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Review

Personalized Palliative and Survivorship Care for Patients With Metastatic Cancer Treated With Radiation Therapy

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Abstract. While the benefits of early palliative care for patients with metastatic cancer are well established, cancer survivorship remains inadequately integrated into the care of patients with distant metastases. Moreover, the optimal model of care delivery is poorly defined. A prognostic model previously developed and validated at Good Samaritan University Hospital identified four groups of patients with metastatic solid tumor malignancy having very favorable, favorable, standard or unfavorable prognoses with median survival of 31, 14, 4 and 1 month, respectively. This framework holds promise for the personalized delivery of supportive, palliative and survivorship care services in the context of radiation therapy. We review the published literature providing the rationale for a novel multidisciplinary care model where the radiation oncology Clinical Nurse Specialist identifies and coordinates interventions to address unmet physical and emotional issues faced by survivors with metastatic cancer with the goal of improving quality of life and overall survival.

The worldwide incidence of cancer is 18 million new cases, and the numbers are projected to double by 2030 (1, 2). With advances in cancer treatment, including high-precision

radiotherapy, many advanced and metastatic cancers are now managed as a chronic disease (3, 4). In a contemporary analysis of whole-body positron-emission tomographic scans for patients with distant metastases, 55% were found to have one to five distant metastases (5). While advances in drug development and more effective local treatment have improved survival for patients with metastatic cancer, cancer survivorship represents an important and relatively unexplored opportunity to further improve outcomes (6, 7).

Palliative care holds promise to reduce the burden of cancer throughout the natural history of metastatic disease by placing the patient and family at the center of the multi-disciplinary healthcare team, improving patient outcomes in symptom management while reducing emergency room and inpatient hospital utilization (8, 9). Specific high-value functions of palliative care include managing symptoms, strengthening coping, cultivating illness understanding, prognostic awareness and establishing advanced directives (9, 10). While palliative care is now well accepted in mainstream oncology practice, cancer survivorship has recently been identified as a major deficiency, particularly for patients with metastatic cancer (3, 4). Specific domains addressed by a comprehensive survivorship program include cardiac health, psychosocial issues, cognitive function, fatigue, lymphedema, pain, hormone-related symptoms, sexual dysfunction, insomnia and metabolic syndrome (3).

The optimal model for delivering and coordinating palliative and survivorship services, which often require resources and providers beyond the scope of the cancer center, remains poorly defined and implementation research is urgently needed (3). Providing primary palliative and survivorship care to patients with metastatic cancer is also an important opportunity to expand the scope of radiation oncology practice (11).

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Table I. Prognosis-informed management of patients with metastatic solid tumor.

NEAT group	Median survival, months	RT plan	Palliative care referral	RT follow-up
Very favorable	31	High dose (stereotactic)	Optional	Yes
Favorable	14	High dose (stereotactic) or standard dose (10 to 15 fractions)	Yes, to improve QOL and possibly survival	Yes
Standard	4	Low dose (5 to 10 fractions)	Yes, to address symptoms, initiate end-of-life planning and for possible QOL advantage	As needed
Unfavorable	1	No RT or single fraction	Yes, hospice strongly considered	No

NEAT: Based on number of active tumors (N), Eastern Cooperative Oncology Group performance status (E), albumin (A) and primary tumor site (T); QOL: quality of life; RT: radiation therapy.

Personalizing Radiation Oncology Management for Patients With Distant Metastases

Metastatic disease has now been recognized as a distinct subspecialty discipline within radiation oncology (12). Dedicated palliative radiation oncology programs have reportedly transformed care for hospitalized patients at several major academic medical centers (12-17). Potential benefits of dedicated palliative radiation oncology programs include more efficient and timely delivery of palliative radiotherapy and improved communication with patients and referring physicians.

The Palliative Radiation Oncology model of longitudinal follow-up for patients with metastatic disease has been described in a community satellite clinic associated with Oregon Health and Science University (18). This model coordinates regular follow-up visits and timely interventions to reduce the suffering of patients with metastasis before further progression of their symptoms (18).

