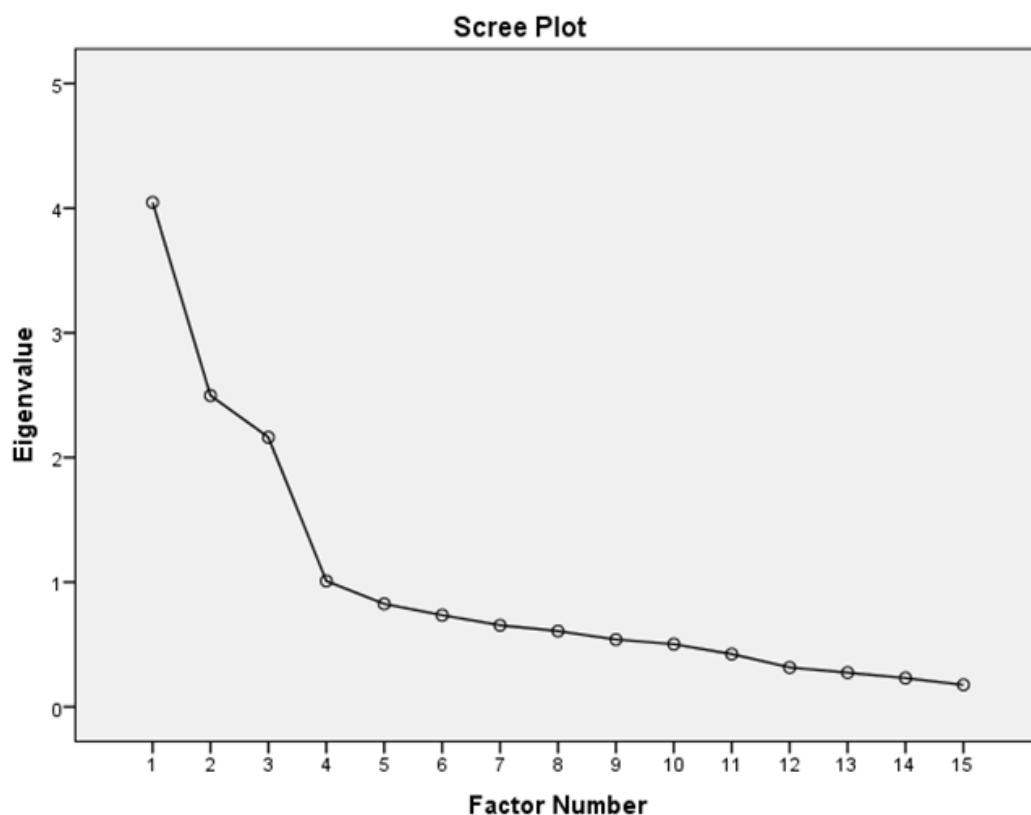


Figure 4. Scree Plot for Factor Solutions

Factors Based on Communalities

The previous discussion detailed an iterative process of examining the symptom variables and taking steps to ensure that the data was appropriate for factor analysis. In order to confirm the set of factors derived, the complete set of variables was reexamined and the original communalities for the full set of variables were reviewed. Variables with a communality value below 0.300 were eliminated, and factor analytic procedures were run using PAF with an oblique rotation in an effort to replicate the derived factors.

Although elimination of variables with communalities below 0.5 has been recommended,

the cut-off of .300 was chosen so that variables demonstrating some evidence of correlation could be retained.

Using the single criteria of communality, variables removed for the first iteration of factor analysis included: diarrhea (0.026), sweats (0.04), changes in finger and toe nails (0.064), problems with urination (0.081), bloating (0.095), pain (0.100), itching (0.112), problems sleeping (0.116), changes in the way things taste (0.133), vomiting (0.142), swelling of arms and legs (0.149), numbness and tingling of fingers and toes (0.168), dizziness (0.179), cough (0.189), nausea (0.201), lack of appetite (0.206), constipation (0.211), mouth sores (0.211), problems with sexual interest or activity (0.219), shortness of breath (0.224), difficulty swallowing (0.232), and weight loss (0.255), and changes in skin (0.279).

The resulting set of symptoms for factor analysis included: feeling nervous, feeling sad, worrying, feeling irritable, feeling drowsy, lack of energy, difficulty concentrating, "I don't look like myself," dry mouth, hair loss, other changes to scalp hair, changes to hair growth on my face, dry skin, changes in my eyelashes, and other changes to my fingers and toes. The KMO for this set of variables was .732 (χ^2 (120) = 331.416, $p = .000$).

For this set of variables, the scree plot and eigenvalues > 1 (Kaiser rule) suggested a three or four factor solution. A four factor solution was examined, but variables (feeling drowsy, "I don't look like myself," dry mouth, difficulty concentrating, lack of energy, changes in hair growth on my face, hair loss, dry skin and feeling irritable) cross-loaded and factor loadings were low ($< .400$) for eleven variables. Therefore, a three

factor solution generated by PAF (Oblimin with Kaiser normalization) was selected and included: Factor 1 (psychological-cognitive), with an eigenvalue of 4.154 (23.02 % of variance explained); Factor 2 (dermatologic skin and hair cluster), with an eigenvalue of 2.638 (13.02% of variance explained); and Factor 3 (mucocutaneous-fatigue), with an eigenvalue of 2.226 (10.8% of variance explained). A cumulative variance of 46.85% was explained by this solution (Table 17).

Approaches comparison for factor analysis. The factors generated by these two methods (the first which took repeated iterations) are very similar, and provide validation of the first method. The first set of factors was used to generate the factor scores used to explore differing effects on outcome variables. All further discussion regarding factors and the identified symptom clusters will relate to those developed using the first (iterative approach) method.

Table 17. Exploratory Factor Analysis Results Based on Communalities (N=56)

Symptom	Factor Loadings		
	Factor 1	Factor 2	Factor 3
Feeling nervous	.885		
Feeling sad	.803		
Worrying	.779		
Feeling irritable	.664		
“I don't look like myself”	.524		
Other changes scalp hair		.610	
Dry skin		.652	
Changes in eyelashes		.578	
Hair loss		.615	
Changes in facial hair growth		.526	
Dry mouth			.646
Feeling drowsy			.602
Lack of energy			.548
Difficulty concentrating	.405		.497

Note: Factor loadings under .40 are suppressed.

Factor 1 Psychologic-Cognitive Eigenvalue of 4.154 (23.02 % of variance explained)

Factor 2 Dermatologic Skin and Hair Eigenvalue of 2.638 (13.02% of variance explained)

Factor 3 Mucocutaneous and Fatigue Eigenvalue of 2.226 (10.8% of variance explained)

Cumulative variance of 46.85% explained.

Factor Correlation Matrix

For the final solution using the first method described, the factor correlation matrix indicates that Factor 1 is not correlated with Factor 2 (.099), and is only weakly correlated with Factor 3 (.228). Factor 2 is not correlated with Factor 3 (.034).

Correlations less than 0.1 are negligible. So despite an oblique rotation where factors are “allowed” to correlate, the factors in this solution do not correlate, so the three factor solution is supported. Only one item (difficulty concentrating) loads on multiple factors (Factors 1 and 3), and this is logical given the clinical meanings of both of these clusters.

Symptom clusters. Three symptom clusters were generated using the procedures described above. A psychological-cognitive cluster, a dermatologic skin and hair cluster, and a mucocutaneous and fatigue cluster. Each of these clusters will be discussed in more depth in chapter five in the context of previous work on symptom clusters.

Factor 1: Psychological-cognitive. A mood-related, affective, emotional, or psychoneurologic cluster, including the symptoms of feeling irritable, feeling nervous, worrying, feeling sad, difficulty concentrating and “I don’t look like myself” was identified in this sample. Previous oncology symptom cluster research has provided ample evidence for similar clusters in patients with various cancer diagnoses.

Factor 2: Dermatologic skin and hair cluster. The second cluster includes dry skin, changes in eyelashes, hair loss, changes in facial hair growth and other changes in scalp hair, and can be interpreted as an EGFR treatment-related dermatologic skin and hair cluster. Although these symptoms have been previously described (Lacouture et al., 2011), the finding of a symptom cluster generated by factor analytic procedures is novel. A skin and hair-related symptom cluster would have been expected to occur in this sample. Nail changes did not cluster with these symptoms.

Factor 3: Mucocutaneous and fatigue cluster. The third factor identified includes dry mouth, feeling drowsy, lack of energy, difficulty concentrating, and other changes to fingers or toes, so it echoes previous work, but includes a new element (other changes to fingers and toes) reflecting EGFR therapy. This cluster has two components: dry mouth and changes to fingers and toes being the mucocutaneous aspect, and feeling drowsy, lack of energy and difficulty concentrating contributing to the fatigue aspect.

Hierarchical Cluster Analysis

In view of the small sample size for this study and the caveats regarding factor analysis with small samples, the data were assessed by hierarchical cluster analyses (HCA) using Ward's method with squared Euclidean distances. This method has been used to generate symptom clusters in patients with heart failure using a version of the MSAS (MSAS-HF) (Song et al., 2010).

Like factor analysis, cluster analysis allows for discovery of relationships between variables. In HCA, each variable starts as a separate cluster and the procedure then reduces the number of clusters until all items are grouped in one large cluster. Distance scores range from 0-25, and as the distance becomes less, the symptoms begin to cluster. By observing the dendrograms generated by the procedures, one can identify how items cluster at various distances. The first HCA was run with all 38 symptoms included, and generated the dendrogram shown in Figure 5. Viewing the clusters from right to left, there is a clear branching of three large clusters with this first iteration. The first cluster includes difficulty with urination, swelling of arms and legs, vomiting, bloating, sweats, dizziness, nausea, difficulty swallowing, mouth sores, "I don't like the way I look,"

numbness and tingling in my fingers and toes, difficulty sleeping, shortness of breath, constipation, pain, cough, drowsiness, other changes to fingers and toes and itching. This cluster might be described as a general sickness cluster.

The second cluster derived by HCA of all 38 symptoms includes lack of energy, dry mouth, skin changes, feeling nervous, feeling sad, feeling irritable, worrying, difficulty concentrating, weight loss, changes in appetite and taste changes. This cluster might be described as a mood-anorexia cluster.

The third cluster generated by the first iteration of hierarchical cluster analysis includes changes in eyelashes, scalp hair changes, hair loss, changes in facial hair growth, dry skin, diarrhea, problems with sexual interest and performance, and changes in fingers and toenails, which could be labeled as a treatment-related dermatologic skin, hair and nail cluster.

