



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Palliative Care

Version 1.2019 — December 10, 2018

[NCCN.org](https://www.nccn.org)

[Continue](#)



**\*Maria Dans, MD/Chair £**  
Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine

**\*Jean S. Kutner, MD/Vice-Chair ▯ P £**  
University of Colorado Cancer Center

**Justin N. Baker, MD €**  
St. Jude Children's Research Hospital/  
The University of Tennessee  
Health Science Center

**Jessica R. Bauman, MD †**  
Fox Chase Cancer Center

**Anna C. Beck, MD**  
Huntsman Cancer Institute  
at the University of Utah

**Toby C. Campbell, MD † £**  
University of Wisconsin  
Carbone Cancer Center

**Amy A. Case, MD £**  
Roswell Park Comprehensive Cancer Center

**Shalini Dalal, MD £**  
The University of Texas  
MD Anderson Cancer Center

**Danielle Doberman, MD £**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**Howard Edwards, MD £**  
Fred & Pamela Buffett Cancer Center

**Andrew S. Epstein, MD † £**  
Memorial Sloan Kettering Cancer Center

**Thomas R. Fitch, MD £**  
Mayo Clinic Cancer Center

**Jennifer Kapo, MD £**  
Yale Cancer Center/Smilow Cancer Hospital

**Richard T. Lee, MD £ †**  
Case Comprehensive Cancer Center/  
University Hospitals Seidman Cancer  
Center and Cleveland Clinic Taussig  
Cancer Institute

**Elizabeth T. Loggers, MD, PhD £ †**  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

**Susan McCammon, MD P £**  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Charles Miller, MD £**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Sumathi Misra, MD ▯ P £**  
Vanderbilt-Ingram Cancer Center

**William Mitchell, MD £ †**  
UC San Diego Moores Cancer Center

**Diane G. Portman, MD £**  
Moffitt Cancer Center

**David Spiegel, MD θ**  
Stanford Cancer Institute

**Linda Sutton, MD † £**  
Duke Cancer Institute

**Eytan Szmilowicz, MD £**  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

**Jennifer Temel, MD † £**  
Massachusetts General Hospital Cancer  
Center

**Jane Thomas, MD £**  
Dana-Farber Cancer Institute

**Susan G. Urba, MD † £**  
University of Michigan Rogel Cancer Center

**Finly Zachariah, MD £**  
City of Hope National Medical Center

**NCCN**  
**Mary Anne Bergman**  
**Jillian Scavone, PhD**

[NCCN Guidelines Panel Disclosures](#)

**Continue**

† Medical oncology	θ Psychiatry and psychology, including health behavior
‡ Hematology/Hematology oncology	ψ Neurology/Neuro-oncology
P Internal medicine	φ Anesthesiology
€ Pediatric oncology	▯ Geriatric medicine
£ Supportive care including palliative and pain management	* Discussion Section Writing Committee



### [NCCN Palliative Care Panel Members](#)

### [Summary of the Guidelines Updates](#)

### [Definition and Standards of Palliative Care \(PAL-1\)](#)

### [Palliative Care General Overview \(PAL-2\)](#)

### [Indications and Assessment by Oncology Team \(PAL-3\)](#)

### [Oncology Team Interventions and Reassessment \(PAL-6\)](#)

### [Criteria for Consultation with Palliative Care Specialist \(PAL-7\)](#)

### [Benefits/Burdens of Anticancer Therapy \(PAL-9\)](#)

### [Symptoms: Pain \(PAL-10\)](#)

### [Symptoms: Dyspnea \(PAL-11\)](#)

### [Symptoms: Anorexia/Cachexia \(PAL-13\)](#)

### [Symptoms: Nausea and Vomiting \(PAL-15\)](#)

### [Symptoms: Constipation \(PAL-17\)](#)

### [Symptoms: Diarrhea \(PAL-18\)](#)

### [Symptoms: Malignant Bowel Obstruction \(PAL-20\)](#)

### [Symptoms: Sleep/Wake Disturbances Including Insomnia and Sedation \(PAL-22\)](#)

### [Symptoms: Delirium \(PAL-23\)](#)

### [Social Support/Resource Management \(PAL-25\)](#)

### [Preparing Patients/Families/Caregivers for End-of-Life and Transition to Hospice Care \(PAL-27\)](#)

### [Advance Care Planning \(PAL-29\)](#)

### [Response to Requests for Hastened Death \(PAL-31\)](#)

### [Care of the Imminently Dying Hospitalized Patient \(PAL-32\)](#)

### [Palliative Sedation \(PAL-33\)](#)

### [After-Death Interventions \(PAL-34\)](#)

### [Palliative Care Drug Appendix \(PAL-A\)](#)

**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/clinicians.aspx](#).

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See [NCCN Categories of Evidence and Consensus](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2018.



Updates in Version 1.2019 of the NCCN Guidelines for Palliative Care from Version 1.2018 include:

### PAL-1

#### Definition of Palliative Care

- **Modified:** "Palliative care is an approach to patient/family/caregiver-centered health care that focuses on optimal management of ~~pain~~ and ~~other~~ distressing symptoms, while incorporating psychosocial and spiritual care according to patient/family/caregiver needs, values, beliefs, and cultures. The goal of palliative care is to anticipate, prevent, and reduce suffering and to support the best possible quality of life for patients/families/caregivers, regardless of the stage of the disease or the need for other therapies. Palliative care can begin at diagnosis and should be delivered concurrently with disease-directed, life-prolonging therapies and should facilitate patient autonomy, access to information, and choice. Palliative care becomes the main focus of care when disease-directed, life-prolonging therapies are no longer effective, appropriate, or desired. Palliative care should be *provided initiated* by the primary oncology team and then augmented as needed by collaboration with an interdisciplinary team of palliative care experts."

#### Standards of Palliative Care

- **Modified 5th bullet:** "Palliative care specialists and interdisciplinary palliative care teams, including board-certified palliative care physicians, advanced practice nurses, physician assistants, social workers, chaplains, and pharmacists, should be readily available to provide consultative or direct care to patients/families/caregivers *and/or health care professionals* who request or require their expertise."

### PAL-2

#### Reassessment

- **Modified 2nd bullet:** Adequate ~~pain~~ and symptom management (throughout the guidelines)
- **Modified 5th bullet:** ~~Decreased Relief of~~ caregiver burden (throughout the guidelines)

#### Footnotes

- Footnote "d" modified: "Patients with one or more positive indicators *may benefit from require* a care plan developed by an interdisciplinary team of physicians, nurses, social workers, mental health professionals, chaplains, advanced practice clinicians and dietitians."

### PAL-3

#### Indications

- **Modified 7th bullet, 10th sub-bullet:** "Palliative stenting or need for

venting gastrostomy."

### PAL-6

#### If unacceptable

Modified 2nd bullet: "Consult with a mental health professional *and/ or addiction specialist* to evaluate and treat undiagnosed psychiatric disorders, substance abuse, and inadequate coping methods"

### PAL-8

#### Assessment/Complex patient/family/caregiver circumstances

- 4th bullet, "*Substance abuse*" is new to the page
- Assessment/Oncology care team/staff challenges
- Modified 1st bullet: "Complex care coordination issues *within and among* multiple care teams"
- Modified 2nd bullet: "*Compromised* resilience including"
- Modified 3rd sub-bullet: "Burnout training"

### PAL-9

#### Interventions

- "Provide *primary palliative care, including anti-cancer treatment and disease-related symptom management and encouragement of advance care planning*" is a new bullet for years to months.
- Modified the last bullet for months to weeks as follows: "Offer ~~best~~ goal-directed supportive care, including referral to *specialized palliative care services* or hospice."

### PAL-11

#### Interventions

- Pharmacologic therapy has been modified as follows:
  - ~~Consider~~ Opioids
  - Consider benzodiazepines *if coexisting anxiety*

#### Footnotes

- "*The addition of benzodiazepines to opioids can increase the risk of respiratory depression*" is a new footnote corresponding to "Consider benzodiazepines if coexisting anxiety."

### PAL-12

#### Interventions

- "*Cooler temperatures*" was added to "fans" under nonpharmacologic therapies to relieve symptoms.

### PAL-13

#### If unacceptable

- Deleted: "Consider clinical trial"

**Updates in Version 1.2019 of the NCCN Guidelines for Palliative Care from Version 1.2018 include:****[PAL-14](#)****Interventions**

- 1st sub-bullet is new to the page for months to weeks: "Consider psychiatric consultation if patient has an eating disorder"
- Deleted the following bullets: "Provide family/caregiver(s) with alternate ways of caring for the patient" and "Treat reversible causes"

**[PAL-15](#)****Nausea and Vomiting/Interventions**

- Medication/Substance-induced, 2nd sub-bullet added: "Review use of marijuana/cannabis for possible cannabis-associated hyperemesis syndrome and counsel regarding cessation if indicated."

**[PAL-16](#)****Persistent Nausea and Vomiting/Interventions**

- *This page has been significantly modified*

**[PAL-17](#)****Constipation**

- Preventive Measures, 2nd sub-bullet: "Increase dose of laxative ~~± osmotic~~ laxative dose with goal of 1 non-forced bowel movement (BM) every 1–2 days"
- Constipation present, 6th bullet: "Add and titrate ~~bisacodyl~~ stimulant and/or osmotic laxative with a goal of 1 non-forced BM every 1–2 days"
- The following references are new to "Constipation":
  - ▶ Wickham RJ. Managing constipation in adults with cancer. J Adv Pract Oncol 2017;8(2):149-161.
  - ▶ Larkin PJ, Cherny NI, LaCarpia D, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018;29 (Suppl 4):iv111-iv125.