Good Samaritan University Hospital is a 437-bed teaching hospital that averages approximately 600 new radiation oncology patients per year, served by 2.0 full-time equivalent radiation oncologists and 3.8 full-time equivalent oncology nurses. Specifically, one oncology nurse received advanced training as a Clinical Nurse Specialist (CNS) and has extensive experience and interest in Palliative Care. Although the radiation oncologists practice general radiation oncology, one of the physicians has a long-standing interest in treating and following patients with oligometastases dating to 2006, while another physician completed an internal medicine residency (19). With this extensive background, our Department took interest in optimizing care not only for patients with oligometastases but all patients presenting to the Department with distant metastases since 2012.

At Good Samaritan University Hospital, a framework was developed to predict prognosis more accurately for adult patients with metastatic disease from solid tumor referred to

radiation oncology. In the validated NEAT model, a composite score determined by the extent of disease, Eastern Cooperative Oncology Group performance status (ECOG PS), serum albumin and primary tumor site predicted four distinct tiers of survival – namely very favorable, favorable, standard or Unfavorable – with median survival of 31, 14, 4 and 1 month, respectively (20, 21). This prognostic model holds promise in informing management and treatment decisions (Table I).

In terms of radiation management, unfavorable prognosis patients are often best approached with supportive care alone often with hospice referral and occasionally single-fraction radiation for severe symptoms. For the standard-risk group, timely and cost-effective radiation regimens are often appropriate to palliate symptoms (22). Patients with favorable and very favorable risk may benefit from radiation schedules with higher dose intensity that have been shown to achieve durable local control and possibly improved overall survival in well-selected patients with metastatic disease (23-25). Importantly, dose-intense radiation is administered using highly conformal techniques, accurate tumor imaging and precision treatment delivery systems, resulting in low toxicity despite ongoing systemic therapy (26).

By personalizing radiation prescriptions in this fashion, recent data from Good Samaritan University Hospital demonstrated that patients with metastatic cancer selected for radiation therapy with low biological equivalent dose (EQD2<40 Gy) had a median survival of 2 *versus* 17 months for those receiving higher doses (6). These data provide proof of principle that appropriately personalized radiotherapy prescriptions can be delivered in a busy community practice where subspecializing in palliative radiation oncology is not practical.

Based on this extensive experience, comprehensively addressing cancer survivorship issues for patients with metastatic disease represents a logical next step to further improve outcomes (3).

Palliative and Spiritual Care for Patients With Poor Prognosis

At Good Samaritan University Hospital, approximately 30% of patients referred to radiation oncology have a predicted survival of 1 month, while another ~35% of patients have an expected median survival of 4 months (20, 21). In a recently published meta-analysis, the benefit of palliative care for inpatients and other subgroups with advanced cancer with poor prognosis was modest and difficult to reproducibly document in randomized controlled trials (27-32). In clinical practice, a common lament of palliative care specialists is that referrals often occur within the last month of life, which reduces the effectiveness of their interventions (8, 33).

By contrast, spiritual care has been associated with improved quality of life for cancer patients near death (34). A multi-institutional investigation found that spiritual care for patients with a cancer prognosis of under 1 year was significantly associated with improved quality of life. This study also described a decrease in religious activity attendance in patients after a cancer diagnosis, while patients reported an increase in personal religiousness and spirituality. If validated, expanded involvement of pastoral care represents a promising strategy to improve outcomes for this poor prognosis population (35).

Intensified Palliative and Survivorship Care to Improve Overall Survival for Favorable Prognosis Patients With Metastatic Cancer

Several trials have explored different methods of intensified care *versus* usual care for metastatic patients with a predicted survival of years to >6 months (Table II). At Good Samaritan University Hospital, approximately 20% of patients referred to radiation oncology have a predicted survival of 14.5 months while another ~15% of patients have an expected median survival of 30 months (20, 21).

