

## Editorial

# Palliative Care Research: Issues and Opportunities

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## Introduction

Supportive and palliative care has been recognized as an important component of quality care for all cancer patients and particularly for those with advanced or incurable disease (1, 2). Given an estimated 1,334,100 new patients diagnosed with cancer in the United States in 2003 (excluding nonmelanoma skin cancers) and ~556,500 cancer-related deaths (3), care for those patients who are near the end of life is an essential aspect of cancer care (4). Cancer survivorship research focuses on the life of individuals diagnosed with, and living with, the late or long-term effects of cancer and its treatments. By definition, survivorship research also includes studies focusing on patients with advanced disease.

Palliative care is an interdisciplinary team approach to care with a focus on comfort and quality of life rather than prolongation of "cure" for a patient and their loved ones. Although many treatments currently exist to manage symptoms and complications of advanced cancer, there continues to be a paucity of well-designed prospective clinical trials examining state-of-the-art practices, impeding the further development of evidence-based guidelines. The absence of an established evidence base in many areas of palliative care is at least in part due to major challenges investigators face in designing palliative care trials. Research challenges include ethical issues in conducting such trials, barriers to collaborative research across specialties, and unclear standards for the types of "best care" practices that should be employed as part of such trials (5, 6). Consequently, the young specialty of palliative medicine is struggling to develop an evidence base commensurate with that of other specialties, threatening its credibility within the academic arena. In other words as stated by Casarett (7), "As long as the randomized controlled trial is the standard by which effectiveness is judged, the field whose interventions have not been proven by this test is at risk of being relegated to second-class status in the medical hierarchy."

In the absence of a firm evidence-based foundation for clinical practice, care for patients with incurable cancer is frequently based on anecdotal evidence and provider experience. Some treatment opportunities may be delayed or never considered at all, and other non-beneficial and burdensome interventions may be instituted. Regardless of whether the resulting bias is one of overtreatment or undertreatment, optimal care of patients with advanced illness requires a commitment to base treatment approaches on scientific fact rather than anecdotal experience. The National Cancer Policy Board (1) recently agreed, noting that research addressing the needs of patients with incurable cancers is severely deficient. Increasing research for this population, however, requires more complete description of the specific methodological and ethical barriers in the realms of palliative and end-of-life care as well as expert consensus on approaches to developing research strategies and design.

## Dilemmas and Barriers

Palliative care researchers must confront distinctive ethical dilemmas and barriers that extend far beyond those of standard research trials (8). While many ethical issues are not unique to patients facing life's end, they are often magnified in this population and compound the potential ethical issues present in all clinical research trials. These include the vulnerability of the population from which study subjects are recruited, high rates of mental incapacity and emotional distress creating challenges to informed consent, addressing conflicts of interest within the dual roles of the clinician-researcher, the invasiveness and increased frequency of testing relative to standard clinical practice, and questions of scientific value that must balance the benefits and burdens of unproven interventions in a population in whom comfort may be a priority. Ethical concerns specific to palliative research include the difficulty in assessing the risks and benefits of research participation, randomization, especially if there is a "no treatment arm," and the unstable mental status of patients with difficulty assessing capacity. Methodological challenges include high rates of loss to follow-up due to physical and mental incapacity and death, the biases introduced by the need for surrogate respondents, and the difficulty of

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determining appropriate outcomes and methods for assessing those outcomes. Within palliative surgery and other invasive specialty areas, specific concerns include the risks of major morbidity and mortality these treatment approaches entail, patient loss of decision-making capacity and management of life-threatening emergencies in the perioperative period, difficulty with equipoise (9) when faced with vastly different treatment options (surgical *versus* nonsurgical), and the “all-or-nothing” nature of surgery making irrelevant the idea that a patient should be free to withdraw from a study at any time.

Despite the challenges alluded to above, the effectiveness of palliative interventions must nevertheless be assessed with the same rigor that is employed in assessing other medical interventions. As with all treatments of uncertain benefit, we must “overcome ethical objections to research and ingrained beliefs in established treatments” (10). While palliative surgery poses some unique dilemmas within the larger scope of palliative care research, even these barriers can usually be overcome with well-constructed studies carried out by thoughtful research teams (11, 12). Indeed, the methodological difficulties in palliative care research are all surmountable through existing techniques and appropriately careful scientific design (13). Communication that these hurdles can be surmounted remains a barrier to the implementation in palliative care settings.

In addition to the challenges described above, designing palliative care research with methodological precision must account for the diversity of ethnic, cultural, and religious backgrounds that patients bring with them into their experience of life-limiting illness. A patient’s experience of illness is both multidimensional—incorporating physical, emotional, social, and spiritual dimensions—and culture dependent, in that the experience is shaped in large part by the cultural milieu in which the patient resides. Researchers have identified deficiencies in the access of racial and ethnic minorities to palliative care services (14), suggesting important opportunities for palliative care research to identify the unique perspectives and service needs of culturally diverse populations.

## Opportunities

The dearth of high-quality clinical research in palliative care relative to other, nonpalliative clinical conditions (15) suggests a clear opportunity to advance the science, and improve the quality of care, for patients afflicted with cancer. At the same time, those interested in pursuing palliative care research could benefit from expert assistance in developing methods for the conduct of palliative care trials that will maximize the chance for trial results to be valid, safe, and ethical. Without such advancements in research methods, policies, and procedures, the field of palliative care risks a future where clinical practices are ill informed, where research may be suboptimally conducted, and, ultimately, where patients will suffer less than optimal care.