**[PAL-18](#)****Diarrhea**

- Interventions, Further Assessment, 3rd bullet: "~~CAUSE~~ Tailor treatment to potential causes."

**[PAL-19](#)****Antidiarrheal Interventions**

- 6th bullet: "GRADE 2:If chemotherapy-induced, *decrease or delay the next dose of chemotherapy*"
- 7th bullet, 4th sub-bullet: "[See Management of Immunotherapy Related Toxicity Guidelines](#) for immunotherapy-related diarrhea"

**[PAL-25](#)****Social Support/Resource Management**

- Interventions, 1st bullet modified: "Assess ~~Consider~~"
- 1st sub-bullet modified: "*Coping and adjustment to illness by patient/family/caregivers*"
- 6th sub-bullet: "~~Consider~~ *Culture-specific needs*"
- 2nd bullet: "*Obtain medical interpreters/translators as needed who are not related to the patient*" is new to the page.
- 4th bullet, 3rd sub-bullet: "*Art and music therapy, if available*"

**[PAL-29](#)****Advance Care Planning/Interventions**

- 2nd bullet: "Assess decision-making capacity and need for identify surrogate decision-maker *if necessary*"
- 3rd bullet: "Explore fears about *the future and provide emotional support dying and address anxiety*"
- 4th bullet: "Initiate discussion of personal values and care preferences ~~for end-of-life care~~"

**If unacceptable**

- 3rd bullet: "Refer to *specialized palliative care service* if the patient is having difficulty engaging in discussion of advance care planning"
- 5th bullet: "Consider *referral to spiritual care counselor*"

**[PAL-30](#)****Interventions**

- Months to weeks, modified last bullet as follows: "Explore fears about *dying and address concerns anxiety the future and provide emotional support*"
- Weeks to days (dying patient), modified last bullet as follows: "Encourage the patient/family/caregiver ~~to limit as appropriate to avoid CPR with the use of do not resuscitate (DNR)/do not attempt resuscitation (DNAR)/allow natural death (AND) orders~~"

**[PAL-31](#)****Response to Requests for Hastened Death**

- 10th bullet, 4th sentence: "Consider a consultation with an ethics committee, *specialized palliative care service*, or experienced colleague"

**[PAL-32](#)****Care of the Imminently Dying Hospitalized Patient****Physical**

- 11th sub-bullet: "*Treat delirium (See PAL-24)*"
- 12th sub-bullet: "Consider palliative sedation ~~treat for~~ refractory restlessness and agitation ~~with palliative sedation (See PAL-33)~~"



Updates in Version 1.2019 of the NCCN Guidelines for Palliative Care from Version 1.2018 include:

### [PAL-32 \(continued\)](#)

#### Care of the Imminently Dying Hospitalized Patient

##### Psychosocial

- 3rd sub-bullet deleted: "Allow the patient/family/caregiver to have uninterrupted time together and encourage continued communication"

##### Practical

- 3rd sub-bullet: "Discuss and document patient/family/caregiver wishes for resuscitation. In the event that CPR is unlikely to be effective, recommend other options such as do not resuscitate (DNR)/ do not attempt resuscitation (DNAR)/ allow natural death (AND) orders and promoting comfort care."
- Sub-bullet deleted: "If the patient/family/caregiver have not documented a DNAR order, intensify patient/family/caregiver education, counsel on the importance of a DNAR or AND order"

### [PAL-33](#)

#### Palliative Sedation

- Reordered the following bullets:
  - *Palliative sedation to unconsciousness, in which the intended effect is deep sedation, remains controversial.*
  - *Refractory symptoms are symptoms that cannot be adequately managed despite comprehensive, interdisciplinary palliative care that does not compromise consciousness.*
- Confirm that the patient has refractory symptoms and is imminently dying.
  - ▶ *Imminently dying patients have a prognosis of hours to days. If palliative sedation is being considered, prognosis should be confirmed by two physicians.*
- 4th bullet, 4th sub-bullet modified: ~~Explain that consent for palliative sedation in some cases requires must be accompanied by consent for:~~ Discontinuation of life-prolonging therapies (such as artificial hydration/nutrition and/or withholding of cardiopulmonary resuscitation) *often accompanies palliative sedation.*

### [PAL-A \(1 of 5\)](#)

#### Secretions

- Modified: "Scopolamine, 0.4 mg SC q4h PRN/1.5 mg patches, 1–3 patches q 72 hours..."
- *Route of administration has been clarified throughout the guidelines.*

### [PAL-A \(2 of 5\)](#)

#### Nausea and Vomiting (NV)-Initial Treatment

- Modified: "Haloperidol, 0.5 mg PO TID OR metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime OR prochlorperazine, 5–10 mg PO 3–4 times/d, maximum 40 mg/d OR olanzapine, 5–10 mg PO 2–3 times/d OR ondansetron, 4 mg PO q4h or 8 mg PO q8h"

#### Nausea and Vomiting (NV)-Initial Treatment

- Modified: "Prescribe oral, sublingual, or rectal agent and titrate to maximum benefit; ~~consider opioid rotation~~"
- Modified: "If NV persists, provide ~~IV administration~~ PRN, scheduled, or continuous parenteral infusion as necessary"
- Deleted: "If NV persists, provide scheduled IV administration or continuous infusion"
- Added: "Consider subcutaneous administration as an alternative"

#### Constipation

- Modified: "Prophylaxis: *Titrate the senna and add polyethylene glycol, recommend starting with polyethylene glycol if the patient is not on opioids and can tolerate the volume of liquid*"

### [PAL-A \(3 of 5\)](#)

#### Diarrhea

- Deleted: "Consider scopolamine, 0.4 mg SC every 4 h PRN"
- Added: "Atropine 0.5–1 mg SC/IV/SL q 4–6h PRN"

### [PAL-A \(5 of 5\)](#)

#### Delirium

- Modified: "Upward titrate haloperidol, risperidone or olanzapine ~~or quetiapine fumarate~~"





### **Definition of Palliative Care<sup>a,c</sup>**

**Palliative care is an approach to patient/family/caregiver-centered health care that focuses on optimal management of distressing symptoms, while incorporating psychosocial and spiritual care according to patient/family/caregiver needs, values, beliefs, and cultures. The goal of palliative care is to anticipate, prevent, and reduce suffering and to support the best possible quality of life for patients/families/caregivers, regardless of the stage of the disease or the need for other therapies. Palliative care can begin at diagnosis and should be delivered concurrently with disease-directed, life-prolonging therapies and should facilitate patient autonomy, access to information, and choice. Palliative care becomes the main focus of care when disease-directed, life-prolonging therapies are no longer effective, appropriate, or desired. Palliative care should be provided by the primary oncology team and augmented as needed by collaboration with an interdisciplinary team of palliative care experts.**

### **Standards of Palliative Care<sup>b,c</sup>**

- **Institutions should develop processes for integrating palliative care into cancer care, both as part of usual oncology care and for patients with specialty palliative care needs.**
- **All cancer patients should be screened for palliative care needs at their initial visit, at appropriate intervals, and as clinically indicated.**
- **Patients/families/caregivers should be informed that palliative care is an integral part of their comprehensive cancer care.**
- **Educational programs should be provided to all health care professionals and trainees so that they can develop effective palliative care knowledge, skills, and attitudes.**
- **Palliative care specialists and interdisciplinary palliative care teams, including board-certified palliative care physicians, advanced practice nurses, physician assistants, social workers, chaplains, and pharmacists, should be readily available to provide consultative or direct care to patients/families/caregivers and/or health care professionals who request or require their expertise.**
- **Quality of palliative care should be monitored by institutional quality improvement programs.**