Studies investigating the addition of palliative care or ongoing electronic reporting of symptoms compared to usual care are summarized in Table II (36-42). Early integration of palliative care for patients with metastatic cancer is now well established. In a landmark randomized controlled trial performed at Massachusetts General Hospital, patients with newly diagnosed stage IV non-small cell lung cancer with ECOG PS of 0 to 2 were randomized to early palliative care combined with standard oncology care *versus* standard oncological care alone (36). Early palliative care was associated with improved quality of life at 12 weeks and higher median overall survival (11.6 *vs.* 8.9 months, $p=0.02$) while reducing depressive symptoms (36). The mechanism of action of early palliative care on improved overall survival is hypothesized to result from improving quality of life and mood compared to standard oncological care (36). Further

evidence supports the notion that increased attention to promoting well-being improves outcomes for patients with advanced cancer. In the ENABLE II study of patients with advanced cancer in rural New Hampshire, those that received nurse-led palliative care had higher scores for quality of life and mood when compared with those under usual care (43). The Ghent University trial confirmed the effectiveness of nursing-led palliative care to improve quality of life in patients with newly diagnosed advanced cancer (39). In the ENABLE III randomized controlled trial, patients receiving early palliative care had improved 1-year survival compared to those under delayed palliative care but did not contribute to significant differences in quality of life and mood (41).

In a randomized controlled trial by Memorial Sloan Kettering of patients receiving chemotherapy for metastatic breast, genitourinary, gynecological or lung cancer, patients randomized to electronic patient-reported outcomes for symptom monitoring had improved overall survival compared to usual care (42). In this study, the clinical nurse was alerted and responded to symptom alerts 77% of the time with discrete clinical interventions. Taken together, these data confirm that enhancements to survivorship care improve outcomes for more favorable cohorts of patients with metastatic cancer.

Implementing Primary Palliative Care and Survivorship in Radiation Oncology

For the majority of patients with stage IV cancer, the medical oncologist remains the primary physician providing longitudinal specialty care over time (44). In addition to medical oncologists, palliative care physicians play an important role during inpatient episodes while radiation oncologists actively manage patients during the course of radiation therapy and during ongoing outpatient follow-up (18, 45). Due to limitations in palliative care staffing, relatively few outpatients benefit from outpatient palliative care.

The well-established community-based radiation oncologist often has a relationship with the patient spanning years after successfully treating their primary tumor or other metastases (6). From our experience, the busy community medical oncologist appreciates radiation oncology input with co-managing many aspects of primary palliative care as long as care is well coordinated. Increasingly, patients with advanced cancer require multiple courses of radiation therapy over time. At our institution, we have instituted a daily inpatient oncology meeting where all patients on the hematology-oncology inpatient service are discussed. Radiation oncology is represented at this meeting for multidisciplinary discussion, and this has further enhanced our longitudinal follow-up of patients with metastatic disease.

There is continuing debate about the various models of palliative care practice and their optimal usage, particularly

Table II. Randomized controlled trials of intensified palliative or supportive care versus usual oncological care for patients with >6 months estimated survival.

Institution (Ref)	Population	Patients, n	Interventions	Findings	Intervention type
Massachusetts General Hospital (36)	Metastatic newly diagnosed non-small cell lung cancer; ECOG PS 0 to 2, 91% ECOG PS 0 to 1	151	Early palliative care vs. usual care	Increased QOL, mood and prolonged survival (median survival 116 vs. 89 months, $p=0.002$) in early palliative care patients	In person, interdisciplinary palliative care with monthly follow-up
Princess Margaret Hospital (37)	Advanced cancer in 5 primary sites (lung, gastrointestinal, genitourinary, breast, and gynecology), ECOG PS 0 to 2, clinical prognosis of 6 to 24 months	461	Early palliative care vs. usual care	Significant difference in QOL at 3 months and significant improvement in symptom severity, satisfaction with care and QOL at 4 months	In person, interdisciplinary palliative care with monthly follow-up and telephone contact
Massachusetts General Hospital (38)	Incurable newly diagnosed lung or non-colorectal GI cancer, ECOG PS 0 to 2, 91% ECOG PS 0 to 1	350	Early integrated palliative care and oncological care vs. standard care	Improved QOL at 24 weeks after enrollment in patients with lung cancer; GI cancer patient showed improvement in QOL in the first 12 weeks	In person, interdisciplinary palliative care with monthly follow-up
Ghent University Hospital (39)	Patient with newly diagnosed follow-up and advanced cancer from solid tumor, ECOG PS 0 to 2, estimated life expectancy of 12 months	468	Early and systematic palliative care intervention vs. standard care	Significantly improved QOL at 12 weeks	Nurse-led palliative care with monthly
University Hospital at Angers (40)	Patients with stage IIA to IV lung cancer within 3 months of treatment without progression; 63% stage IV; ECOG PS 0 to 2; lower baseline symptom burden	133	Electronic patient-reported symptoms vs. usual care	Survival advantage favoring electronic patient-reported symptoms (median survival 22.5 vs. 14.9 months, $p=0.03$), improved performance status at relapse allowing optimal treatment	Electronic patient-reported severe or worsening of symptoms alerting treating oncologist
ENABLE III (41)	Patients with advanced cancer diagnosis, progression or recurrence with a 6 to 24 month prognosis	207	Early vs. delayed palliative care	Survival advantage favoring early palliative care group (1-year survival 63% vs. 48%, $p=0.04$). No statistical difference between patient reported outcomes	In person, physician-led palliative care consultation followed by nurse-led telehealth coaching appointments
Memorial Sloan Kettering (42)	Patients with metastatic breast, genitourinary, gynecologic or lung cancer initiating chemotherapy	766	Electronic patient reported symptoms vs. usual care	Survival advantage favoring electron patient reported symptoms (median survival 31.2 vs. 26.0 months, $p=0.03$), improved health-related QOL, less ER use	Electronic patient-reported severe or worsening of symptoms alerting clinical nurse