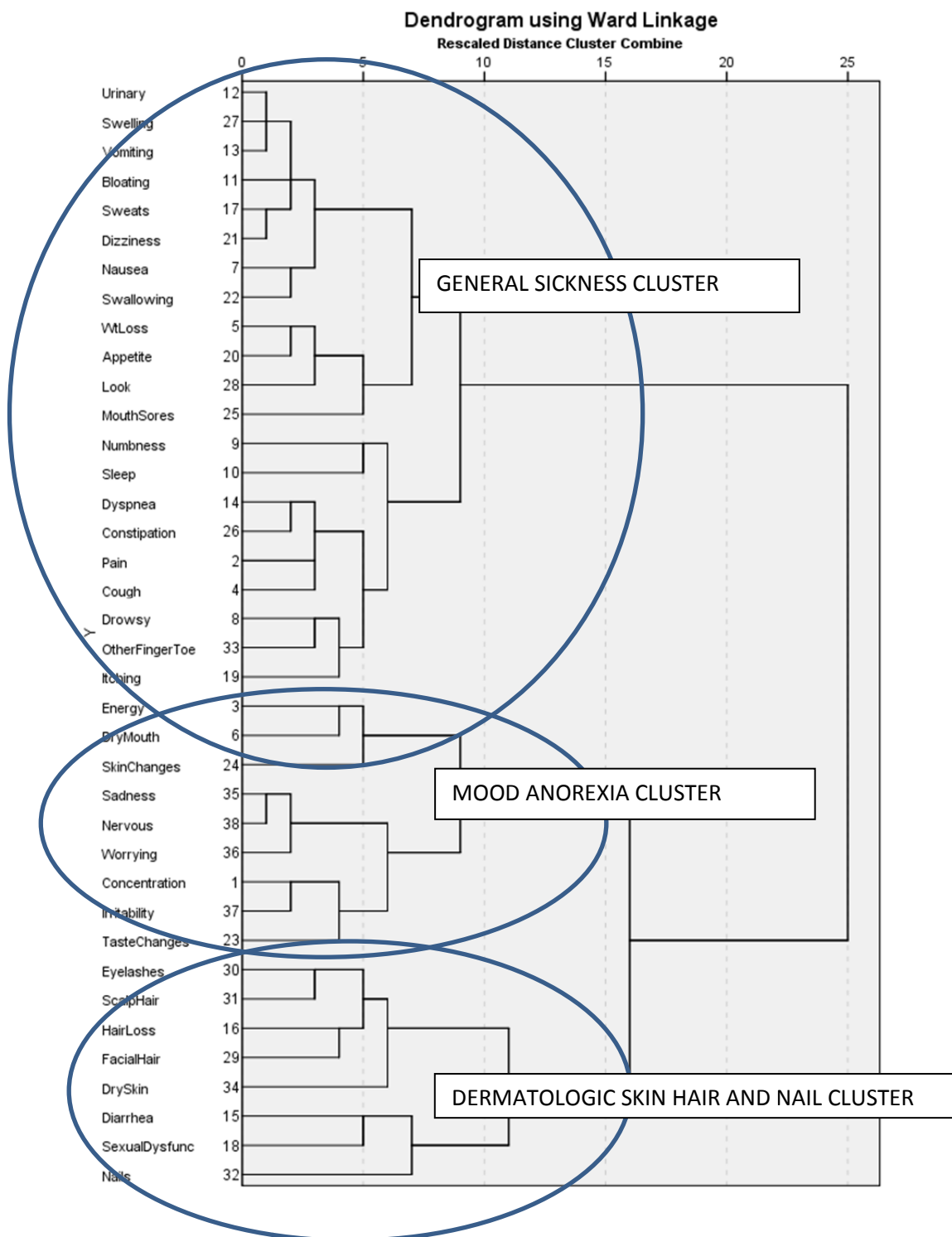


Figure 5. Hierarchical Cluster Analysis of All Symptoms

Another HCA was run with the final set of symptoms included in the initial (iterative) exploratory factor analysis procedures previously described. The dendrogram presented in Figure 6 indicates the presence of three symptom clusters which mirror those generated by factor analysis. The first cluster (psychological-cognitive) includes difficulty concentrating, feeling irritable, feeling nervous, feeling sad, worrying, and “I don’t look like myself,” the second cluster (mucocutaneous and fatigue) includes dry mouth, lack of energy, feeling drowsy, and other changes in fingers and toes. Changes in eyelashes, other changes in scalp hair, hair loss, changes in facial hair growth and dry skin are included in the final cluster (dermatologic skin and hair). As depicted on the dendrogram, symptoms cluster together at lower distance scores.

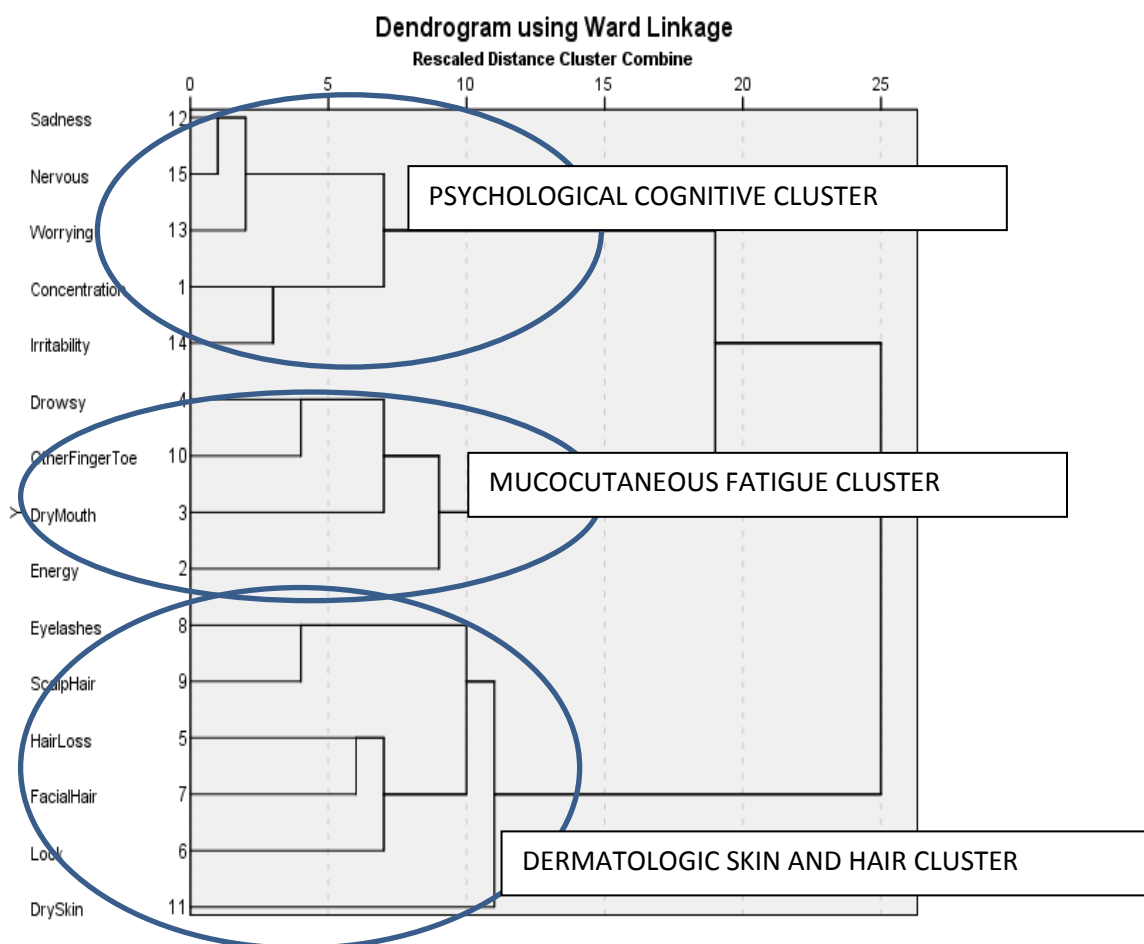


Figure 6. Hierarchical Cluster Analysis with Symptoms Retained in Factor Analysis

Study Aim 4

Explore the relationships between any identified co-occurring symptoms or symptom clusters and key variables, including gender, age, primary cancer, type of EGFR, and the outcome variables of quality of life, functional performance and psychological status.

The factor solution identified by an iterative process in exploratory factor analysis (the first method described) was used for all analyses. Factor scores were used to identify the symptom cluster membership of each participant so that group differences could be explored. Several options are available for generating factor scores, including the three so-called “refined” methods: regression, Bartlett, and Anderson-Rubin, all of which are included as options in SPSS. In order to generate factor scores in this study, the regression method was selected. In this method, the regression factor score estimates the location of each individual on the factor (DiStefano, Zhu, & Mindrila, 2009). When using this approach to factor score generation, the scores are standardized to a mean of zero and a standard deviation equal to the squared multiple correlations between factors and variables in a PAF (Tabachnik & Fidell, 2001).

First, regression factor scores were obtained, and then the scores were described by quartile. Each participant was then assigned a 0 or 1 to describe membership in each of the three factors (symptom cluster groups). If a participant’s factor score was at or above the 70th percentile, they were assigned to the factor; scores below the 70th percentile were not described as exhibiting that symptom cluster. Because an individual could be experiencing multiple symptoms, membership in more than one cluster was

permitted. Members of the symptom cluster group could then be compared on outcome variables to non-members of the cluster. An alternative approach was also used, examining the correlation of the regression scores for each participant with the outcome measures. Results from each of these methods are described below.

For the hierarchical regression procedures, the regression factor scores were then used as independent variables in a multiple regression model to identify predictors of the outcome variables: quality of life, functional performance, and psychological status. Independent t-tests and one-way ANOVA assessed the impact of membership in each symptom cluster on psychological status and quality of life. The impact of symptom clusters on performance was tested using a non-parametric test. All of these findings should be replicated in an adequately powered sample.

Factor 1: Psychological-Cognitive Cluster

Independent t-tests compared members with non-members of this cluster. Both psychological status and quality of life were significantly different in the psychological-cognitive cluster. The psychological outcome, measured by the MHI-5, demonstrated a highly significant difference. As would be expected, participants with this symptom cluster experienced an effect on psychological status as illustrated by lower mean scores on MHI and FACT-G (Tables 18 & 19).

Table 18. Independent Samples t-Test Comparing Means of Psychological-Cognitive Cluster to Others

	<i>t</i>	<i>df</i>	Sig. (2-tailed)	<i>M</i>	<i>SD</i>
<i>Psychological Status</i>					
Factor 1 (n=17)	-5.357	54	.000	60.47	16.55
Others (n=39)				81.23	11.72
<i>Total QOL</i>					
Factor 1	-2.544	54	.014	118.06	19.04
Others				135.03	24.41
<i>FACT-G</i>					
Factor 1	-3.101	54	.003	65.12	17.98
Others				80.69	16.98

Quality of life, as measured by the Total QOL score (FACT-G plus EGFRI-18), was also significantly different between the two groups, with members of the cluster ($N=17$) indicating a lower QOL ($M = 118.06$, $SD = 19.04$, $N = 17$) compared to non-members ($M = 135.02$, $SD = 24.41$, $N = 39$), $t(54) = -2.544$, $p = .014$. Scores for the FACT-G, as well as three of the four subscales, (SWB, PWB, EWB), which are not shown here, were also significant, with cluster group members indicating a lower quality of life. Non-parametric Mann-Whitney U independent t-tests were also run including these dependent variables, confirming these results.

Using the alternative approach examining correlations, the Cluster 1 factor score demonstrated highly significant negative correlations with the MHI-5 scores ($r = -.726$,

$p = .000$), the FACT-G score ($r = -.559, p = .000$), and the Total QOL score ($r = -.416, p = .001$), again confirming the association between the presence of the psychological-cognitive factor and lower psychological well-being and quality of life.

Factor 2: Dermatologic Skin and Hair Cluster

An interesting finding related to quality of life emerged when examining the group means for Factor 2, the dermatologic skin and hair cluster. Contrary to expectations, no significant difference between the Factor 2 members ($M = 51.47, SD = 14.75, N = 17$) and non-members ($M = 56.42, SD = 10.49, N = 38$) was demonstrated on the EGFRI-18 score, which is designed specifically to measure quality of life in this patient population. The sensitivity of the EGFRI-18 to the impact of dermatologic skin and hair symptoms on quality of life should be further explored.

However, the Total QOL score (FACT-G plus EGFRI-18 scores), and the PWB subscale $t(54) = -3.245, p = .002$ all revealed significant differences, suggesting a differing impact of this cluster on QOL. In addition, the results for the MHI-5 (psychological status) were significant, indicating a negative effect of this cluster on psychological status when compared with the group without this symptom cluster. A nonparametric Mann-Whitney U was run because of non-normality of the FACT-G and ECOG scales, with significant results for both the FACT-G QOL ($p = .014$) and the Total QOL ($p = .031$) confirming a significant impact of the dermatologic skin and hair cluster on quality of life and performance.