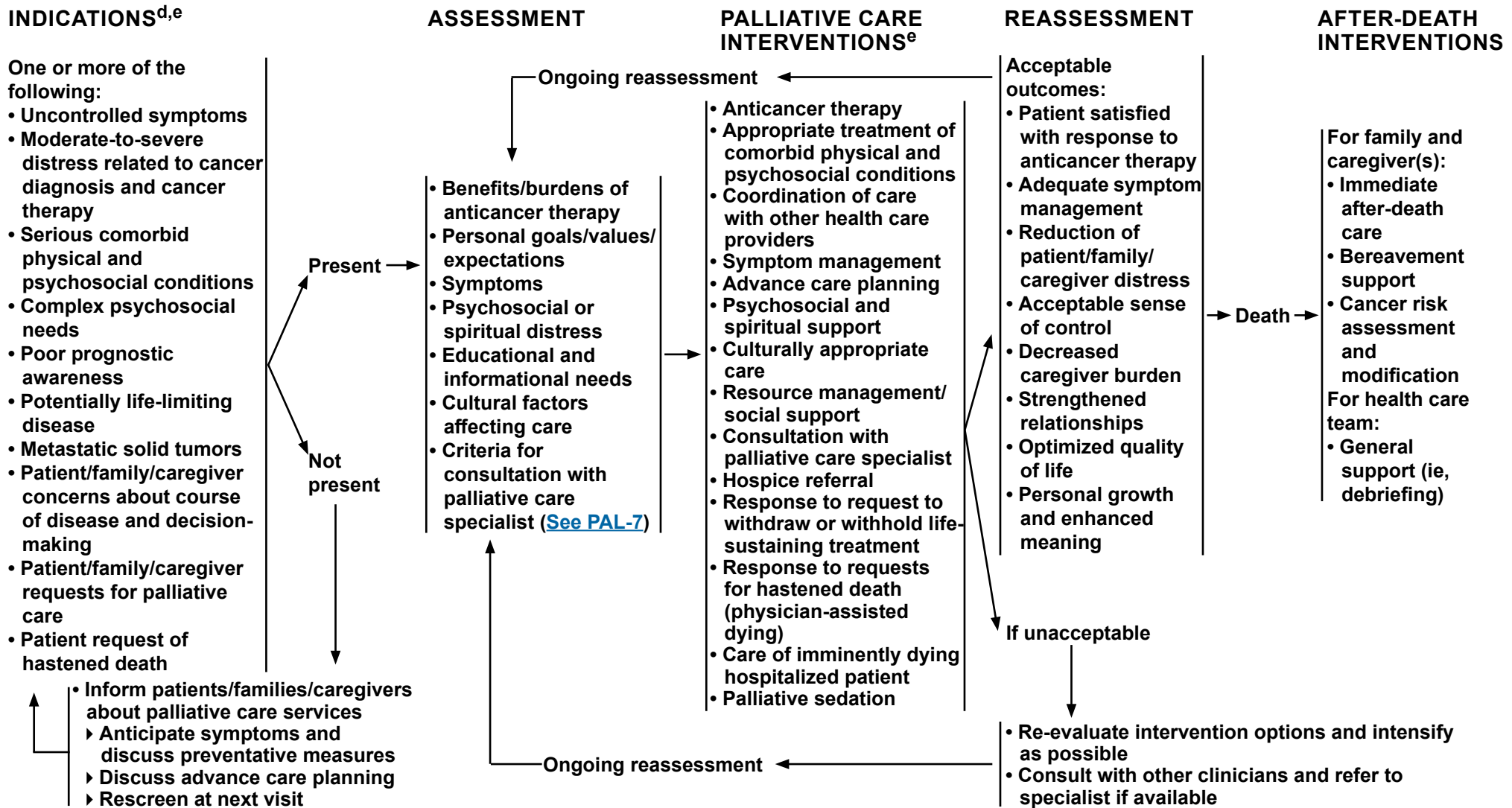
<sup>a</sup>Hui D, Mori M, Parsons HA, et al. The lack of standard definitions in supportive and palliative oncology literature. *J Pain Symptom Manage* 2012;43:582-592.

<sup>b</sup>Ferris FD, Bruera E, Cherry N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps – from the American Society of Clinical Oncology. *J Clin Oncol* 2009;27:3052-3058.

<sup>c</sup>IOM (Institute of Medicine). 2014 *Dying in America: Improving quality and honoring individual preferences near the end of life*. Washington, DC: The National Academies Press. ([www.nap.edu/read/18748/chapter/1](http://www.nap.edu/read/18748/chapter/1))

**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



<sup>d</sup>Patients with one or more positive indicators may benefit from a care plan developed by an interdisciplinary team of physicians, nurses, social workers, mental health professionals, chaplains, advanced practice clinicians, and dietitians.

<sup>e</sup>Oncologists should integrate palliative care into general oncology care. Early consultation/collaboration with a palliative care specialist/hospice team should be considered to improve quality of life and survival.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Assessment by Oncology Team \(PAL-3\)](#)





### INDICATIONS<sup>d,e</sup>

- Uncontrolled symptoms  
or
- Moderate-to-severe distress related to cancer diagnosis and/or cancer therapy  
or
- Serious comorbid physical, psychiatric, and psychosocial conditions  
or
- Patient/family/caregiver concerns about course of disease and decision-making  
or
- Patient/family/caregiver requests for palliative care  
or
- Metastatic solid tumors and refractory hematologic malignancies
- Additional indicators may include:
  - ▶ Poor performance status ECOG ≥3 or KPS ≤50
  - ▶ Persistent hypercalcemia
  - ▶ Brain or cerebrospinal fluid metastasis
  - ▶ Delirium
  - ▶ Malignant bowel obstruction
  - ▶ Superior vena cava syndrome
  - ▶ Spinal cord compression
  - ▶ Cachexia
  - ▶ Malignant effusions
  - ▶ Palliative stenting or need for venting gastrostomy
- Potentially life-limiting disease

### ASSESSMENT BY ONCOLOGY TEAM

- Benefits/burdens of anticancer therapy → [See PAL-4 and PAL-5](#)
- Symptoms
- Psychosocial distress
  
- Personal goals/values/expectations → [See PAL-4 and PAL-5](#)
- Educational and informational needs
- Cultural factors affecting care
  
- Criteria for consultation with a palliative care specialist → [See PAL-7](#)

Present

Not present

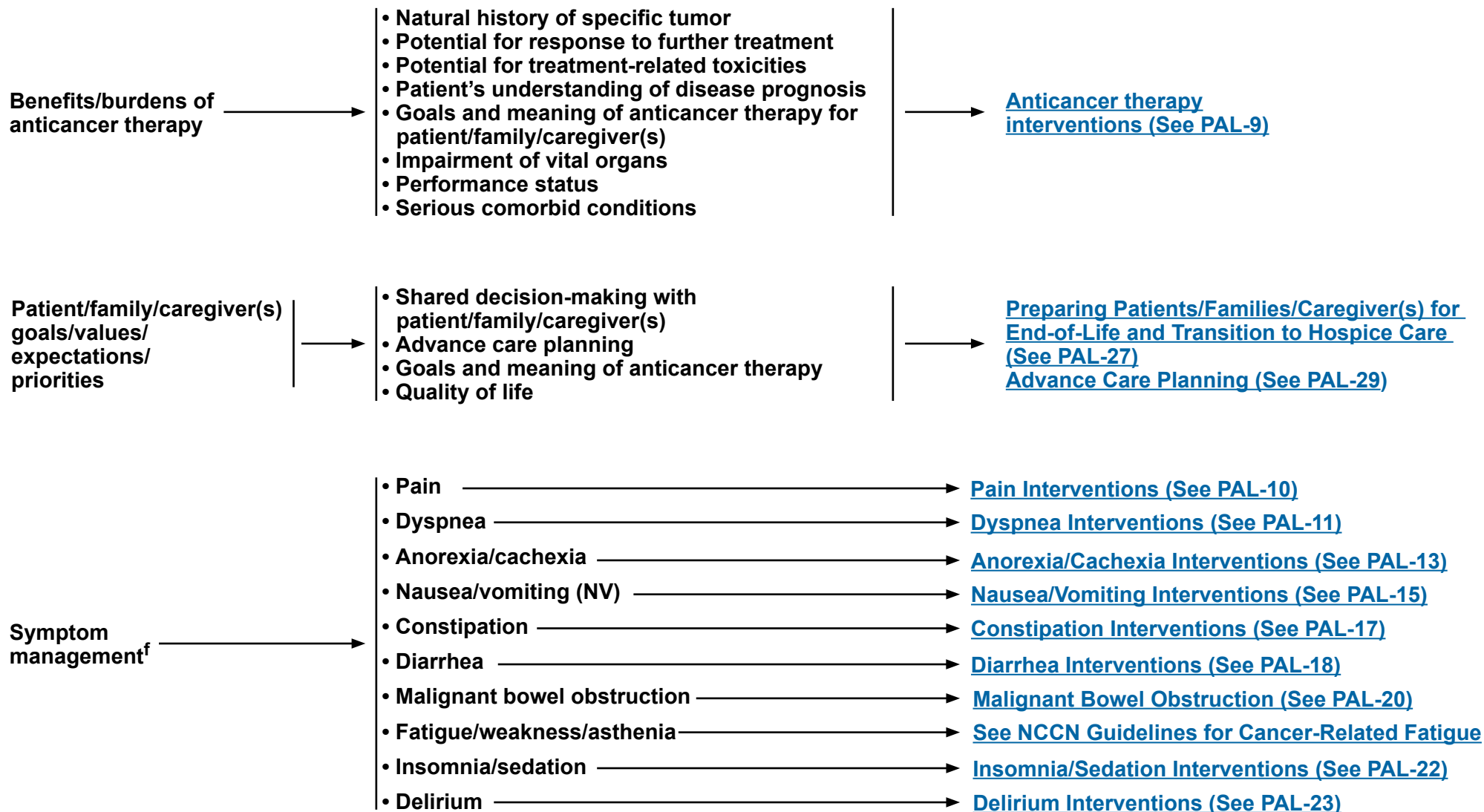
- Inform the patient/family/caregiver about palliative care services
  - ▶ Anticipate symptoms and discuss preventative measures
  - ▶ Discuss advance care planning
  - ▶ Rescreen at next visit

<sup>d</sup>Patients with one or more positive indicators may benefit from a care plan developed by an interdisciplinary team of physicians, nurses, social workers, mental health professionals, chaplains, advanced practice clinicians, and dietitians.