ECOG PS: Eastern Cooperative Oncology Group performance status; ER: emergency room; GI: gastrointestinal; QOL: quality of life.

Table III. Common long-term survivorship issues and management options.

Survivorship issue	Cause	Medical management	Non-medical interventions
Response assessment and surveillance		History and physical with particular attention to radiation toxicity, radiological testing to assess response to therapy or recurrence, blood work, referral to palliative care, referral for cardiac surveillance, coordinating additional testing	Edmonton Symptoms Assessment Scale and NCCN Survivorship Assessment
Pain	Bone or visceral, metastases neuropathy, pathologic fracture	Non-opioid medications (ibuprofen, acetaminophen), opioids, gabapentin, palliative radiation therapy, referral for nerve blocks and/or kyphoplasty,	Referral for physical therapy, cognitive behavioral therapy, meditation, hypnosis, acupuncture
Fatigue	Treatment-related pain Treatment and tumor related fatigue	referral for medical marijuana Corticosteroids, referral for antidepressants, anxiolytics, psychostimulants	Referral for physical therapy, cognitive behavioral therapy, meditation, acupuncture, yoga
Cognitive dysfunction	Treatment-related	Memantine	Referral for cognitive rehabilitation, cognitive behavioral therapy, physical therapy
Anxiety, depression, trauma and distress	Exacerbated by advanced cancer and treatment	Referral for medical management (antidepressants, anxiolytics)	Referral for cognitive behavioral therapy, mindfulness practice, physical therapy
Anorexia cachexia	Tumor-related, symptoms interfering with oral intake	Referral for appetite stimulant, medical marijuana Effective systemic therapy	Nutrition evaluation
Insomnia	Corticosteroids, distress	Hypnotics, melatonin, diphenhydramine	Sleep hygiene, increase physical therapy, cognitive behavioral therapy
Sexual dysfunction	Treatment, advanced age, comorbidity, psychological issues	5-Phosphodiesterase inhibitors, referral to urology or gynecology, antidepressants	Referral to counseling, sexual health, increased physical activity, vaginal moisturizers

NCCN: National Comprehensive Cancer Network.

in the outpatient setting (46). While specialist-led palliative care programs are the traditional model, there is greater recognition of an increasing mismatch between the demand and supply of physician-led palliative care services, particularly in the outpatient setting of a busy community hospital (46, 47).

Primary palliative care functions include basic management of pain, anxiety and depression, and discussions about prognosis, goals of treatment, suffering and code status can be addressed by both primary care physicians and oncologists (46). In the oncology-led primary palliative care model, both oncologists and oncology nurses can practice empathy as a beneficial therapeutic intervention that is maintained over time (48). Wider implementation of primary palliative care by oncology practices would free the specialty palliative care practice to address refractory pain or symptoms, manage complex depression, anxiety, grief and existential distress, address conflicts regarding goals and methods of treatments within families and treatment teams and to transition to comfort care only (45, 49). Based on these emerging data, current National Comprehensive Cancer Network (NCCN) guidelines recommend that primary

palliative care should be provided by the oncology team for most patients with a more favorable estimated life expectancy of years to months (50).