Table 19. Independent Samples t-Test Comparing Means of Dermatologic Skin and Hair Cluster to Others

	t	df	Sig. (2-tailed)	Mean	SD
<i>Psychological status</i>					
Factor 1 (n=17)	-2.162	54	.035	68.00	19.13
Others (n =39)				77.95	14.21
<i>Total QOL</i>					
Factor 1	-2.320	54	.024	119.00	23.82
Others				134.62	22.87
<i>FACT-G QOL</i>					
Factor 1	-2.331	54	.024	67.53	16.79
Others				79.64	18.32

In the alternative approach using regression scores in a correlation procedure, Factor 2 correlated with the Total QOL score ($r = -.344, p = .00$), the FACT-G ($r = -.344, p = .01$), the ECOG Performance Scale ($r = -.409, p = .002$), and the MHI ($r = -.282, p = .035$), suggesting an impact of this cluster on all outcome variables.

Factor 3: Mucocutaneous and Fatigue Cluster

For Factor 3, the mucocutaneous and fatigue cluster, there are several statistically significant findings. FACT-G scores were significantly different in a positive direction between members of this cluster and non-members. This trend continued for two subscales of the FACT-G, with the both the FWB subscale scale score higher ($M = 21.06, SD = 5.14, N = 17$) than non-members ($M = 16.18, SD = 6.77, N = 38$), $t(39.763) = 2.953^*, p = .005$, and the SWB subscale higher ($M = 24.65, SD = 4.07, N = 17$) than non-

members ($M = 20.38$, $SD = 7.08$, $N = 38$), $t(49.64) = 2.83^*$, $p = .007$, two-tailed, indicating a better QOL in cluster members.

Conversely, there appears to be a negative effect of Factor 3 membership on the EGFRI-18 score (dermatologic quality of life) compared to non-members. This is an interesting finding, as the only dermatologic symptom retained in this cluster was *other changes to my fingers and toes*, so further exploration of this relationship is warranted. However, this statistical significance did not hold for the total QOL score (FACT-G and EGFRI-18), which indicated no difference between the groups.

Table 20. Independent Samples Comparing Means of Mucocutaneous-Fatigue Cluster to Others

	t	df	Sig. (2-tailed)	Mean	SD
<i>Dermatologic QOL</i>					
Factor (n=17)	-2.689	53	.010	48.70	13.79
Others (n =38)				57.66	10.21
<i>QOL</i>					
Factor 3 (n =17)	2.71	45	.010	84.35	12.99
Others (n =39)				72.31	19.59

Since both the FACT-G and the EGFRI-18 (separately) are not normally distributed, a nonparametric Mann-Whitney U test was performed for each of these outcome variables, and both confirmed a significant difference associated with cluster

membership in cluster members for both the FACT-G, $U = 208.5$, $p = .028$, and the EGFRI-18, $U = 187.00$, $p = .013$. The test for ECOG was non-significant.

In the alternative procedure, the EGFRI-18 score yielded the only significant finding ($r = -.429$, $p < .001$), suggesting a relationship between Cluster 3 and dermatologic quality of life.

Symptom Clusters and Outcomes

The relationship between the identified symptom clusters and outcomes is summarized in Table 20. Both Factors 1 and 2, the psychologic-cognitive cluster, and the dermatologic skin and hair cluster have a negative relationship with quality of life. Factor 3, the mucocutaneous-fatigue cluster, has a highly significant negative impact on dermatologic quality of life, but the other symptom clusters do not. Both the psychological-cognitive cluster and the dermatologic skin and hair cluster (Factors 1 and 2) are related to psychological status, with the greatest negative correlation between Factor 1 and this outcome. A positive correlation between Factor 2, the dermatologic skin and hair cluster and functional performance suggests a possible connection between treatment with EGFRI therapy and improvement in performance status, but this possible relationship requires further study. All of these findings should be confirmed in an adequately powered sample.

Table 21. Correlation between Symptom Clusters and Outcome Measures

	Factor 1	Factor 2	Factor 3
Dermatologic QOL n=55			-.429 .001
Psychological status n =56	-.727 .000	-.282 .035	
Total QOL n=56	-.416 .001	-.389 .003	
Quality of Life n=56	-.559 .000 56	-.344 .009 56	
Performance/ Functional Status n=56		.409 .002	

Note: Factor 1 is the psychological-cognitive symptom cluster; Factor 2 is the dermatologic skin and hair cluster; Factor 3 is the mucocutaneous-fatigue cluster.

Multiple Regressions

Stepwise hierarchical multiple regressions were used to determine which, if any, of the independent variables, including symptom clusters, significantly predicted the various outcome variables. Demographic variables, including gender, level of education, age, stage of illness, primary diagnosis, concurrent therapy, relationship status, method of survey completion (online vs. paper), length of EGFR therapy, and specific EGFR therapy were entered into each regression. The results of the regression are as follows.

Quality of Life

Factors 1 and 2 predicted the Total QOL score (sum of the FACT-G and EGFRI-18), explaining about 31 % of the variance of the overall score, $R^2 = .311$, $F(2, 53) = 11.95$, $p < .001$. For the FACT-G alone, Factors 1 and 2 predicted about 41% of the variance in quality of life $R^2 = .415$, $F(2, 53) = 18.79$, $p < .001$. For dermatologic quality of life, as measured by the EGFRI-18, Factor 3 predicted 18% of the variance, $R^2 = .184$, $F(1, 53) = 11.95$, $p < .001$. Regression models for quality of life are presented in Tables 22 and 23. As noted, results should be confirmed in a larger, adequately powered sample.

Table 22. Regression Model with Predictors for Quality of Life

	Unstandardized Coefficients		Standardized Coefficients		t	Sig.
	B	Std. Error	Beta			
<i>Total QOL</i>						
(Constant)	129.875	2.720			47.749	.000
Factor 2	-10.134	3.116	-.371		-3.252	.002
Factor 1 Score	-10.133	2.894	-.400		-3.501	.001
<i>FACT-G QOL</i>						
(Constant)	75.964	1.935			39.253	.000
Factor 1	-10.675	2.059	-.545		-5.183	.000
Factor 2	-6.742	2.217	-.320		-3.041	.004

Table 23. Regression Model with Predictors for Dermatologic Quality of Life

	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
<i>EGFRI-18</i>					
(Constant)	54.944	1.482		37.083	.000
Factor 3	-5.79	1.675	-.429	-3.457	.001

Psychological status. The independent predictors Factor 1 (psychological-cognitive), Factor 2 (dermatologic skin and hair), as well as marital status, significantly contributed to the prediction of scores on the MHI-5, as noted on the regression model in Table 24. These variables explain about 63% of the variance in this measure, with Factor 1 explaining the largest proportion of variance in psychological status scores, $R^2 = .528$, $F(1, 54)$, $p < .001$.

Table 24. Regression Model with Predictors for Psychological Status

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	69.348	2.633		26.333	.000
Marital status	3.634	1.468	.216	2.476	.017
Factor 1	-13.207	1.493	-.767	-8.844	.000
Factor 2	-5.076	1.570	-.274	-3.234	.002

Note: Dependent variable is MHI-5.

Inspection of the correlations of the (Table 25) psychological symptoms with the MHI-5 reveals that all of the symptoms had a highly significant and negative correlation, yielding preliminary evidence of the importance of addressing psychological symptoms in an effort to improve patient outcomes such as psychological status. These results should be replicated in an adequately powered sample. Clearly, psychological symptoms exert a major impact on outcomes in patients receiving EGFRIs, so psychological assessment should be conducted on all patients receiving these medications.

Table 25. Correlations of Psychological Symptoms and Outcomes

	FACT-G	QOL Total	MHI-5	ECOG PS
Feeling sad	-.566** .000	-.458** .000	-.769** .000	
Worrying	-.473** .000	-.291* .029	-.572** .000	
Feeling irritable	-.288* .032	-.272* .043	-.506** .000	
Feeling nervous	-.530** .000	-.411** .002	-.682** .000	.284* .034

Note. QOL Total includes FACT-G: Functional Assessment of Cancer Therapy-General; FACT-EGFRI-18: Functional Assessment of Cancer Therapy-Epidermal Growth Factor Receptor Inhibitor-18 subscale; ECOG: Eastern Cooperative Oncology Group; MHI-5: Mental Health Index-5. ** indicates $p < .001$, * indicates $p < .05$, two-tailed.

Performance status. For the ECOG scale, Factor 2 explained 16% of the variance in functional status, but the other symptom clusters did not contribute to the model, $R^2 = .167$, $F(1, 54) = 10.857$, $p < .002$.

Table 26. Regression Model with Predictors for Performance Status

Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
(Constant)	.661	.089		7.452	.000
Factor 2	.334	.101	.409	3.295	.002

Note: Dependent variable is ECOG PS.

CHAPTER FIVE

DISCUSSION

This study was designed to characterize the symptom experience of patients receiving EGFR therapy and to describe how this experience affects key outcome variables, including quality of life, performance and psychological status. Patients with solid tumors including lung cancer, colon cancer, head and neck cancer, and breast cancer who were receiving an EGFR for at least four weeks were included in the sample. This chapter will review the key findings from this study, highlight new data, and integrate this information with current knowledge on this topic.

The theory of unpleasant symptoms guided the conception and design of this study. In this model, the symptom experience is viewed as multidimensional, encompassing aspects of distress, quality, intensity and timing. Consideration is given within the model's framework to the coexistence of symptoms and their collective impact on performance, as well as to the idea that symptoms may both influence and be influenced by the interaction of situational, psychological and physiologic factors. Performance in this study was conceived broadly to include the dimensions of quality of life, psychological status and functional performance. The collective impact of symptoms (as symptom clusters) on these outcomes was explored. Three symptom clusters were identified, including one that is well-established in the literature, a novel

dermatologic skin and hair cluster likely related to EGFRi therapy, and a third cluster similar to another well-established cluster, but with an additional mucocutaneous component that is also related to EGFRi therapy.

Study Aim 1

Describe the symptom experience (symptom frequency and distress) of patients receiving EGFRi therapy.

Symptom Experience

An extensive symptom battery, the MSAS-SF (adapted), was used to capture the most common and distressing symptoms associated with EGFRi therapy, using the past seven days as a time frame. The instrument included 38 symptoms, and participants were asked to select the symptoms that they experienced over the last week, and to indicate how much the symptom distressed them (physical symptoms) or how frequently the symptom occurred (psychological symptoms). Participants were also asked to identify any symptoms they were experiencing that did not appear on the instrument.

As noted in chapter four, several symptoms known to occur with frequency in patients taking EGFRis were added for the purposes of this study. Although all symptoms were endorsed by some patients, the symptoms that were selected by over 40% of participants are discussed below. The EGFRi-18, a dermatologic quality of life instrument specifically designed for use with EGFRis, was also used to gain an additional understanding of the symptom experience, and will be discussed in the section on outcomes.

Most Frequently Identified Symptoms

The most frequent symptoms identified by over 40% of participants included *dry skin*, lack of energy, dry mouth, changes in skin, feeling sad, *changes to fingers or toe nails*, worrying, diarrhea, feeling drowsy, problems with sexual interest or activity, *changes in facial hair growth*, difficulty sleeping, feeling nervous, numbness or tingling in hands or feet, and feeling irritable. The most distressing or prevalent symptoms were *dry skin*, lack of energy, worrying, *changes to finger and toe nails*, problems with sexual interest or activity, changes in skin, dry mouth, feeling sad, diarrhea, feeling nervous, feeling irritable, and *changes in facial hair growth*.