<sup>e</sup>Oncologists should integrate palliative care into general oncology care. Early consultation/collaboration with a palliative care specialist/hospice team should be considered to improve quality of life and survival.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

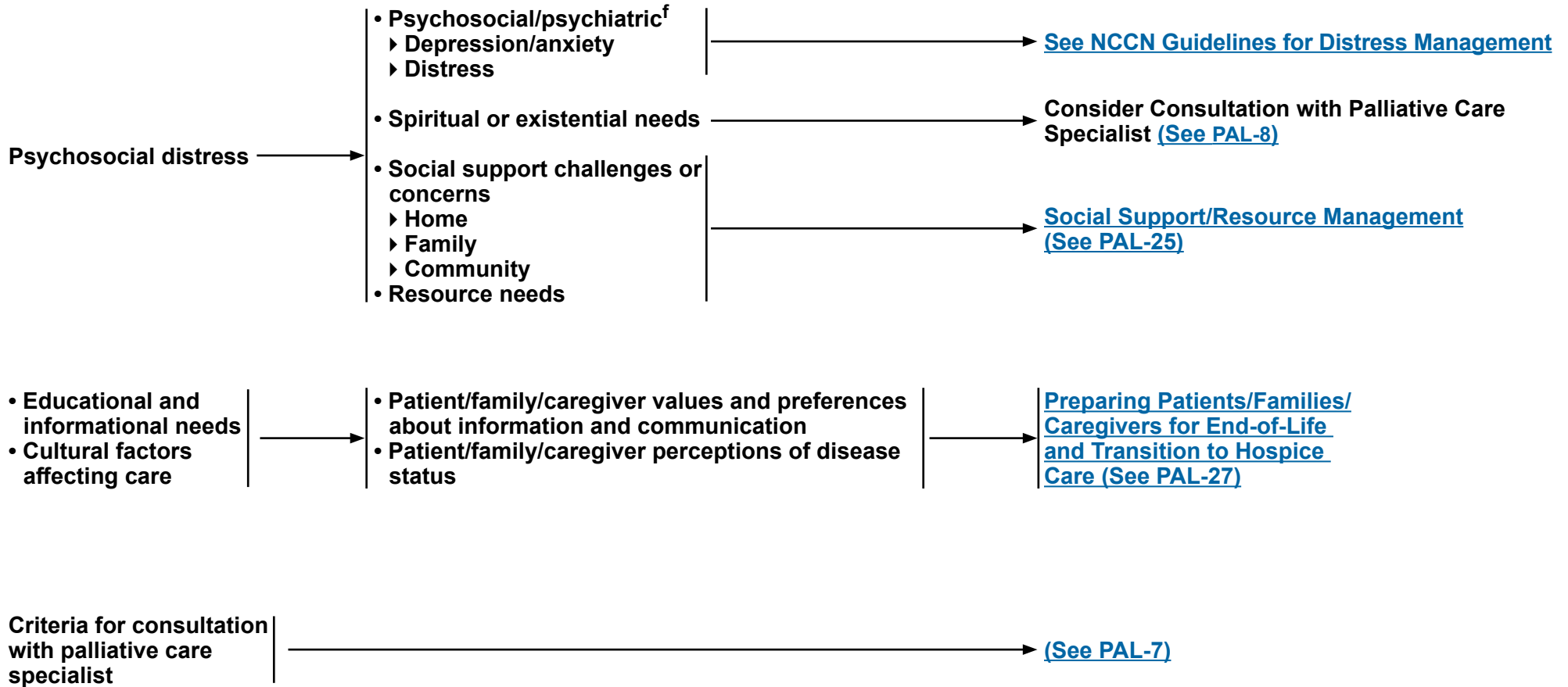
### ASSESSMENT BY ONCOLOGY TEAM



<sup>f</sup>Look for opportunities to use single agents to treat multiple symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

### ASSESSMENT BY ONCOLOGY TEAM



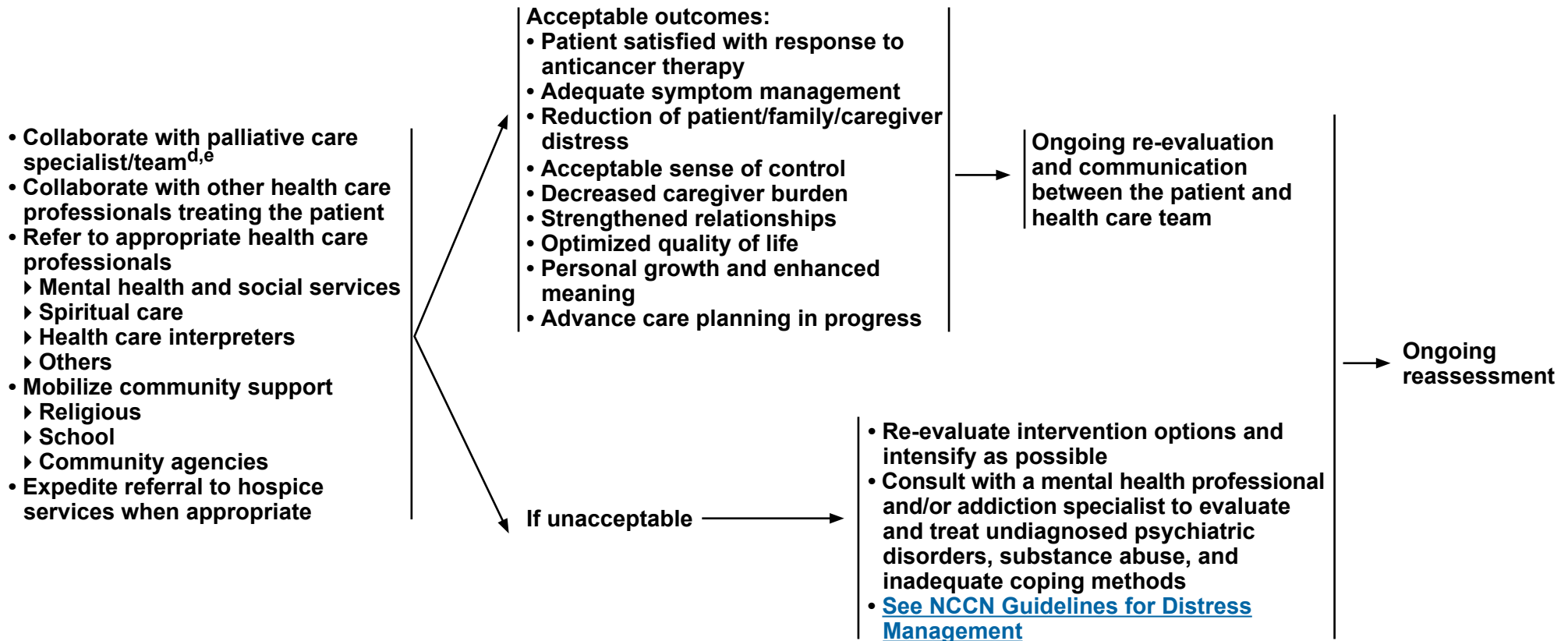
<sup>f</sup>Look for opportunities to use single agents to treat multiple symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### ONCOLOGY TEAM INTERVENTIONS

### REASSESSMENT



<sup>d</sup>Patients with one or more positive indicators may benefit from a care plan developed by an interdisciplinary team of physicians, nurses, social workers, mental health professionals, chaplains, advanced practice clinicians, and dietitians.

<sup>e</sup>Oncologists should integrate palliative care into general oncology care. Early consultation/collaboration with a palliative care specialist/hospice team should be considered to improve quality of life and survival.

**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



**CRITERIA FOR CONSULTATION WITH PALLIATIVE CARE SPECIALIST ASSESSMENT**

Patient characteristics →

- Patient with life-limiting cancer diagnosis
- Limited anticancer treatment options due to:
  - ▶ Limited access to anticancer treatment
  - ▶ Advanced disease process
  - ▶ Multiple and/or severe comorbid conditions
  - ▶ Rapidly progressive functional decline or persistently poor performance status
- Need for clarification of goals of care
- Resistance to engage in advance care planning
- High risk of poor pain management or pain that remains resistant to conventional interventions, eg:
  - ▶ Neuropathic pain
  - ▶ Incident or breakthrough pain
  - ▶ Pain with severe associated psychosocial and/or family distress
  - ▶ Rapid escalation of opioid dose
  - ▶ Multiple drug “allergies” or a history of multiple adverse reactions to pain and symptom management interventions
  - ▶ Concerns regarding drug or alcohol abuse — see addiction specialist as needed ([See NCCN Guidelines for Adult Cancer Pain](#))
- High non-pain symptom burden, especially those resistant to conventional management ([See PAL-4](#) for symptoms)
- High distress score (>4) ([See NCCN Guidelines for Distress Management](#))
- Need for invasive procedures (eg, palliative stenting or venting gastrostomy)
- Frequent emergency department visits or hospital admissions
- Need for ICU-level care (especially involving multi-organ system failure or prolonged mechanical support)
- Communication barriers
  - ▶ Language
  - ▶ Literacy
  - ▶ Physical barriers
  - ▶ Cognitive impairment
- Request for hastened death

→ [See Oncology Team Interventions \(PAL-6\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)



### CRITERIA FOR CONSULTATION WITH PALLIATIVE CARE SPECIALIST

#### ASSESSMENT

Complex patient/family/caregiver circumstances

- Family/caregiver challenges
- High risk for persistent complex bereavement disorder<sup>9</sup>
- Inadequate social support
- Substance abuse
- Intensely dependent relationship(s)
- Financial limitations
- Limited access to care
- Family discord
- Spiritual or existential crisis
- Unresolved or multiple prior losses
- Patient's concerns regarding family/caregiver well-being
  - Dependent children and/or older relatives requiring care living in the household