For patients with metastatic cancer with a more favorable prognosis, identifying common long-term effects of cancer and cancer treatment, including cardiac damage, psychosocial distress, cognitive dysfunction, fatigue, lymphedema, pain, hormone-related symptoms, sexual dysfunction, insomnia and metabolic syndrome, could result in effective intervention (3) (Table III). While optimizing medical management is important, better integration of non-pharmacological interventions may represent the greatest opportunity for improvement (Table III). Integrative services as exercise, cognitive behavioral therapy, massage, music therapy, meditation, mindfulness practice, acupuncture, sleep hygiene, cognitive rehabilitation and hypnosis have been proposed as non-pharmacological treatments for a variety of physical and psychosocial symptoms related to advanced cancer (3). These services are generally not available within a community oncology clinic and increasing access to these services *via* robust referral patterns is a goal of a robust survivorship intervention.

Towards a Comprehensive Survivorship Program After Radiation Therapy for Metastatic Cancer

As radiation oncology technology has advanced over the past decade, the workload of individual radiation oncologists has increased (51). A partnership between the radiation oncologist and an advanced practice nurse is particularly attractive for community-based oncology practices with limited resources to deliver optimal survivorship care (52, 53).

Radiation oncologist-led survivorship visits have historically focused on assessing response to therapy and managing treatment-related toxicity. A CNS, an advanced practice nurse with an advanced degree, can compliment the radiation oncologist by utilizing current NCCN survivorship guidelines with a special emphasis on non-pharmacologic approaches (Figure 1 and Table III).

The CNS holds promise in effectively delivering primary palliative and supportive care of patients with metastatic disease (53). Recent data from Good Samaritan University Hospital demonstrates that experienced oncology nurses are able to predict survival in patients with metastatic cancer at least as well as an attending radiation oncologist (54). This study highlights the complementary and often non-overlapping strengths physicians and nurses in evaluating patients with advanced cancer.

The radiation oncology CNS works with the patient, educates the nursing staff and facilitates the goals of the organization by providing holistic care. Utilizing Joanne Olson’s Theory of Empathetic Process, the oncology CNS concentrates on the authentic process of therapeutic interaction in which empathy is expressed, allowing the nurse to confirm the patient’s feelings and thereby reducing patient distress (55). Validation of patient perceptions is critical across the oncology disease continuum. This process enables the patient to identify their feelings, thereby reducing distress, and encourages participation in goal-setting to improve outcomes. It incorporates concepts of instantaneous reaction, interaction, exploration, verification, and enhancing outcomes (55).

In the continuum of oncology care, the CNS can incorporate elements of palliative care and survivorship at an earlier stage to offer support, validation, and comfort. The holistic empathetic approach to patient care uniquely positions the CNS to assess changes in patient response to oncology treatment that may dictate the trajectory of palliative care and survivorship in the oncology continuum of care. At our clinic, patients pass the nursing station to and from treatment. Daily assessment and treatment of physical, emotional, psychological, social, and spiritual health of the patient is essential in the empathetic process. Daily therapeutic interactions associated with traditional fractionated external beam radiotherapy contributes to prompt management of patient response to treatment with the support of our multidisciplinary team. With the increasing adoption of shorter

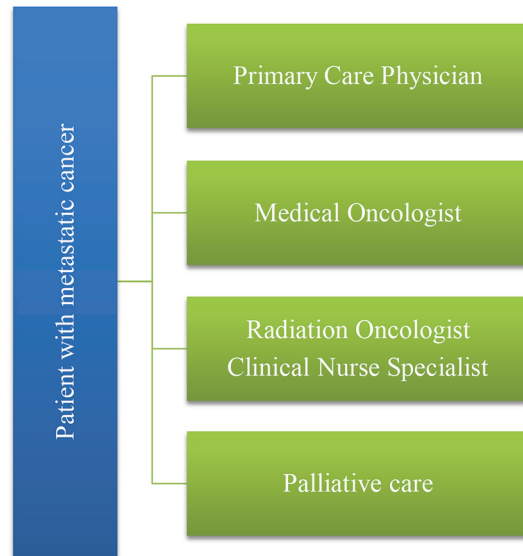


Figure 1. A multidisciplinary model for survivorship care for metastatic cancer.

radiation schedules, we envision a reframing of interactions with the CNS with regular continuing touchpoints over time.