These symptoms differ substantially from the typical set of symptoms associated with cancer treatment. Recognition of the unique symptom profile of the EGFRIs by health care providers is essential. Recently, following a systematic review of the literature and consensus process, a panel of experts recommended a set of 12 symptoms to be included as patient-reported outcomes for clinical trials. The group recommended that fatigue, insomnia, pain, anorexia, dyspnea, cognitive problems, anxiety, nausea, depression, sensory neuropathy, constipation and diarrhea be included in this dataset (Reeve et al., 2014). Approximately half of these symptoms are not relevant in to this study, but they are symptoms that have been prominent in oncology care for a prolonged period of time. Whether all patients are best served by this core set of measures remains to be evaluated, and this study suggests that traditionally important symptoms may still be important, but are being eclipsed by the side effects of new treatments.

Symptom prevalence and distress studies in oncology are limited by the instruments used to measure them, and most of the common symptom measurement batteries do not include symptoms relevant to the patient receiving EGFR therapy. This same scenario probably applies to other novel agents as well, so practitioners, educators, and researchers should be aware of this when reviewing and adopting assessment tools and instruments for research, as well as when consulting the literature for patient management issues.

Participant-identified symptoms. Eleven participants responded to a question asking them to list other symptoms that did not appear on the study questionnaire. Two participants mentioned severe dry eye, with one describing it as very distressing and another noting that it interfered with vision, caused blurring and required the use of artificial tear drops and eye ointment at night. One participant described “swollen eyelids with oozing quasi liquid that hardens into a dry crust,” and that was painful to remove. Another noted excessive nasal mucous that hardened into a crust that was also painful to remove. The additional symptoms identified by participants are similar to responses provided in an evaluation of the EGFR-18, where nasal crusts and eye sensitivities were also among several additional suggested by patients (Boers-Doets et al., 2013). These findings point to the need for possible ophthalmologic or oncodermatology referral for patients receiving EGFR therapy.

Several items appeared on the instrument but were understood differently by participants, so they were suggested as additions, including “fatigue” (lack of energy),

“rash” (changes in skin), and “changes to my eyebrows” (*changes to hair growth on my face*). Other physical symptoms each mentioned by one participant included occasional long bone pain at night, lip swelling quite a bit, and feet hurting in the morning. Finally, one participant offered “I don’t know what I am supposed to be doing with my life. Uncertainty, I guess.” This comment underscores the existential plight of the patient with advanced cancer, and draws attention to the need to address not only physical, but psychological symptoms as well in assessment, care and research related to oncology patients.

Additional work is needed to identify an optimal set of items to measure the EGFRi symptom experience, as the current study captured most, but not all relevant symptoms. In future research on EGFRis, more explicit reference to a rash that is more specifically described would be beneficial, rather than addressing it generally as changes in skin. Additional symptoms such as eye changes and crusting, changes in eyebrows, and nasal crusts should also be included. In the present study, more general items (changes to skin and changes to hair growth on my face) were chosen in an effort to minimize the number of variables, but they may not have fully captured the nuances of the dermatologic toxicities experienced by patients. Future studies could continue to refine the list of symptoms relevant to EGFRi therapy, and to explore the validity and reliability of a revised MSAS instrument, the MSAS-EGFRi.

Study Aim 2

Describe the quality of life, functional performance status and psychological status of patients receiving EGFRi therapy.

As described in chapter four, participants in this study reported reasonably good quality of life, functional performance status and psychological well-being. The impact of EGFR therapy on these outcomes was not consistent, with the most significant effects seen on dermatologic quality of life and psychological well-being, so these are areas that should be explored further.

Various instruments should be compared in order to identify the optimal measurement strategy for these outcomes. Whether the EGFR-18 is the best dermatologic quality of life instrument for this patient population remains an open question, so comparisons with other tools are suggested. Future studies could compare the relative merits of the Skindex instruments with the EGFR-18 in order to establish an optimal dermatologic quality of life measurement strategy in the setting of EGFR therapy. The MHI-5 is a simple instrument that could be used more frequently in the clinical setting, and could also be compared to other instruments that assess psychological distress.

Study Aim 3

Identify any co-occurring symptoms or symptom clusters in patients receiving epidermal growth factor receptor inhibitors.

Symptom Clusters

Data derived from MSAS-SF (adapted) provided the basis for identification of symptom clusters using exploratory factor analysis. A three cluster solution was identified, including one symptom cluster similar to others previously identified (a psychological-cognitive cluster), a novel cluster possibly related to treatment

(dermatologic skin and hair cluster) that has not been previously identified in symptom cluster research, and a third cluster similar to previously described clusters (lack of energy, difficulty concentrating, feeling drowsy) but with a mucocutaneous component (dry mouth and other changes to fingers and toes), which may reflect the impact of EGFR therapy and is labeled as a mucocutaneous and fatigue cluster. The symptom clusters are identified here both by their factor number, indicating the order in which they were identified by factor analysis, and the descriptive name given to them to characterize the symptoms that grouped together. All three of these clusters must be replicated using a larger sample and a longitudinal design.

Factor 1, the *psychological-cognitive cluster*, comprised of feeling irritable, feeling nervous, worrying, feeling sad, difficulty concentrating, and “I don’t look like myself,” is similar to clusters described in other work, as stated in chapter four. Although there are several similar clusters described in the literature, they are not identical, largely due to differences both in instrumentation (instruments with fewer or different symptoms) and in the sample (e.g. all breast cancer patients). These psychoneurologic clusters often include sleep disturbances, as well as anxiety, depression and other mood-related symptoms. However, despite some variation in specific symptoms, this type of symptom cluster does seem to be prevalent and consistent across many different studies (Kirkova, Walsh, Aktas, & Davis, 2010; Jiménez et al., 2011; Kirkova, Aktas, Walsh, & Davis, 2011; Yennurajalingam et al., 2013; Thomas et al., 2014), and is consistent with the experience of living with advanced cancer.

Researchers have theorized that clusters including emotional or behavioral symptoms and general sickness symptoms may be attributable to underlying psychological or neurological dysfunction (Kim, Barsevick, Fang, & Miaskowski, 2012), with the suggestion that a common biological pathway, such as proinflammatory cytokines, the hypothalamic-pituitary-adrenal axis system and the 5-HT system, may contribute to the development of these symptoms. Sickness symptoms have been linked to cytokine neuroimmunologic mechanisms (Lee et al., 2004; Myers, 2008), as has been demonstrated in the animal model, with comparisons drawn to the responses seen in oncology patients (Cleeland et al., 2003).

Although definitive work in this area remains to be conducted (Dantzer, Meagher, & Cleeland, 2012), those experienced in caring for oncology patients recognize that these symptoms often cluster together. Symptoms such as fatigue, reduced appetite, sleep disorders, and altered mood and cognition may be related to the expression of inflammatory mediators that can affect the brain and the subjective symptom experience (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Beginning evidence that EGFRIs play a role in cytokine regulation has been published (Paul et al., 2014). In vitro work in EGFR-treated head and neck cancer cells suggested that EGFRIs are associated with the production of proinflammatory cytokines, but the mechanisms for this need to be more fully explained and then explored in the clinical setting (Fletcher et al., 2013).

Factor 2, a possibly treatment-related *dermatologic skin and hair cluster* has not been described before in symptom cluster research using factor analytic procedures. This cluster includes dry skin, changes in eyelashes, hair loss, changes in facial hair

growth and other changes in scalp hair. Notably, nail changes and changes in fingers and toes did not correlate with the other symptoms in this cluster, which is an unexpected finding. As noted in chapter four, other treatment-related and diagnosis-related symptom clusters have been described, but no EGFR-related clusters have yet been identified using factor analytic techniques or any other statistical approach. This work represents the first documentation of a symptom cluster that appears to be associated with EGFR therapy, and this finding should be replicated in a larger sample.

Other treatment-related symptom clusters have been previously described in various patient populations (Honea, Brant, & Beck, 2007; Kirkova et al., 2011), such as in patients receiving chemotherapy (Aprile, Ramoni, Keefe, & Sonis, 2008; Yamagishi, Morita, Miyashita, & Kimura, 2009; Hockenberry et al., 2010; Baggott et al., 2012); chemoradiation (Wang et al., 2006) and radiation therapy (Kim et al., 2009b; Kim et al., 2009a), but not in patients receiving EGFRs. Treatment-related clusters have also been identified in patients with breast cancer (Kim, Barsevick, Tulman, & McDermott, 2008); in head and neck cancer, with symptoms including radiodermatitis, dysphagia, pain, taste disturbance, fatigue, radiomucositis, and dry mouth (Xiao et al., 2013); in patients treated with specific therapies for liver cancer, as evidenced by a gastrointestinal symptom cluster with higher severity scores (Wang, O'Connor, Xu, & Liu, 2012); with brain tumors, including a language cluster and a mood cluster (Gleason, et al., 2007); and in patients with prostate cancer where bowel and bladder symptoms were observed (Maliski, Kwan, Elashoff, & Litwin, 2008).

Factor 3, a *mucocutaneous and fatigue cluster*, includes dry mouth, other changes to fingers or toes, feeling drowsy, lack of energy and difficulty concentrating. While lack of energy, dry mouth and psychological symptoms have long been documented in oncology patients, skin and nail changes have not been commonly reported in previous work. Skin, hair and nail issues, as well as mucocutaneous symptoms, have emerged as key problems for intervention in this population of patients, so their inclusion in a symptom cluster is an important finding. Aside from the symptom *other changes to fingers and toes*, clearly linked to EGFR therapy, this symptom cluster could also be related to the same proinflammatory mechanisms described above in the discussion on Factor 1.

Others have described similar clusters (without the changes to fingers or toes) that include feeling drowsy and lack of energy, albeit with some variation in the symptoms secondary to instrumentation. Similar fatigue-related clusters have included lack of energy, feeling drowsy, difficulty sleeping, problems with urination, feeling irritable (Kim et al., 2009a); pain, lack of energy, feeling drowsy, difficulty sleeping, and sweats (Kim et al., 2009b); fatigue, sleep disturbance, lack of appetite, and drowsiness (Chen & Tseng, 2006); fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, and taste change (Walsh & Rybicki, 2006); sadness, dry mouth, drowsiness, shortness of breath, sleep disturbance, appetite changes, fatigue, pain, and numbness (Wang, Tsai, Chen, Lin, & Lin, 2008).

Findings Contrary to Previous Studies

Contrary to previous work in symptoms clusters (Chen & Lin, 2007; Fan et al., 2007; & Skerman, Yates, & Batistutta, 2012), gastrointestinal symptoms were not reported by a majority of patients, and no appetite or gastrointestinal symptom cluster was identified in the present study. In previous studies, an array of different gastrointestinal clusters have been documented, often including nausea and vomiting, lack of appetite, feeling bloated, dry mouth, changes in the way food tastes, and similar symptoms (Cherwin, 2012), often associated with chemotherapy or radiation therapy. However, in the present study, the majority of patients did not receive concurrent chemotherapy.

Dry mouth was a very prevalent and distressing symptom for participants in this study, experienced by over 57%, and ranked fifth in distress. However, it did not seem to cluster with other gastrointestinal symptoms. Although diarrhea and changes in the way food tastes were experienced respectively by 48.2 and 39.3% of participants, these symptoms also did not correlate strongly with other gastrointestinal symptoms, or even any other symptoms at all as they were not retained in factor analysis.

Other symptoms long associated with cancer therapy, including weight loss, lack of appetite, nausea, mouth sores, constipation, feeling bloated, and vomiting, also did not occur in a majority of participants. Perhaps these findings may be a function of the smaller sample size, so it is possible that with a larger sample, such symptoms would have emerged with greater frequency. However, this variation from previous research is likely explained by the prevalence of targeted therapies in this sample, with only 19

participants reporting that they were also receiving additional therapies, as described in chapter four, and of this group, only 8 were receiving drugs classified as chemotherapy, while two reported receiving concurrent radiation therapy.