[See  
Oncology  
Team  
Interventions  
\(PAL-6\)](#)

Oncology care team/staff challenges

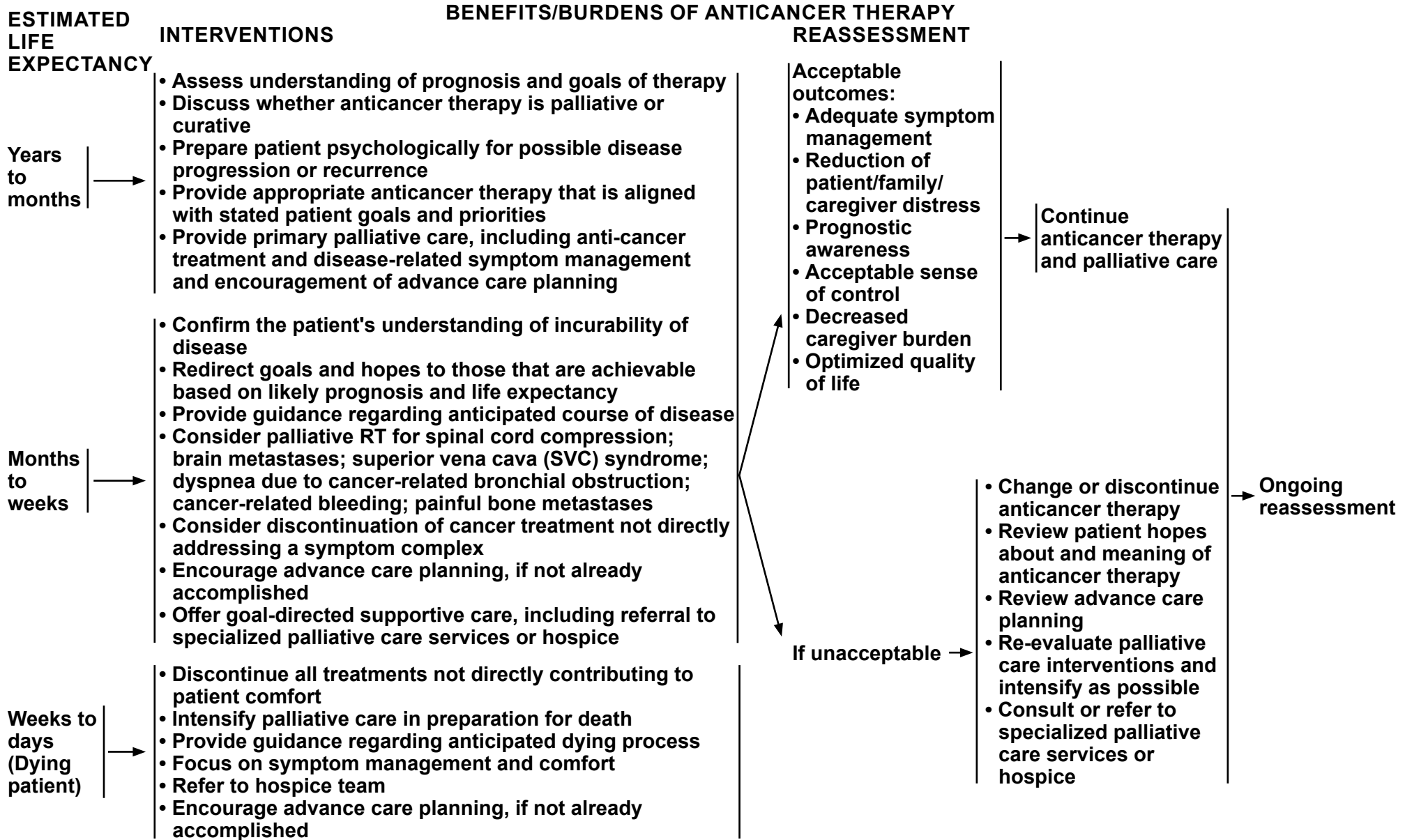
- Complex care coordination issues within and among multiple care teams
- Compromised resilience including:
  - Compassion fatigue
  - Moral distress
  - Burnout

<sup>9</sup>Persistent complex bereavement disorder is a chronic heightened state of mourning that significantly impairs functioning.

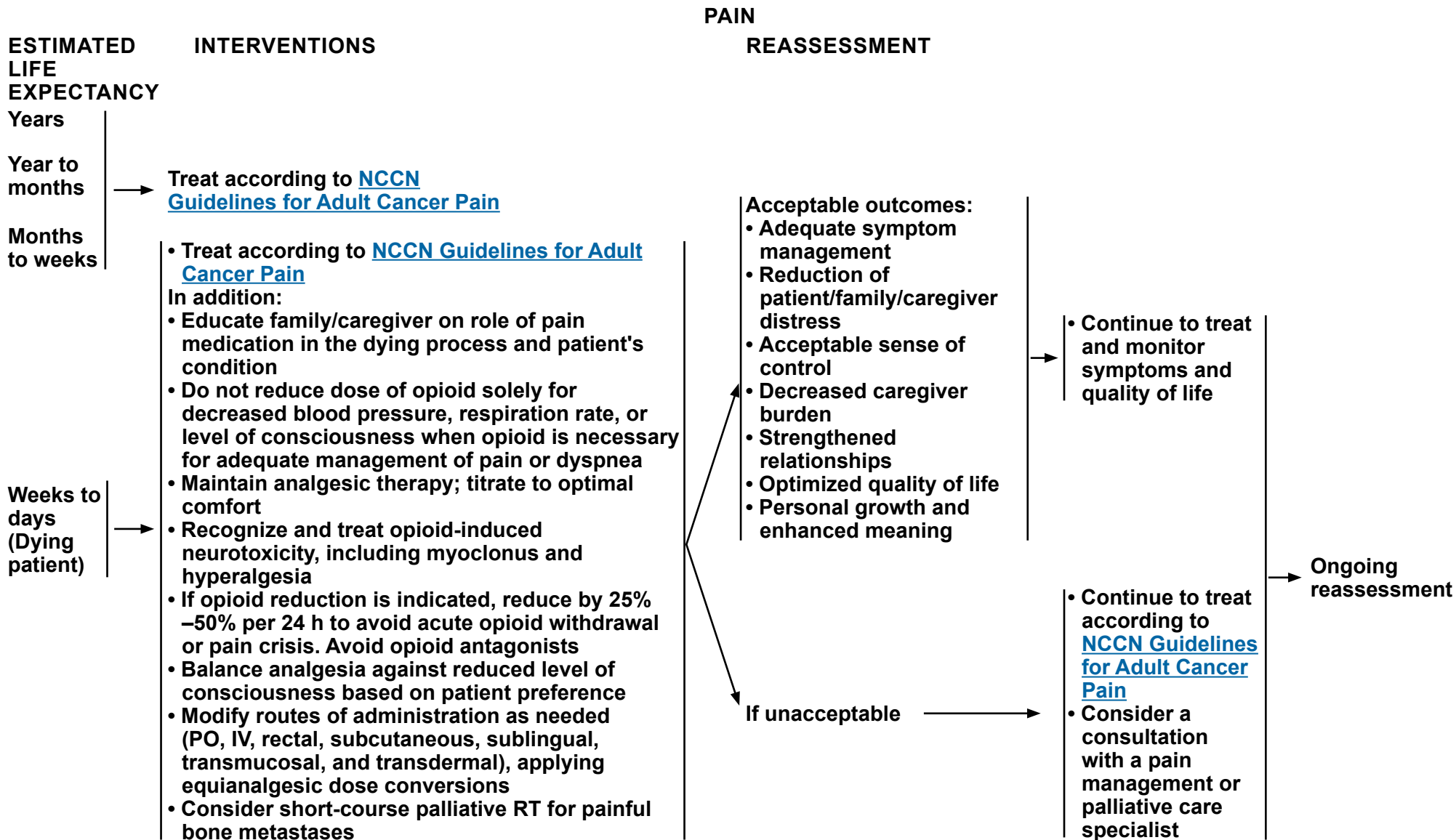
**Note: All recommendations are category 2A unless otherwise indicated.**