Because the goal of the National Cancer Institute, as outlined by Director Andrew C. von Eschenbach, MD, is to relieve suffering and death related to cancer by 2015, it implies an imperative to address immediately the needs of those patients suffering from the effects of cancer or its

treatment. To ensure that these patients receive the best possible care, we must determine the optimal treatment regimens. As with all cancer therapies, the gold standard continues to be the randomized prospective clinical trial. This goal has admirably been pursued with regard to cancer trials, which focus on cure; it is urgently needed in the palliative care of patients with advanced cancer and terminal disease.

## Future Directions

In response to the current deficiencies in clinical palliative care research, in November 2004, an international consensus conference will convene in Pasadena, CA to address methodological issues in this area. The conference’s primary goal is to develop a “road map” for meeting the challenges of developing a palliative care evidence base and will specifically address the following objectives:

1. Use the clinical dilemma of malignant bowel obstruction (MBO) as a model to explore clinical, research, ethical, and cultural barriers to prospective studies of patients with advanced cancer;
2. Develop an integrated methodological framework for the implementation of prospective randomized studies of patients with advanced cancer;
3. Apply integrative palliative care research methods and an implementation framework to a prospective randomized trial for patients with MBO; and
4. Disseminate methodologies and implementation strategies for use by researchers and clinicians working with patients who have advanced cancer.

Conference organizers selected MBO as a target condition given that it is a relatively common complication of advanced cancer (16, 17) causing significant morbidity and mortality. A wide range of treatment options currently exists for MBO, including surgical, endoscopic, and medical approaches, without a single dominant standard of care. Although invasive management approaches are often considered in patients who may regain an acceptable quality of life for at least a period of time, decision-making remains complex and must account for a wide range of patient and caregiver preferences and significant variation in cross-cultural values, attitudes, and preferences toward end-of-life care. In addition, in cases of MBO, there is often substantial uncertainty associated with both the risks of surgical intervention in an individual patient and a patient’s survival expectancy with or without surgery. Experts in the fields of palliative medicine, quality of life research, surgical oncology, gastroenterology, intercultural issues, and patient advocacy are committed to this conference, for which the findings will be disseminated to researchers, clinicians, and policymakers who care for those facing the end of life.

In addition to the stated objectives of this meeting, there are many other research questions that can also be examined based on the guidance from this meeting, such as the following:

1. What is the appropriate management of malignant ascites?

2. For tumor-related breast cancer wound complications, will major resection and reconstruction be an improvement in quality of life versus local wound care and pain management?
3. For recurrent rectal cancer, what is the best management of pain control between systemic, epidural, nerve ablation, or resection?
4. What is the most rational approach to invasive esophageal tumors?

Based on the consensus findings of this meeting, conference organizers hope to provide guidance to prospective palliative care researchers, which ultimately should advance scientific knowledge in the care of patients near the end of life. Once clear guidelines for palliative care trials are available, the possible research questions and studies are unlimited. This will ultimately place palliative research and care on the same level as those directed at a cure for patients with cancer.

## References

1. Foley KM, Gelband H, editors. Improving palliative care for cancer, summary and recommendations. Washington, DC: National Cancer Policy Board, Institute of Medicine and National Research Council, National Academy Press; 2001.
2. Anonymous. Cancer care during the last phase of life. *J Clin Onc*, 1998;16(5):1986–96.
3. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin*, 2003;53:5–26.
4. Byock I. Completing the continuum of cancer care: Integrating life-prolongation and palliation. *CA-A Cancer Journal for Clinicians*, 2000;50(2):123–32.
5. Casarett D, Karlawish J. Are special ethical guidelines needed for palliative care research? *J Pain Symptom Manage*, 2000;20:130–9.
6. Casarett D, Karlawish J, Hirschman K. Are hospices ready to participate in palliative care research? Results of a nationwide survey. *J Palliat Med*, 2001;5:397–406.
7. Casarett D. "Randomize the first patient": old advice for a new field. *AAHPM Bull*, 2002;2:4–5.
8. Krouse RS, Easson AM, Angelos P. Ethical considerations and barriers to research in surgical palliative care. *J Am Coll Surg*, 2003;196:469–74.
9. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*, 1987;317:141–5.
10. Sunshine J. Federal research helps debunk time-honored myths. *Fed Pract*, 2002;19:47–8.
11. Byock I, Teno J, Field M. Measuring quality of care at life's end. *J Pain and Symptom Manage*, 1999;17(2):73–4.
12. Teno J, Byock I, Field M. Research agenda for developing measures to examine quality of care and quality of life of patients diagnosed with life-limiting illness. *J Pain and Symptom Manage*, 1999;17(2):75–82.
13. Sloan J, Symonds T, Vargas-Chanes D, Fridley B. Practical guidelines for assessing the clinical significance of health-related quality of life changes within clinical trials. *Drug Inf J*, 2003;37:23–31.
14. Fiscella K, Franks P, Gold MR, Clancy CM. Inequality in quality: addressing socio-economic, racial and ethnic disparities in health care. *J Am Med Assoc*, 2000;283:2579–84.
15. Teno J. The new family evaluation of hospice care: Web-based benchmarking. NHPCCO 18th Management and Leadership Conference; 2003 Sep 7; Phoenix, AZ.
16. Krouse RS, McCahill LE, Easson AM, Dunn GP. When the sun can set on an unoperated bowel obstruction: management of malignant bowel obstruction. *J Am Coll Surg*, 2002;195:117–27.
17. Fainsinger RL, Spachynski K, Hanson J, Bruera E. Symptom control in terminally ill patients with malignant bowel obstruction (MBO). *J Pain Symptom Manage*, 1994;9:12–8.

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