Study Aim 4

Explore the relationships between any identified symptom clusters and key variables, including gender, age, primary cancer diagnosis, EGFR, and the outcome variables of quality of life, functional performance and psychological status.

No consistent relationships were identified between any demographic or clinical variables, although the distress and prevalence of several symptoms did vary on the basis of gender, primary cancer diagnosis, and specific EGFR therapy. For example, dry mouth was most distressing in head and neck and colorectal cancer patients, who are likely to be receiving MOABs, and diarrhea was more common in breast cancer patients who could be taking lapatinib. Gender played a role with regard to some symptoms. Men reported more symptoms, and were more likely to report lack of energy, dry mouth, problems with sexual interest or activity and dry skin, while women were more likely to report worry. The finding with dry skin is interesting, and may suggest that men are less likely to apply lotions and creams as part of routine skin care, so they may need to be educated to do so.

Symptom Clusters and Outcomes

The relationships between the identified symptom clusters and the outcome measures were explored to determine any differing impact of symptom clusters with the intention of generating hypotheses for further exploration. This study is among the first

to explore how symptom clusters, including a newly identified symptom cluster, affect quality of life, psychological status, and performance. Although the findings here are preliminary, it appears that different symptom clusters can impact outcomes to varying degrees. Identifying those symptom clusters that create the most negative impact on performance and other outcomes would be beneficial for patients.

For example, the association between the psychologic-cognitive symptom cluster and adverse psychological status should be confirmed, providing evidence of the need for more widespread implementation of psychosocial interventions for patients with cancer.

The effect of symptoms on performance, as postulated in the theory of unpleasant symptoms, was demonstrated by a patient comment reflecting the unique impact of dermatologic symptoms associated with EGFRi therapies. This narrative offered by a participant highlights the distress and inconvenience of both skin and nail issues, and underlines how performance of everyday activities and recreational pursuits can be affected:

The problem with my fingernails sometimes gets so bad that I cannot use a knife and fork. The limitation of having to stay out of the sun has resulted in my giving up golf, biking and vacations at beach. I run from the sun and must wear a hat at ALL times. I find this very confining.

Other studies have demonstrated a negative impact in subgroups of patients with high levels of predetermined symptoms on functional status and quality of life (Miaskowski et al., 2006; Pud et al., 2008; Dodd et al., 2010), but these studies explored an a priori symptom cluster of fatigue, sleep disturbance, depression and pain. For example, Miaskowski et al. (2006) found that in participants reporting “all high” levels of symptom severity for pain, fatigue, sleep disturbance and depression reported a lower

quality of life and lower functional status in contrast to those who reported less symptom severity. Future studies with larger samples could evaluate high, moderate and low distress in symptom clusters to explore the impact on outcomes. To some extent, this was addressed by comparing symptom cluster members to those without the symptom cluster, but this work could be extended.

Future work in this area could also address the concept of the sentinel symptom, which is defined as a candidate symptom that heralds the presence of a symptom cluster (Brown et al., 2011), and could further explore the role of age and gender. Based on the factor loadings in the present study, the symptoms of feeling nervous, dry skin and changes to fingers and toes could be possible sentinel symptoms that could signify other symptoms that cluster together. Assessment strategies that call attention to such sentinel symptoms could help prioritize which symptoms to focus on in clinical encounters.

Limitations

This exploratory study is a preliminary work, and as such, has several significant limitations, but perhaps the most relevant to its validity is inherent self-selection. The “passive” study recruitment strategy could result in selection bias affecting the findings. When respondents opt in to research, there may be pre-existing differences between study participants and others who either choose not to participate or who are unaware of a study. However, participants may be more likely to self-select when the research is about something that affects them. Women are more likely to complete health-related surveys (Eysenbach & Wyatt, 2002), which is reflected in the study sample. Specific issues

related to the sample characteristics that impact the validity of this study are outlined below.

Sample Characteristics

A number of sample characteristics in this study may limit applicability to the general population of patients receiving EGFR therapy, including sample size, educational status, social engagement, performance status, and gender.

Small Sample Size

Because a larger sample size ($n = 100$) was sought, this study primarily used a web-based survey. This approach was designed to facilitate recruitment and study enrollment from a broad population, and the majority (80%) did complete the study online. Participant recruitment occurred over an eleven month time frame, and multiple direct and indirect recruitment strategies were utilized. Recruitment materials were posted at multiple sites online, on a study web site, and at cancer support locations; letters explaining the study and research flyers were mailed to a large number of practitioners. Despite multiple study recruitment procedures over an extended time period, however, the desired sample size could not be accrued, so this may limit both the internal and external validity of the study.

Performance Status

Even with advanced disease, most participants were well enough to use a computer or to complete a paper survey. In addition, most reported a good performance status, so the findings of this study are applicable to patients with a similar performance status and may not reflect those whose performance is compromised by illness.

Participants who completed the study online were well enough to use technology to access information and support; those with a limited performance status may not have spent the time online that would lead them to study recruitment materials, or they may have begun the study, but did not complete it. In addition, those who received recruitment flyers from their health care provider may also have had a better performance status, as sicker patients may not have been told about the study.

Race and Ethnicity

As this was an exploratory study, questions about race and ethnicity were not included. In future work, this information, along with skin phenotype, could be included. There is a possible link between skin phenotype and increased skin toxicity (Lacouture, 2006), as noted in chapter two. At least one study suggests that erlotinib skin toxicity is associated with skin phenotype (Luu et al., 2011), so consideration of this patient characteristic could be an area for additional study related to EGFR-related skin symptoms.

Educational Level and Access to Technology

Computer literacy and greater comfort with online activities may be associated with educational level, so it is possible that the study sample was self-selected with regard to comfort with online activities, impacting the external validity of these findings. Although a recent survey suggests that over 80% of the US population uses the Internet, including an equal number of men and women, there are variations in terms of utilization with respect to age, educational level, ethnicity, and household income ("The Web at 25.," 2014). Participants in this study were highly educated, with most reporting a

college education, so findings may not apply to those with less education or less computer literacy.

Support Group Engagement

Because study information was posted in various cancer support groups and in cancer support settings, the study may also be biased to reflect the experience of participants who are more socially engaged rather than those who are isolated and not connected to live or online support groups. Patients who participate in support groups have been described as more likely to be female, younger, educated, without a partner, and with more formal support than those who do not choose to participate in such groups (Grande, Myers, & Sutton, 2006). With the exception of partner status, this sample reflects these characteristics.

Although the research on support group engagement is inconsistent, what is available suggests that a minority of patients express an interest in becoming engaged with support groups of any kind, whether live or online (Van Uden-Kraan et al., 2011). A recent study reported that only about one-third of lung cancer patients planned to participate in support groups (Xu et al., 2014), while another survey of NexCura panel participants indicated that only about 25% of patients participated in support groups (Morse, Gralla, Petersen, & Rosen, 2014). As the latter sample was drawn from a population of patients who agreed to be a part of an online research panel (inactive as of this writing), it is likely that this estimate is high and far fewer patients actually do participate in cancer support groups. Many online studies utilize panels for recruitment, and this option was explored with the current study, but was cost-prohibitive. With

funding, a more purposeful sampling strategy could be implemented to reflect demographics of patients receiving EGFR therapy. Since this study was launched, additional options for research participant recruitment have become available, and could be used in the future.

Cross-Sectional Design

Consistent with the descriptive nature of this study, a cross-sectional design was used, so changes in symptom clusters over time were not assessed. The natural course of symptoms associated with EGFR therapy may evolve over time, so this snapshot of the patient experience does not characterize its changing course. The temporal evolution of EGFR-related symptoms is discussed below.

Skin changes. Skin changes, such as folliculitis, are monomorphic, suggesting that lesions develop simultaneously at a point in time (Sinclair, 2014). Palliation of these changes in order to enhance adherence to therapy may be essential to optimal treatment outcomes. More experience has been gained with prophylactic treatment, so it is possible that patients in this study benefited from the suggested therapies. Over half of patients reported using a special cream, and about one-third indicated that they were receiving a medication for treatment of skin changes.

Dry skin. The onset of dry skin (xerosis) often occurs after four weeks of therapy, but will increase over time as therapy continues, with almost all patients demonstrating this symptom after six months of treatment (Lacouture & Lai, 2006; Mitchell, Perez-Soler, Van Cutsem, & Lacouture, 2007; Osio et al., 2009; Sinclair, 2014). Because the study was cross-sectional, the extent of dry skin experienced by patients

receiving EGFRi therapy in this sample may be underestimated. However, it is the most commonly occurring symptom reported, experienced by about 70% of participants.

Utilizing a longitudinal approach, this percentage could be significantly higher.

Nail changes. Incidence of paronychia also increases over time, so nail changes could be more prevalent in with a longitudinal time frame (Chanprapaph et al., 2014), and may be a more distressing and frequent symptom as time on therapy increases.

Hair changes. Hair changes are considered a late toxicity and would also be more pronounced after several months of therapy. Therefore, hair changes could become a more prevalent symptom over time, a finding that would be noted with a longitudinal study design. Patients treated over six months experience many different changes to hair texture and growth, as well as alopecia that can affect the scalp and other areas of the body. Although well over a third of participants reported various changes in hair growth, the frequency of these changes could also be significantly greater over time.

Interestingly, there is a tendency for hair growth on the face to increase, particularly in patients who receive erlotinib, as well as for changes to occur in eyelashes, with most of these changes occurring between 4-8 weeks of therapy and persisting over time (Wu et al., 2011).

Given the changing nature of the symptoms associated with EGFRi, whether the impact of these symptoms on quality of life, functional performance and psychological status would be different over time is a question that could be pursued in future research. All of these outcomes could be positively impacted by successful therapy, as well as adversely affected by failing therapy, so a longitudinal time frame would capture these

changes. In addition, more research about basic demographic variables, such as age and gender, could reveal new insights into the symptom experience in patients treated with EGFRIs.

Measurement Issues

In this exploratory study, a key aim was to describe the symptom experience of patients receiving EGFRIs. The MSAS-SF was adapted to include additional symptoms associated with EGFRi therapy, including dry skin, changes to my finger or toe nails, changes in hair growth on my face, other changes to scalp hair, changes in my eyelashes and other changes to my fingers and toes. The results indicate that the EGFRi symptom experience differs from that traditionally associated with cancer therapy. Many of the symptoms listed on the original MSAS-SF were not selected by respondents to this survey, and future studies might include fewer items, eliminating those experienced by few patients. Additional items, as suggested by participants, could include dry eyes, eye discharge and crusting, changes to eyebrows, changes to hair texture, eyelid changes, itchy scalp, rash and nasal changes.

In preparation for this study, the Skindex instruments were reviewed for possible inclusion in the study (Chren, Lasek, Quinn, Mostow, & Zyzanski, 1996; Chren et al., 1997; Chren, Lasek, Sahay, & Sands, 2001). As the Skindex instruments were not specific to this type of oncologic therapy, and were designed for quality of life measurement in general dermatologic practice, an instrument specifically designed for an oncology population was selected instead. It would be interesting to revisit these

instruments and evaluate them against the FACT-EGFRI-18 in measuring dermatologic quality of life in patients receiving EGFRIs.

As noted in chapter four, the items in the EGFRI-18 selected by most participants were included in the Physical subscale (e.g. “My skin or scalp itches,” “My skin or scalp feels dry,” “My skin or scalp feels irritated,” “My eyes are dry.”) or reflected a response to a physical symptom (“I am bothered by hair loss.”)

Implications for Nursing

Practice

This exploratory study of the symptom experience of patients receiving EGFRIs represents the first attempt to more fully characterize the multidimensional effects of this treatment on the whole person and not just on hair, skin and nails. Previous work has been focused primarily on dermatologic side effects of treatment while performance, quality of life and psychological well-being have not been holistically assessed (White et al., 2011). The present study underscores that although skin, hair and nail changes are prominent components of this experience, other symptoms may also be frequent and patients would benefit from thorough, systematic assessment and from effective palliative and preemptive management. With an average of 11 symptoms reported by patients in this sample, the question is raised as to whether clinicians are addressing that number of symptoms in the course of routine care, and if not, how are patients navigating their symptom experience?