Recent research suggests that the presence of a CNS in a multi-disciplinary team is strongly related to improved outcomes for patients. A survey of cancer patients in the United Kingdom found that giving the name of a CNS to patients was associated with overall improved treatment experience (56). In an observational study of Lung Cancer Nurse Specialists in the United Kingdom, the CNS was described by team members as a ‘hub’ of the group’s activities (57). While less well-established in the United States, in the United Kingdom, the CNS serves a unifying role in a multidisciplinary care team, working to connect the patients with optimal services and care.

The CNS works in identifying patient feelings and perceptions in their understanding of their health status. Emphasis is placed on patient-centered strengths, needs and concerns relating to physical, emotional psychosocial and spiritual wellbeing. Validation by the nurse establishes a therapeutic relationship with the patient at each interaction. Palliative care and survivorship care is introduced as a way to support the patient clinically through the oncology care continuum. Weekly on-treatment patient assessments and continued patient follow-ups by nursing staff and the multidisciplinary team after treatment completion allow the patient to recognize and verbalize changes in their perceived health status over time, facilitating the intervention of palliative care. This holistic care model is informed by the mission and philosophy of a faith-based organization dedicated to improving the health of our community. Structured patient reported outcomes including the 10 item

Edmonton Symptom Assessment Scale or the 28 item NCCN survivorship assessment will be utilized to identify problems and to monitor progress. We hypothesize that including a ‘human in the loop’ will allow the CNS to more accurately focus on the primary barriers that reduce health-related quality of life and psychological well-being (Figure 1).

In the proposed survivorship model, the primary care physician manages comorbid medical issues and receives communication from all oncology providers. The radiation oncologist and medical oncologist co-manage routine oncological follow-up. The medical oncologist often administers ongoing systemic therapy with frequent physical examinations and blood work. Management of acute toxicities from systemic therapy and assessment of response to systemic therapy are the primary domains of the medical oncologist.

The radiation oncologist may deliver multiple separate courses of radiotherapy over time and has particular interest in late toxicities from radiation therapy and assessing response to local therapy during regular follow-up visits. The radiation oncology CNS maintains regular contact with the patient in between radiation oncology office visits. In contrast to the oncologists, their focus is on primary palliative care, and physical and emotional issues. The Edmonton Symptom Assessment Scale and NCCN Survivorship Assessment are used as standardized screening and monitoring tools. The CNS coordinates non-pharmacological and integrative interventions. When necessary, the radiation oncologist will assess the need for medical management and need for referrals.

Ideally, palliative care would be routinely integrated into general oncology care for all outpatients with distant metastases. Depending on staffing levels, universal outpatient palliative care is not feasible and other providers administer primary palliative care. Palliative care referral is mandatory for unacceptable outcomes and uncontrolled symptoms.

Based on the compelling evidence reviewed, we hypothesize that a CNS-led palliative care and survivorship program represents a novel, cost-effective and practical approach to achieving optimal quality of life and survival for patients with advanced cancer receiving radiation therapy; this is currently being tested in an Institutional Review Board-approved randomized controlled trial.

Conflicts of Interest

None.

Authors' Contributions

Sana Siddiqui: Investigation, writing, reviewing, editing and data curation. LuAnn Rowland: Writing, editing, conceptualization and visualization. Emily Copel: Reviewing, supervision and conceptualization. Ashish Sangal: Reviewing, supervision and conceptualization. Vikram Soni: Reviewing, supervision and conceptualization. Patricia Eckardt: Writing, reviewing, supervision

and conceptualization. Johnny Kao: Investigation, writing, editing, conceptualization, and supervision.

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