**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

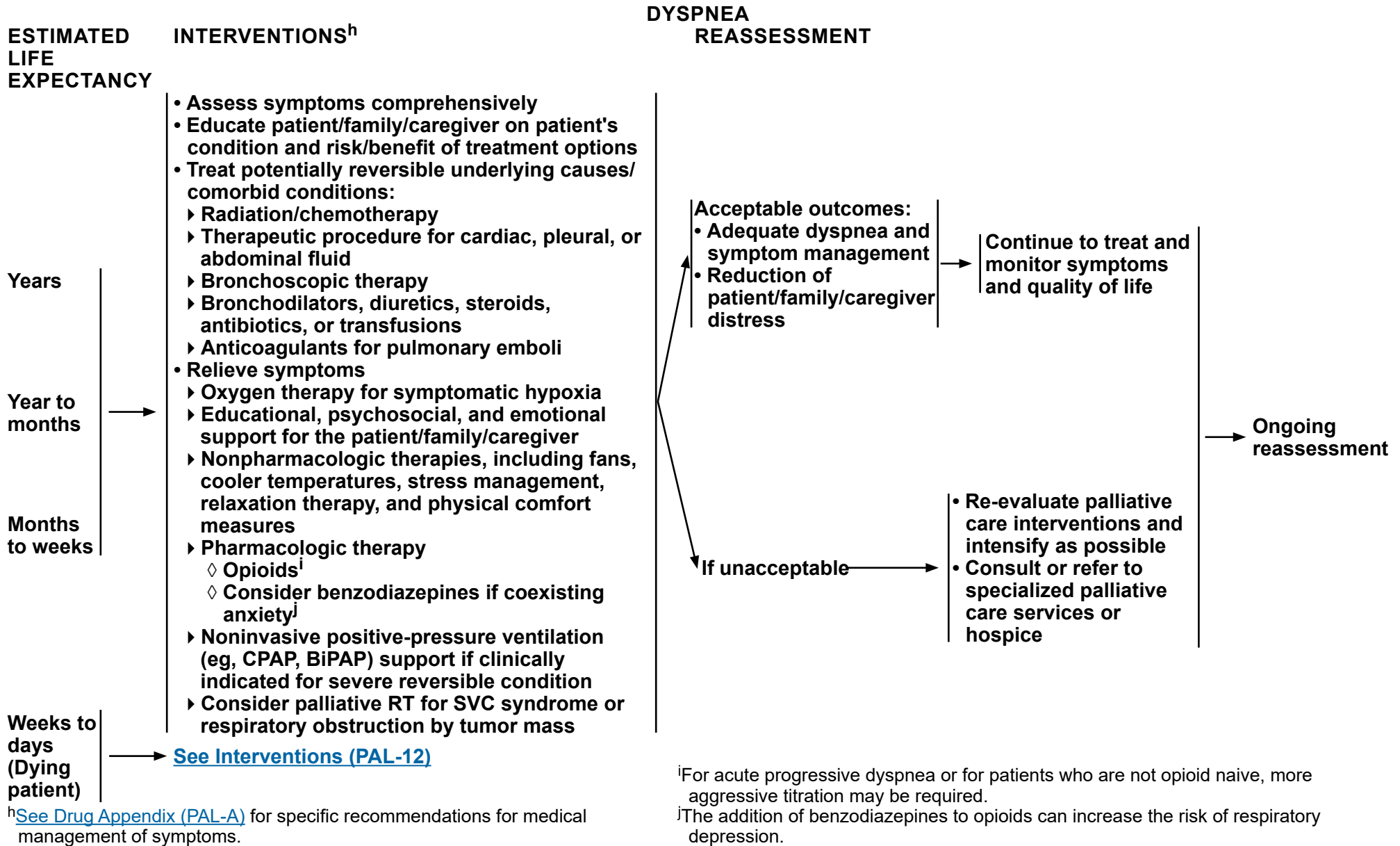




**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

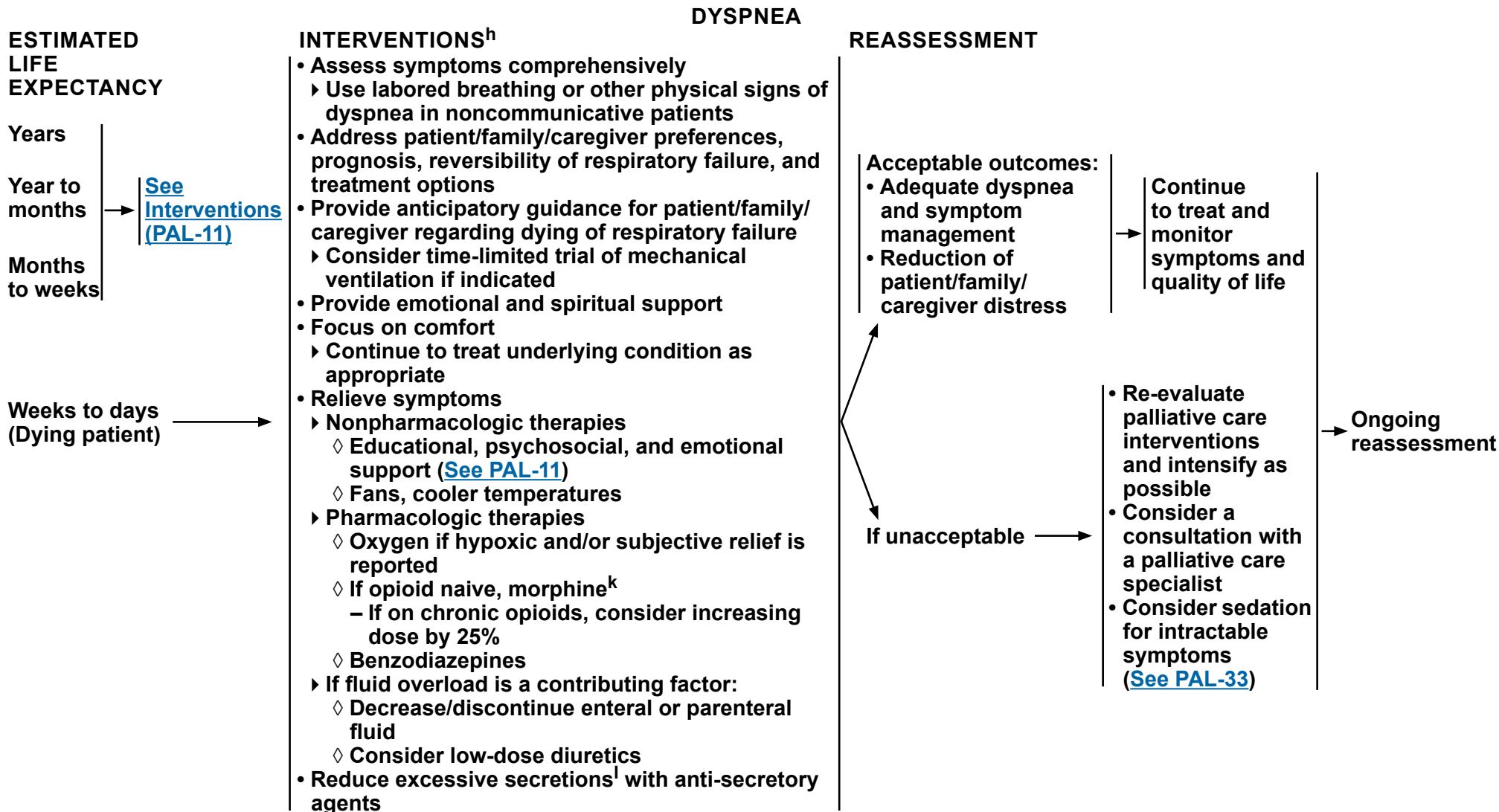


<sup>h</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

<sup>i</sup>For acute progressive dyspnea or for patients who are not opioid naive, more aggressive titration may be required.

<sup>j</sup>The addition of benzodiazepines to opioids can increase the risk of respiratory depression.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



<sup>h</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

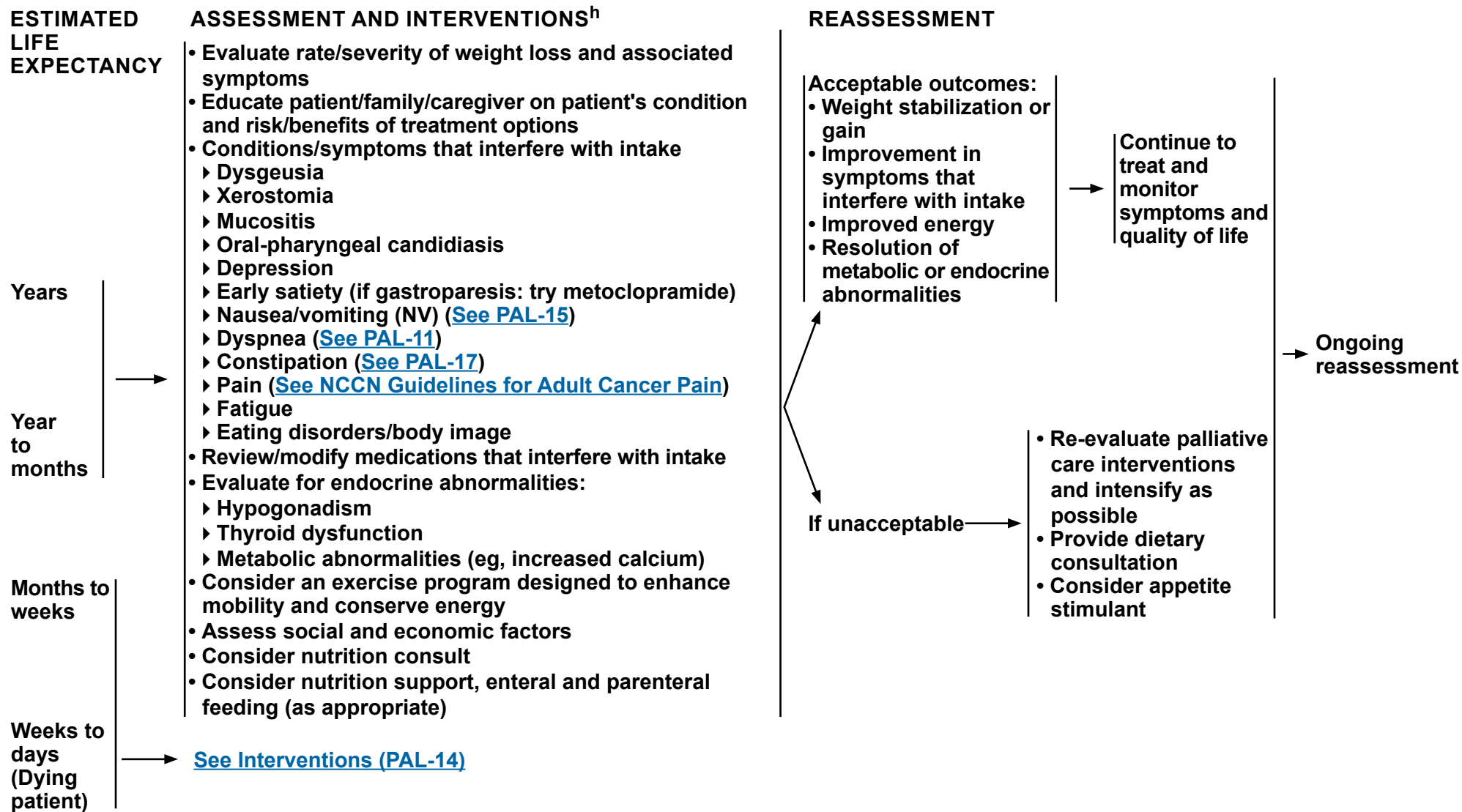
<sup>k</sup>For acute progressive dyspnea or for patients who are not opioid naive, more aggressive titration may be required.