As part of the recruitment process for this study, many patient support and information sites were visited by the researcher. Common topics of conversation on

these sites included rash and other skin, nail, and hair changes, with patients exchanging suggestions and their own experiences. Some mentioned that their nurse or physician provided guidance to them, but many were turning to the wisdom of experienced group members for practical suggestions. If this is where patients gather their self-care information, that may be empowering to patients, but it does reflect possible missed opportunities for nursing care to guide patients to evidence-based care management strategies.

Consistent with exemplary oncology nursing practice, holistic assessment of the patient experience should be the basis of comprehensive patient care that incorporates multiple disciplines. Identification of co-occurring symptoms or symptom clusters should be a priority in order to streamline and deliver care more effectively and economically. Nurses should be aware of the most common and the most distressing symptoms experienced by patients, and should be aware of the concept of symptom clusters and how to assess them.

This study suggests that outcomes such as quality of life, performance and psychological status may be impacted differently depending on the constellation of symptoms, or symptom clusters, that patients may be experiencing. An awareness of the impact of symptom clusters on specific outcomes can guide busy practitioners to provide tailored and pre-emptive support, education and self-management strategies for patients based on their symptom experience.

Psychosocial assessments, in particular, should be undertaken with all patients receiving these therapies. The first factor to emerge in factor analysis procedures was the

psychological-cognitive cluster, which suggests that patients on EGFRi therapy should be evaluated as to their psychological status across the treatment continuum. A variety of brief screening tools for assessing anxiety, depression and psychological status are available, and their implementation at various points along the EGFRi therapy trajectory could help identify patients with issues related to psychological status.

Nursing interventions for the psychological-cognitive cluster could include a set of interventions such as skin toxicity management (e.g. antibiotics and topical therapies), cognitive behavioral strategies (Wagner & Lacouture, 2007), a telephone or online support group, a sleep hygiene plan (pharmacologic and non-pharmacologic), a plan for energy conservation, and an exercise program. This anticipatory guidance would be an improvement over the prevailing standard of care which tends to focus primarily on skin issues, which if severe enough, might generate a referral for dermatologic care or psychological support. Helping patients to continue therapy through enhancing their coping skills and by addressing symptoms and associated quality of life issues could improve adherence and the effectiveness of treatment.

Education

A paradigm shift in the education of oncology nurses to embrace a wider range of treatment-related symptoms is underway and should continue as new therapies emerge. Competency in the assessment and management of skin, hair and nail changes, as well as other symptoms caused by EGFRis, should be fostered in settings where EGFRis are included in patient treatment plans. In addition, wider dissemination of the recommended management strategies for EGFRi side effects is necessary. Although some patients

require referral to dermatologists, nurses working at the top of their licensure are capable of making patient self-care recommendations, as well as advising patients about over the counter products, as long as they have participated in continuing education and professional development regarding these symptom management strategies. When medical management is necessary, the astute nurse can be instrumental in making timely referrals.

Patient education materials highlighting proactive symptom management and preventive care strategies should be included in the teaching materials for patients who are receiving EGFR therapy. As each individual patient may have varying needs based on occupation, social roles, activities of daily living, and lifestyle considerations, nurses should be attuned to how high frequency and highly distressing symptoms may impact a given patient and should augment patient education accordingly. For example, individuals who use their hands frequently in their work, such as homemakers, nurses or other health care workers, massage therapists, restaurant workers, clerical and retail staff, hospitality and service workers, mechanics and others, as well as those who enjoy hobbies requiring manual work like gardening or fishing, are at particular risk for exacerbation of EGFR-related issues.

Research

Skin, hair and nail changes are frequently experienced by patients receiving these therapies, but evidence-based therapies are lacking for many of the symptoms. Dose modifications and therapy interruption may occur in a significant number of patients (Boone et al., 2007), so optimal preventive and management strategies will provide a

basis for optimal therapy. Most recommendations for EGFRi symptom management are anecdotal in nature and have not been rigorously evaluated, with some exceptions.

The Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group recently published clinical practice guidelines for the prevention and treatment of dermatologic toxicities (Lacouture et al., 2011). Although some of the guidelines are based on research, other recommendations are based on expert opinion and panel consensus due to a lack of relevant studies. As noted by MASCC, data from other similar skin conditions provided the basis for some recommendations; as a result, it is entirely possible that outcomes from these treatments may not be optimal for the dermatologic changes caused by EGFRis. As a result, many opportunities for interventional and comparative effectiveness trials remain.

Nurses have long managed patients' skin conditions, and oncology nurses have claimed symptom management as their forte. Since patients report itchy, dry, flaky and irritated skin, changes in hair, and changes in fingers and toes frequently, nurse-led protocols to ameliorate these symptoms should be evaluated in partnership with practitioners with dermatologic experience. While many of the interventions suggested by MASCC are pharmacologic agents, many are not, so teams including dermatologists, advanced practice nurses and oncology nurses could collaborate on research evaluating these treatments. Such interdisciplinary work would be an ideal approach to generating evidence-based care protocols. Implementation of funded, longitudinal research is also essential in order to document not only the trajectory of the symptom experience of

patients receiving EGFRIs, but also to determine optimal points for intervention across the treatment continuum.

In a sample of colorectal cancer patients receiving panitumumab and combination chemotherapy, a pre-emptive skin treatment regimen that included skin moisturizer, sunscreen, topical steroids, doxycycline, and an educational video aimed at minimizing skin irritation, was compared to a reactive treatment protocol. Participants kept a diary of symptoms that also recorded treatment compliance (Lacouture, Mitchell, et al., 2010). Results indicated that patients receiving the pre-emptive regimen experienced a significantly lower rate of \geq Grade 2 or greater skin toxicity (29% vs. 62%). The reactive treatment group demonstrated a greater decline in quality of life scores. Although this regimen only evaluated one EGFRi, the findings are encouraging and might be evaluated with other therapies. Interestingly, diarrhea was also lessened in the pre-emptive treatment group, most likely due to treatment with an antibiotic, providing an example of how a set of interventions could target multiple symptoms.

Cognitive-behavioral strategies that address the psychological impact of symptoms associated with EGFRIs could be evaluated in collaboration with psychologists and social workers as a strategy to address multiple symptoms, such as those represented in the psychological-cognitive cluster. Cognitive-behaviors skills can help patients to cope with physical discomfort, and also with mood-related symptoms (Wagner & Lacouture, 2007), such as worrying or feeling nervous, and could impact overall performance outcomes as well. Specific strategies, such as symptom reframing and positive imagery, have been described (Wagner & Lacouture, 2007).

As noted in the discussion on Factors 1 and 2, exploration of the underlying mechanisms of the psychological-cognitive cluster and the general sickness cluster, including the role of cytokines, is an area for future research.

Conclusion

In summary, this study has added to nursing science in several key areas. First, the symptom experience of patients receiving EGFRIs has been more fully characterized. Evidence has been presented that those patients who receive EGFRi therapy experience a significant symptom burden related to their disease and treatment that includes dermatologic symptoms, but also includes a wide variety of other symptoms that require assessment and management, such as mood and affective symptoms. Not all symptoms that are common in the oncology patient population are relevant in these patients, and other symptoms that are less well recognized can cause distress and impact performance. In addition, psychological symptoms should be assessed as they are commonly experienced by patients receiving EGFRIS. Future work should include updated symptom instruments that incorporate high frequency symptoms associated with specific therapies.

Secondly, three symptom clusters have been identified in this patient population: a psychological-cognitive cluster, which can impact psychological status; a treatment-related dermatologic cluster with skin and hair changes that has not been previously identified as a symptom cluster; and, a mucocutaneous and fatigue cluster which can affect performance and elements of QOL and which included a treatment-related symptom not previously included in similar clusters. The identification of these symptom

clusters offers an opportunity to explore interventions that impact more than one symptom and which may enhance care while reducing costs.

Finally, the theory of unpleasant symptoms (TOUS) provided a multidimensional infrastructure for the measurement of symptoms and their impact on outcomes in patients receiving EGFRIs. In the TOUS model, a synergistic effect occurs when several symptoms are experienced simultaneously and have a multiplicative effect (Lenz et al., 1997). Interaction between and among concurrent symptoms resulted in different impacts on outcomes, supporting a basic premise of the model. In addition, the notion that psychological symptoms should be included in the model, separate and apart from psychological influencing factors, was enhanced through this work. Future work can explore and test whether interventions aimed at psychological symptoms can ameliorate or modify other symptoms and the subsequent performance outcomes experienced by these patients.

Future studies should include larger samples, equal numbers by gender, and a longitudinal design in order to confirm the findings of the current study. Because there were variations in symptoms experienced by patients receiving TKIs vs. MOABs, future studies could compare symptom clusters between these groups in order to further refine identified symptom clusters and to enhance tailoring of symptom management interventions. Careful evaluation and comparison of instruments to assess symptoms in this group of patients should be undertaken, as it is possible that the ideal instrument does not exist, and could be developed or further refined in future work. Evaluation of the available instruments for dermatologic quality of life is recommended. In addition, more

comprehensive assessment of patients receiving EGFRIs should be undertaken in order to identify effects of therapy on psychological status and all facets of quality of life. Care management strategies for skin, nail and hair changes should be evaluated in interventional studies that include both physiologic and psychological assessments.

APPENDIX A
DISTRESSING PHYSICAL AND PREVALENT
PSYCHOLOGICAL SYMPTOMS OVERALL

N = 56	Mean	Std. Deviation
Dry skin	1.757	1.4902
Lack of energy	1.657	1.3802
Worrying	1.607	1.2746
Changes to my finger or toe nails	1.429	1.4925
Problems with sexual interest or activity	1.429	1.6552
Changes in skin	1.414	1.3814
Dry mouth	1.386	1.4269
Feeling sad	1.357	1.1666
Diarrhea	1.286	1.5077
Feeling nervous	1.232	1.1907
Feeling irritable	1.196	1.1349
Changes in hair growth on my face	1.100	1.3522
Changes in the way food tastes	1.057	1.3991
Difficulty sleeping	1.029	1.2646
Numbness/tingling in hands/feet	1.000	1.3495
Hair loss	.971	1.4206
Changes in my eyelashes	.929	1.3796
Other changes scalp hair	.929	1.3014
Feeling drowsy	.914	1.1760
Difficulty concentrating	.829	1.2009
Weight loss	.786	1.2440
Itching	.757	1.1459
Cough	.729	1.1342
Pain	.700	1.1320
Other changes to my fingers or toes	.686	1.2340
Mouth sores	.686	1.3072
Lack of appetite	.671	1.1083
Shortness of breath	.614	1.1415
"I don't look like myself"	.557	1.1809
Nausea	.543	.9167
Constipation	.457	.9262
Difficulty swallowing	.443	1.0110
Dizziness	.314	.7423
Sweats	.286	.7062
Feeling bloated	.257	.7795
Vomiting	.186	.6288
Swelling of arms and legs	.186	.5706
Problems with urination	.157	.5588