<sup>l</sup>Hughes A, et al. Audit of three antimuscarinic drugs for managing retained secretions. Palliat Med 2000;14:221-222.

**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



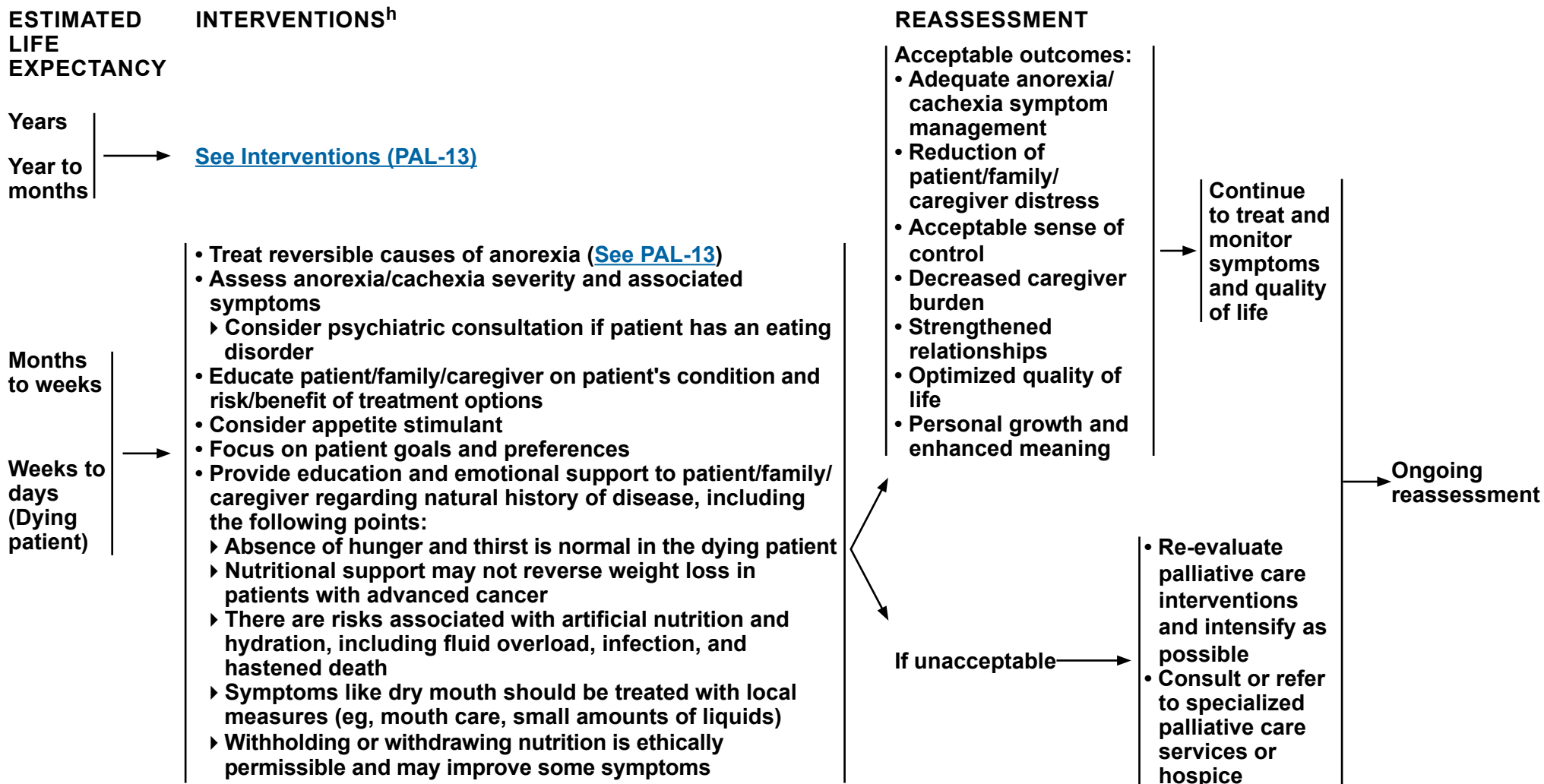
### ANOREXIA/CACHEXIA



<sup>h</sup>See [Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**ANOREXIA/CACHEXIA**



<sup>h</sup>See [Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.





### NAUSEA AND VOMITING

#### INTERVENTIONS<sup>h</sup>

- Assess NV severity and associated symptoms
- Educate patient/family/caregivers on patient's condition and treatment options
- Chemotherapy/radiation therapy-induced  
([See NCCN Guidelines for Antiemesis](#))
- Severe constipation/fecal impaction  
([See PAL-17](#))
- Gastroparesis
  - ▶ Prokinetic agent
- Bowel obstruction ([See PAL-20](#))
- Central nervous system (CNS) involvement
  - ▶ Corticosteroids
  - ▶ Palliative radiation therapy
- Gastric outlet obstruction from intra-abdominal tumor or liver metastasis
  - ▶ Consider treatment with corticosteroids, a proton pump inhibitor, and metoclopramide
  - ▶ Endoscopic stenting
  - ▶ Decompressing G-Tube
- Gastritis/GERD
  - ▶ Proton pump inhibitor
  - ▶ H2-blocker
- Treat other causes (hypercalcemia, uremia, dehydration)

- Medication/substance-induced
  - ▶ Review medication list, including non-prescribed supplements and herbs, and discontinue any unnecessary medications
  - ▶ Review use of marijuana/cannabis for possible cannabis-associated hyperemesis syndrome and counsel regarding cessation if indicated.
  - ▶ Check available blood levels of necessary medications (eg, digoxin, phenytoin, carbamazepine, tricyclic antidepressants)
  - ▶ Treat medication-induced gastropathy (eg, proton pump inhibitor, prokinetic agent)
  - ▶ Consider rotating and/or reducing opioid requirement with non-nauseating coanalgesics or procedural interventions
- Psychogenic
  - ▶ Consider psychiatric consultation if patient has an eating disorder, somatization, phobia, or panic disorder causing NV. [See NCCN Guidelines for Distress Management](#)
- Non-specific NV
  - ▶ Initiate pharmacologic management with dopamine receptor antagonists or 5-HT<sub>3</sub> receptor antagonists
  - ▶ If anxiety contributes to NV, consider adding benzodiazepine
  - ▶ If vertiginous component, consider anticholinergic/antihistamine
  - ▶ Consider non-pharmacologic therapies, such as acupuncture, hypnosis, and cognitive behavioral therapy

If NV stops:  
[See Reassessment \(PAL-16\)](#)

If NV persists:  
[See Interventions \(PAL-16\)](#)

<sup>h</sup>[See Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### PERSISTENT NAUSEA AND VOMITING

#### INTERVENTIONS<sup>h,m,n</sup>

- Titrate dopamine antagonist to maximum benefit and tolerance.
- For continued NV, consider additional drug classes with potential antiemetic properties: [See drug appendix \(PAL-A\)](#)
  - ▶ Corticosteroid
  - ▶ 5-HT3 antagonist
  - ▶ Antipsychotic
  - ▶ Anticholinergic
  - ▶ Antihistamine
  - ▶ Oral cannabinoid
  - ▶ Antidepressant (mirtazapine)
- Consider appropriate route of administration
  - ▶ Prescribe oral, sublingual, or rectal agent and titrate to maximum benefit; consider opioid rotation
  - ▶ If NV persists, provide PRN, scheduled, or continuous parenteral infusion as necessary
  - ▶ Consider subcutaneous administration as an alternative

#### REASSESSMENT

- Acceptable outcomes:
- Adequate NV symptom management
  - Reduction of patient/family/caregiver distress
  - Acceptable sense of control
  - Decreased caregiver burden
  - Optimized quality of life

Continue to treat and monitor symptoms and quality of life

If unacceptable

- Re-evaluate palliative care interventions and intensify as possible
- Consult or refer to specialized palliative care services or hospice
- Consider palliative sedation ([See PAL-33](#))

[Ongoing reassessment \(See Interventions, PAL-15\)](#)

<sup>h</sup>[See Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

<sup>m</sup>An around-the-clock dosing schedule may provide the most consistent benefit to the patient.