APPENDIX B
EGFRI-18 RESULTS

N = 55

	Percent (n)	Mean, SD
Physical		
I am bothered by a change in my skin's sensitivity to the sun.	29 (16)	2.84 (1.36)
My skin or scalp itches.	76 (42)	2.31 (1.32)
My skin bleeds easily.	53 (29)	3.02 (1.15)
My skin or scalp is dry or "flaky."	80 (44)	2.07 (1.35)
My skin or scalp feels irritated.	76 (42)	2.53 (1.20)
My eyes are dry.	64 (35)	2.62 (1.37)
I am bothered by sensitivity around my fingernails or toenails.	31 (17)	2.51(1.43)
Social/emotional		
My skin condition affects my mood.	35 (19)	3.45 (.899)
I feel unattractive because of how my skin looks.	35 (19)	3.29 (1.15)
I am embarrassed by my skin condition.	44 (24)	3.27 (1.05)
I avoid going out in public because of how my skin looks.	16 (9)	3.69 (.79)
I am bothered by increased facial hair.	44 (24)	3.02(1.31)
I am bothered by hair loss.	55 (30)	2.71 (1.46)
Functional		
My skin condition interferes with my social life.	18 (10)	3.29 (1.15)
Sensitivity around my fingernails makes it difficult to perform household tasks.	47 (26)	2.96 (1.31)
My skin condition interferes with my ability to sleep.	15 (8)	3.76 (.693)
Changes in my skin condition make daily life difficult.	27 (15)	3.6 (.74)
The skin side effects from treatment have interfered with household tasks.	29 (16)	3.55 (.84)

APPENDIX C
RECRUITMENT LETTER

NAME of HEALTH CARE PROFESSIONAL
ADDRESS

Dear Dr. or Nurse:

I am writing to tell you about an oncology nursing research study being conducted as part of my doctoral nursing program at Loyola University, Chicago. As an oncology clinical nurse specialist certified as an advanced practice nurse in oncology, I am interested in learning how to help patients manage the symptoms associated with their cancer treatment. This study is an anonymous survey that focuses on the ***symptom experience of patients receiving epidermal growth factor receptor inhibitors (EGFRIs)*** as part of their therapy. As you know, the dermatologic symptoms associated with EGFRIs have been studied, but less is known about the overall impact of these treatments on the development of other symptoms, such as pain and insomnia, and on health-related quality of life.

I am asking for your help in identifying patients who may meet the following criteria:

- At least 18 years old
- Currently taking one of these medications: cetuximab (Erbix®), panitumumab (Vectibix®), erlotinib (Tarceva®), gefitinib (Iressa®), and lapatinib (Tykerb®) for at LEAST FOUR WEEKS
- Able to read and understand English
- Willing to complete an anonymous online or paper survey
- NOT diagnosed with a skin condition NOT related to treatment, such as acne vulgaris, erythema multiforme, psoriasis, or rosacea

Participation in the study would involve completion of online OR paper instruments. The survey instruments will take no longer than 20-30 minutes to complete. There are no interventions associated with this study, and no blood samples or other lab work will be performed. No personal health information or other identifying information will be collected, and participants will not be asked for your name or the name of any care providers.

We hope that the study will benefit future patients receiving these medications.

Please contact me at 224-735-1118 for questions about the study. Several patient flyers are included in this mailing, so if you have patients who you feel would be appropriate for participation, please share this information with them. Patients may contact me directly if they have any questions or an interest in participating and I will pre-screen them for the study.

Thank you in advance for considering this request for assistance in identifying patients eligible for this study.

Sincerely,

Josie Howard-Ruben, MS, RN, APN-CNS, AOCN, CHPN

Doctoral Student, Loyola University

XXXXXXX(VM)

APPENDIX D
RECRUITMENT FLYER

The Symptom Experience of Patients Receiving Epidermal Growth Factor Inhibitors (EGFRIs)



Would you like to be part of a nursing research study that explores the symptom experience of patients who take EGFRIs as part of their cancer treatment?

EGFRIs include drugs such as cetuximab (Erbix), panitumumab (Vectibix), erlotinib (Tarceva), gefitinib (Iressa), or lapatinib (Tykerb).

These medications are used to treat several cancers such as breast cancer, colon cancer, head and neck cancer, lung cancer, and pancreatic cancer.

- Are you at least 18 years old?
- Are you currently taking one of these medications: cetuximab (Erbix®), panitumumab (Vectibix®), erlotinib (Tarceva®), gefitinib (Iressa®), and lapatinib (Tykerb®)?
- Have you been taking this medication for AT LEAST FOUR WEEKS?
- Able to read and understand English?
- Are you willing to complete an anonymous online or paper survey?
- Are you NOT diagnosed with a skin condition NOT related to treatment, such as acne vulgaris, erythema multiforme, psoriasis, or rosacea?

If you answered YES to these questions, you may be eligible to participate in a nursing research study.

The purpose of this trial is to create a complete picture of the symptoms experienced by patients receiving drugs classified as epidermal growth factor inhibitors (EGFRIs). These drugs may cause skin, nail, and hair changes, as well as other symptoms.

This study will explore the impact of these symptoms on patient well-being and quality of life.

To participate in the study, you will complete an anonymous survey. The survey will take about 20-30 minutes to complete.

This study is being conducted as part of a doctoral nursing program at Loyola University, Chicago.

For information and to be screened for participation, please call Josie Howard-Ruben at 224-XXXXX or email XXXXXX@luc.edu.

APPENDIX E
WEB SITE CONTENT

Home page

The Symptom Experience of Patients Receiving Epidermal Growth Factor Receptor Inhibitors (EGFRIs)

This nursing research study explores symptoms experienced by patients who are taking EGFRIs, and is being conducted by a doctoral nursing student at Loyola University, Chicago.

We are interested in learning more about the symptoms experienced by patients who take EGFRIs, as well as the impact of these symptoms on quality of life and well-being.

If you are taking one of these medications for cancer, you may qualify to participate in this study. Please click on the **STUDY PARTICIPATION** link at the top of this page.

If you would like more information, or you have questions about the study, please click on the link **FOR MORE INFORMATION**.

*What is an EGFR? Page***EGFRIs**

Epidermal growth factor receptor inhibitors (EGFRIs) are a newer kind of cancer treatment called targeted therapy. They are used to treat several different cancers, including breast cancer, colon cancer, head and neck cancer, lung cancer and pancreatic cancer. To qualify for this study, you would have to be taking one of the following:

- cetuximab (Erbix)
- panitumumab (Vectibix)
- gefitinib (Iressa)
- erlotinib (Tarceva)
- lapatinib (Tykerb)

*STUDY PARTICIPATION page***Do I qualify?**

If you meet the following criteria, you are eligible to participate in this study.

- You are at least 18 years of age.
- You are **CURRENTLY** taking one of these medications: cetuximab (Erbix®), panitumumab (Vectibix®), erlotinib (Tarceva®), gefitinib (Iressa®), or lapatinib (Tykerb®).
- You have been taking the medication for at least four weeks.
- You are able to read and understand English.
- You are willing and able to complete the study questionnaires, either online or on paper.
- You do **NOT** have a skin condition **UNRELATED TO YOUR TREATMENT**, such as acne vulgaris, erythema multiforme, psoriasis, or rosacea.

If you choose to participate in this research study, you will be asked to complete a 20-30 minute online survey one time only.

There are no costs to participating in this survey other than the time you spend completing it.

No information will be collected that will reveal your identity, so the survey is anonymous.

If you prefer a paper copy of the survey, or if you have any questions about the survey, please contact Josie Howard-Ruben by email at XXXXXX@luc.edu or by using the *For More Information link*.

APPENDIX F
INSTRUMENTS

Q1 The Symptom Experience of Patients Receiving Epidermal Growth Factor Receptor Inhibitors

This study has been approved as exempt by a Loyola University of Chicago Institutional Review Board. This nursing research study is being conducted as part of my doctoral nursing program at Loyola University in Chicago. Purpose of the study: The purpose of this survey is to learn more about the symptom experience of patients receiving treatment with epidermal growth factor receptor inhibitors (EGFRIs), and to find out how these symptoms affect quality of life, well-being and performance. These treatments may cause skin, hair, and nail side effects, and other symptoms. We would like to know more about all of these side effects in order to help patients manage the symptoms better. If you have been receiving one of these medications, including cetuximab (Erbix®), panitumumab (Vectibix®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib (Gilotrif®) and lapatinib (Tykerb) for at least four weeks, you may be eligible for this study. Use the arrow keys at the bottom left to move to the next page.

Q2 Are you eligible to participate?

You must meet the following criteria to be eligible to participate in this study.

You must be at least 18 years old.

You are currently taking one of these medications: cetuximab (Erbix®), panitumumab (Vectibix®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib (Gilotrif®) and lapatinib (Tykerb®).

You have been taking this medication for at least four weeks.

You are able to read and understand English.

You are willing and able to complete the study questionnaires.

You do NOT have a skin condition UNRELATED TO YOUR TREATMENT, such as acne vulgaris, erythema multiforme, psoriasis, or rosacea.

If you choose to participate in this research study, you will be asked to complete an online survey that will take less than 20-30 minutes to finish.

There are no costs to you for participating in this survey other than the time you spend completing it. If you prefer a paper copy of the survey, one can be mailed to you.

XXXXX@luc.edu.

If you would like to volunteer for this survey, please go to the next question where your consent will be recorded.

Q3 You are invited to participate in a research study about your experiences with your cancer treatments.

We are interested in learning more about the symptoms you are experiencing as a result of your treatment and how those symptoms are affecting your quality of life, ability to function and well-being.

The survey will take no more than 20-30 minutes.

No costs are associated with this survey, and there are no risks associated with participation.

Please verify that the following statements are correct by checking ALL of the boxes.

- I understand that participation in this study is voluntary.
- I understand that participation or lack of participation in this study has no effect on my care.
- I have been taking one of the listed medications for at least four weeks.
- I am at least 18 years old.
- I can read and understand English.
- I do not have one of the skin conditions listed: acne vulgaris, erythema multiforme, psoriasis or rosacea.
- I agree to participate in this study.

If I agree to participate in this study Is Not Selected, Then Skip To End of Survey

Q4

Thank you so much for agreeing to complete this survey, and your willingness to share your experience to help others.

Please answer the following questions so that we can get a complete picture of the symptoms you are experiencing.

Ideally, you should complete the survey in one sitting, but you can pick up where you left off if you are interrupted.

Josie Howard-Ruben, MS, RN, APN-CNS, AOCN, CHPN Doctoral Student Loyola University, Chicago

Q5 Which of the following medicines are you currently taking as part of your treatment?

- erlotinib or Tarceva
- gefitinib or Iressa
- lapatinib or Tykerb
- cetuximab or Erbitux
- panitumumab or Vectibix
- afatinib or Gilotrif
- None of the above

If None of the above Is Selected, Then Skip To End of Survey

Q6 How long have you been on this medication?

- Less than four weeks
- At least four weeks
- More than four weeks
- More than eight weeks

If Less than four weeks Is Selected, Then Skip To End of Survey

Q7 Please tell us your gender.

- Male
- Female

Q8 Please tell us about your marital status.

- Married
- Single, but not widowed or divorced
- Divorced
- Widowed

Q9 Please choose the description that best describes your living arrangements.

- Live with spouse
- Live with spouse and children
- Live with children
- Live alone
- Live with others not listed

Q10 What is your highest level of education?

- Elementary school
- High school
- College
- Graduate school

Q11 Please tell us your age.

- 18-29
- 30-39
- 40-49
- 50-59
- 60-69
- 70-79
- 80-89
- 90-99

Q12 First, please tell us about your overall health. Which of these choices best describes your health right now?

- Fully active, able to carry on all pre-disease performance without restriction
- 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
- Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Q13 What is your primary cancer diagnosis?

- Breast cancer
- Colorectal cancer
- Head and neck cancer
- Lung cancer
- Pancreatic cancer
- Do not know
- Other (please write in below) _____

Q14 Do you know the stage of your cancer?

- Stage I
- Stage II
- Stage III
- Stage IV
- Do not know

Q15 Are you receiving any other medication for your illness that is not listed above, such as chemotherapy?

- Yes
- No

Answer If Are you receiving any other medication for your illness t... Yes Is Selected

Q16 You indicated that you are receiving other chemotherapy treatments. Can you tell us what those medications are?

Q17 Are you receiving radiation therapy at this time?

- Yes
- No

Q18 Are you being treated for any of the following illnesses, other than cancer?

- No
- Heart disease
- Diabetes
- Stroke
- Respiratory disease, including asthma or COPD
- Osteoporosis
- Vascular disease
- Gastrointestinal disease, including stomach, colon, liver or pancreas
- Obesity
- Other _____
- I choose not to answer this question

Q19 Are you receiving any treatment for your skin condition RELATED TO YOUR CANCER THERAPY? You can check all that apply.

- I am not receiving treatment for my skin.
- I use a special soap.
- I use sunscreen.
- I apply a cream that my health care provider suggested.
- I take an oral medication. If you know the name of the medication, please write it in below. _____

Q20 Please describe your current tobacco use.

- I currently smoke tobacco products.
- I currently use other tobacco products.
- I quit using tobacco products when I was diagnosed with this illness.
- I do not currently use tobacco products.

Q21 Redacted instrument due to copyright.

Q26 Mental Health Inventory 5 items (MHI-5) (Ware & Sherbourne, 1992) How much, during the past 4 weeks, did you feel very nervous?

- All the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Q27 How much, during the past 4 weeks, have you felt so down in the dumps, nothing could cheer you up?

- All the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Q28 How much, during the past 4 weeks, have you felt calm and peaceful?

- All the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Q29 How much, during the past 4 weeks, have you felt down-hearted and depressed?

- All the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Q30 How much, during the past 4 weeks, have you been happy?

- All the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

Q31 Next, we would like to ask you more about your symptoms. Learning more about symptoms you are experiencing may help us to identify better ways to help you manage these symptoms. If you have not experienced the symptom in the last seven days, mark "no." If you have experienced the symptom, please tell us how much it has DISTRESSED or BOTHERED you. Please follow the directions below.

Q32 Memorial Symptom Assessment Scale-SF (Adapted)

This survey asks about your symptoms.

Instructions: Symptoms that patients may experience will be listed. If you have had the symptom DURING THE PAST WEEK, please check that symptom. If you check yes for a symptom, you will be asked how much the symptom DISTRESSED or BOTHERED you.

Q33 During the PAST WEEK, did you have any of the following symptoms?

Please scroll down the page to make sure you see all the symptoms.

	CHECK if you had symptom in last week		If you checked YES, how much did the symptom DISTRESS or BOTHER you? Click on the box and select the description for this symptom.			
	YES	Not all	A little Bit	Somewhat	Quite a bit	Very much
Difficulty concentrating	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pain	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Lack of energy	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cough	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Changes in skin	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dry mouth	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nausea	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Feeling drowsy	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Numbness/tingling in hands/feet	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Difficulty sleeping	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Feeling bloated	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Problems with urination	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Vomiting	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Shortness of breath	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Diarrhea	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Constipation	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Sweats	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Mouth sores	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Problems with sexual interest or activity	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Lack of appetite	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dizziness	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Difficulty swallowing	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Changes in the way food tastes	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Weight loss	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hair loss	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other changes to the hair on my scalp	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Changes in hair growth on my face	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Changes in my eyelashes	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Swelling of arms and legs	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
"I don't look like myself"	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Itching	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dry skin	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other skin changes	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Changes to my finger or toe nails	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Other changes to my fingers or toes	<input type="checkbox"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q34 Below are other commonly listed symptoms.

Please indicate if you have had the symptom DURING THE PAST WEEK, and if so, how OFTEN did it occur?

	IF YES, how often did it occur?				Check YES if you had the symptom in the last week
	Rarely	Occasionally	Frequently	Almost constantly	
Feeling sad	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Worrying	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Feeling irritable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Feeling nervous	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Q35 IF YOU HAD ANY OTHER SYMPTOMS DURING THE PAST WEEK, PLEASE TYPE IN BELOW AND INDICATE HOW MUCH THE SYMPTOM HAS DISTRESSED OR BOTHERED YOU.

Q36 Redacted due to copyright.

Q37 Overall, how would you rate the experience of completing this survey?

- Very Difficult
- Difficult
- Somewhat Difficult
- Neutral
- Somewhat Easy
- Easy
- Very Easy

Q38 Thank you for participating in this nursing research study. If you would like to learn about the results of this study, please visit www.symptomclusters.com where we will post information about any publications that result from this research study. You may also contact me by email at XXXXXX@luc.edu or by phone at XXXXXX. THANK YOU!

APPENDIX G
RESEARCH GRIDS

Qualitative Research Matrix: Impact of Epidermal Growth Factor Receptor Inhibitors on Quality of Life

<p><u>Author/Citation:</u> Wagner, L. and Lacouture, M., 2007. Dermatologic toxicities associated with EGFR inhibitors: the clinical psychologist's perspective.</p>	<p><u>Author/Citation:</u> Wagner, L, Berg, S., Gandhi, M., Hlubocky, F., Webster, k., Aneja, M., Cella, D., and Lacouture, M. (2013) The Development of a Functional Assessment of Cancer Therapy (FACT) questionnaire to assess dermatologic symptoms associated with epidermal growth factor receptor inhibitors. (FACT-EGFRI-18)</p>	<p><u>Author/Citation:</u> Coleman, S., Kovtun, I., Nguyen, P. L., Pittelkow, M. and Jatoi, A. (2011), A qualitative study of the ramifications of rash from epidermal growth factor receptor (EGFR) inhibitors.</p>	<p><u>Author/Citation:</u> Boers-Doets, C.B., Gelderblom, H., Lacouture, M.E., Epstein, J.B., Nortier, J.W., & Kaptein, A.A. Experiences with the FACT-EGFRI-18 instrument in EGFRI-associated mucocutaneous adverse events. Support Care Cancer. 2013</p>
<p><u>Purpose:</u> To explore dermatologic-related symptom burden and HRQL in patients receiving an EGFRI.</p>	<p><u>Purpose:</u> To describe the process of developing the FACT-EGFRI-18, used to measure HRQOL in patients receiving EGFRI.</p>	<p><u>Purpose:</u> To explore the full impact of the EGFRI rash.</p>	<p><u>Purpose:</u> The aim of this study was to identify how the EGFRI-18 performed as a measure of quality of life in patients taking EGFRI.</p>
<p><u>Theoretical framework:</u> Not stated.</p>	<p><u>Theoretical framework:</u> Not stated, but presumed to be HRQOL.</p>	<p><u>Theoretical framework:</u> Not stated.</p>	<p><u>Theoretical framework:</u> Not stated.</p>
<p><u>Research question:</u> What are the most bothersome aspects of dermatologic toxicities associated with EGFRI? What is the impact of these symptoms on HRQOL?</p>	<p><u>Research question:</u> What are the most bothersome aspects of dermatologic toxicities associated with EGFRI? What is the impact of these symptoms on HRQOL?</p>	<p><u>Research question:</u> Not stated.</p>	<p><u>Research question:</u> Is the EGFRI-18 linguistically valid in a Dutch population?</p>
<p><u>Participants/Setting:</u> 20 oncology patients at Northwestern University and 12 expert clinicians Clinicians included four</p>	<p><u>Participants/Setting:</u> 20 oncology patients at Northwestern University and 12 expert clinicians Clinicians included four oncology</p>	<p><u>Participants/Setting:</u> 15 patients at Mayo Clinic who had a past or current rash from an EGFRI, including 10 men, and 5 women with an average age of 58.</p>	<p><u>Participants/Setting:</u> 10 participants in the Netherlands, including 6 males, 4 females. Most colon cancer, followed by lung cancer and breast.</p>

<p>oncology nurses, three oncologists, three dermatologists, one dermatology nurse and one ophthalmologist. Patient participants were predominantly white women with a mean age of 57 years. Diagnoses included 55% lung cancer, 35% colorectal cancer, and 5% pancreatic sample.</p>	<p>nurses, three oncologists, three dermatologists, one dermatology nurse and one ophthalmologist. In the second part of the study, patient participants included 16 women and 7 male patients receiving EGFRIs.</p>	<p>Diagnoses included colon cancer (7), head and neck cancer (5), lung cancer (2) and pancreatic cancer (1). About half of the patients were receiving cetuximab.</p>	
<p>Ethics: Not discussed</p>	<p>Ethics: IRB approval Northwestern.</p>	<p>Ethics IRB Approval Mayo Clinic.</p>	<p>Ethics: Stated that study was exempt from review due to the non-interventional nature.</p>
<p>Method: Triangulation approach included 20 interviews with patients and 12 expert clinicians.</p>	<p>Method: A sequential, iterative process was described including literature review, open-ended qualitative interviews with both experts and two groups of patients.</p>	<p>Method: Structured interview with follow-up questions that were recorded and transcribed.</p>	<p>Method: Proctored administration of EGFRi-18 followed by a structured interview to assess items/s personal relevance to participant, as well as their comprehension of each item.</p>
<p>Data Gathering and Analysis: Qualitative interviews; method of analysis not described. Lists of items that were rated by patients and clinicians.</p>	<p>Data Gathering and Analysis: Qualitative interviews analyzed by thematic content analysis (symptom burden, interference in physical and social function, emotional well-being including distress and self-image). Separate counts of frequency by clinicians and patients were used to generate priority items.</p>	<p>Data Gathering and Analysis: Questions focused on rash and were based on the literature and clinical concerns. Questions were structured, but an opportunity for free response was allowed. Transcripts were reviewed and when new themes no longer emerged, enrollment stopped. An inductive qualitative approach was used to identify and categorize</p>	<p>Data Gathering and Analysis: Verbatim recording of comments. No formal analysis process.</p>

	<p>Patients and clinicians rated 62 candidate items and could add any of their own items if not included, and ten were asked to rate the top 20 items relevant to EGFR toxicity. A second group of patients (n=24) completed preliminary questionnaires with 38 items, as well as interviews.</p>	<p>themes, with two investigators reviewing transcripts.</p>	
<p>Results/Findings: Patients identified physical symptoms as most important, rating burning, stinging, irritation, pain and dry eyes as their top five concerns. Clinicians also selected physical symptoms, but put a greater priority on items reflecting social well-being. NCI-CTC grading: 15% Grade 1, 40% Grade 2, and 45% Grade 3, indicating fairly significant symptom burdens.</p>	<p>Results/Findings: The 38-item version of the EGFR toxicity was reduced to an 18-item version to measure HRQOL developed to measure HRQL among patients receiving EGFRIs.</p>	<p>Results/Findings: The face and nose were described as the most problematic areas for rash, and most patients reported discomfort associated with it. One patient reporting being hospitalized for a morphine drip for pain control. 60% reported that the rash made them feel hopeful (in that the treatment was working). Four key themes emerged: physical discomfort, concerns about appearance, social isolation, and medical morbidity. Patients initially denied social isolation, but their comments proved otherwise.</p>	<p>Results/Findings: Participants could not always relate an item to quality of life. Family members often prompted participants about specific situations where QOL was impacted by EGFR treatment. Physical symptoms were most associated with an impact on quality of life. Patients had a tendency to rate severity of symptom rather than its impact on QOL. Other items were suggested such as eye sensitivity, runny nose, bloody or crusty nasal cavity, skin sensitivities, and oral issues. Instrument more focused on cutaneous than mucosal adverse events.</p>

<p><u>Limitations—Comments</u> Small sample size. Not well developed in terms of formality of qualitative method. No IRB information.</p>	<p><u>Limitations—Comments</u> Extension of previous work. Small sample and one setting of care.</p>	<p><u>Limitations—Comments</u> Small sample size with majority of patients receiving cetuximab so may not apply to TKIs.</p>	<p><u>Limitations—Comments</u> Small sample size. May not be applicable across cultures.</p>
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