<sup>n</sup>Continuous intravenous or subcutaneous infusions of different antiemetics may be necessary for the management of intractable NV.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

### INTERVENTIONS<sup>h</sup> CONSTIPATION<sup>1,2</sup>

- If constipation is present:**
- Educate patient/family/caregivers on patient's condition and treatment options
  - Assess for cause and severity of constipation
    - Discontinue any non-essential constipating medication
  - Rule out impaction, especially if diarrhea accompanies constipation (overflow around impaction)
  - Rule out obstruction (physical exam, abdominal x-ray/ consider GI consult)
  - Treat other causes (eg, hypercalcemia, hypokalemia, hypothyroidism, diabetes mellitus, medications)
  - Add and titrate stimulant and/or osmotic laxative
- If impacted:**
- Administer glycerine suppository ± mineral oil retention enema<sup>o</sup>
  - Perform manual disimpaction following pre-medication with analgesic ± anxiolytic
- If constipation persists:**
- Reassess for cause and severity of constipation
  - Recheck for impaction or obstruction
  - Consider adding other laxatives
  - Consider peripherally acting mu-opioid receptor antagonist (PAMORA) for opioid-induced constipation
    - Avoid if concern for post-op ileus and/or mechanical bowel obstruction
  - Administer tap water enema until clear
  - Consider use of a prokinetic agent

- Preventive measures<sup>h</sup>**
- Increase fluids
  - Increase dietary fiber if patient has adequate fluid intake and physical activity
  - Exercise, if appropriate
  - Administer prophylactic medications
    - Stimulant laxative ± osmotic laxative
    - Increase laxative dose with goal of 1 non-forced bowel movement (BM) every 1–2 days

### REASSESSMENT

- Acceptable outcomes:**
- Adequate constipation symptom management
  - Reduction of patient/family/caregiver distress

Continue to treat and monitor symptoms and quality of life

If unacceptable

- Re-evaluate palliative care interventions and intensify as possible
- Consult or refer to specialized palliative care services or hospice

Ongoing reassessment

<sup>h</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

<sup>o</sup>Use suppository and enema with caution in patients receiving chemotherapy due to risk of cytopenia.

<sup>1</sup>Wickham RJ. Managing constipation in adults with cancer. J Adv Pract Oncol 2017;8(2):149-161.

<sup>2</sup>Larkin PJ, Cherny NI, LaCarpia D, et al. Diagnosis, assessment and management of constipation in advanced cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2018; 29 (Suppl 4):iv111-iv125.

**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

**DIARRHEA**

**INTERVENTIONS/FURTHER ASSESSMENT**

**SCREENING AND ASSESSMENT**

- Evaluate diarrhea severity and cause
- Educate patient/family/caregiver on condition and treatment options

**SEVERITY**

Determine Diarrhea Grade<sup>P</sup>

- **Grade 1:** Increase of <4 stools/day over baseline; mild increase in ostomy output
- **Grade 2:** Increase of 4–6 stools/day over baseline; moderate increase in ostomy output
- **Grade 3:** Increase of >7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output; limiting self-care; interferes with activities of daily living (ADLs)
- **Grade 4:** Life-threatening consequences; urgent intervention indicated



- Provide immediate antidiarrheal therapy indicated by grade
- If chemotherapy induced, decrease or delay the next dose of chemotherapy
- Tailor treatment to potential causes
  - ▶ IBS/Crohn's disease
  - ▶ Post-surgical/anatomic changes (ie, short bowel syndrome)
  - ▶ Recent antibiotic use
  - ▶ Chemotherapy regimen
  - ▶ RT side effects
- OR
- Radiation-induced enteritis or other adverse effects
  - ▶ Drugs that frequently induce diarrhea
  - ▶ GVHD and/or immunotherapy-related colitis
  - ▶ Pancreatic insufficiency in pancreatic cancer
  - ▶ Dietary changes
  - ▶ Infection
    - ◊ Screen for C. diff, HIV, and other comorbid infections (ie, ova/parasites)
- If fecal impaction is suspected, [See PAL-17](#)



See Anti-Diarrheal Interventions, Grades 1-4 ([PAL-19](#))

PNCI Table 3: [http://www.cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional/page5#section\\_5.8](http://www.cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional/page5#section_5.8)

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**ANTIDIARRHEAL INTERVENTIONS**

**SCREENING**

**INTERVENTION<sup>h</sup>**

- Provide immediate antidiarrheal therapy indicated by grade

<p><b>GRADE 1</b> →</p>	<ul style="list-style-type: none"> <li>• If chemotherapy induced, decrease or delay the next dose of chemotherapy</li> <li>• Provide oral hydration and electrolyte replacement</li> <li>• Initiate antidiarrheal (eg, diphenoxylate/atropine) if patient not already on opioids</li> </ul>
<p><b>GRADE 2</b> →</p>	<ul style="list-style-type: none"> <li>• Provide IV fluids if patient is unable to tolerate oral fluids</li> <li>• Initiate/continue antidiarrheal—as above</li> <li>• Consider anticholinergic agents</li> <li>• If non-C.diff infection-related: Treat with appropriate antibiotics</li> <li>• If C. diff infection-related: Administer antibiotics and probiotics as appropriate</li> <li>• If chemotherapy-induced, decrease or delay the next dose of chemotherapy</li> <li>• If immunotherapy-mediated diarrhea, consider                         <ul style="list-style-type: none"> <li>▶ Corticosteroids</li> <li>▶ Infliximab</li> <li>▶ Probiotics</li> <li>▶ <a href="#">See Management of Immunotherapy Related Toxicity Guidelines</a> for immunotherapy-related diarrhea</li> </ul> </li> </ul>
<p><b>GRADES 3/4</b> →</p>	<ul style="list-style-type: none"> <li>• Inpatient hospitalization (intensive care for Grade 4 if consistent with goals)</li> <li>• For GVHD diarrhea, consider limiting diet, steroids, and IV nutrition</li> <li>• Provide IV fluids and use antidiarrheal agents and anticholinergics as mentioned above</li> <li>• Consider somatostatin analog</li> <li>• Consider parenteral hydration in home setting</li> </ul>

<sup>h</sup>[See Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



### MALIGNANT BOWEL OBSTRUCTION<sup>q</sup>

#### ESTIMATED LIFE EXPECTANCY

#### ASSESSMENT

Years

Year to  
months

- Evaluate severity and cause(s) of malignant bowel obstruction
- Educate patient/family/caregivers on patient's condition and treatment options
- Screen for and treat underlying potentially reversible causes
  - Adhesions
  - Radiation-induced strictures
  - Internal hernias
- Assess for malignant causes
  - Tumor mass
  - Carcinomatosis
- Assess the goals of treatment for the patient, which can help guide the intervention<sup>r</sup> (eg, decrease NV, allow patient to eat, decrease pain, allow patient to go home/to hospice)
- Consider patient prognosis and relative invasiveness of intervention proposed and incorporate life-span post procedure

[See  
Procedural  
Interventions  
\(PAL-21\)](#)

Months  
to weeks

Weeks to  
days  
(Dying  
patient)

- Consider medical management rather than surgical management
- Assess the goals of treatment for the patient, which can help guide the intervention<sup>r</sup> (eg, decrease NV, allow patient to eat, decrease pain, allow patient to go home/to hospice)
- Provide education and support to patient/family/caregiver

- Pharmacologic management
- Intravenous or subcutaneous fluids
- Enteral tube drainage
  - Consider only if other measures fail to reduce vomiting
- Endoscopic management

[See  
\(PAL-21\)](#)

<sup>q</sup>Plain film radiography may be helpful in confirming the clinical diagnosis of bowel obstruction. Consider a CT scan if surgical intervention is contemplated, as it is more sensitive and may help identify the cause of obstruction.

<sup>r</sup>Most malignant bowel obstructions are partial, allowing time to discuss appropriate intervention with the patient/family/caregiver.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.





### MALIGNANT BOWEL OBSTRUCTION

#### PROCEDURAL INTERVENTIONS<sup>h</sup>

- **Operative management**
  - ▶ Discuss treatment options with patient/family/caregiver
    - ◊ Risk of mortality, morbidity, and re-obstruction
    - ◊ Overall prognosis
    - ◊ Invasiveness of the proposed intervention
- Risk factors for poor surgical outcome include ascites, carcinomatosis, palpable intra-abdominal masses, multiple bowel obstructions, previous abdominal radiation, very advanced disease, and poor overall clinical status
- **Endoscopic management**
  - ▶ Percutaneous endoscopic gastrostomy tube for drainage
  - ▶ Endoscopic stent placement
- **Interventional radiology management**
  - ▶ Gastrostomy tube for drainage
- **Pharmacologic management when the goal is maintaining gut function:**
  - ▶ Use rectal, transdermal, subcutaneous, or intravenous routes of administration
  - ▶ Opioids
  - ▶ Antiemetics: Do not use antiemetics that increase gastrointestinal mobility such as metoclopramide; however, these may be beneficial in incomplete bowel obstruction
  - ▶ Corticosteroids
- **Pharmacologic management when gut function cannot be maintained:**
  - ▶ Administer antisecretory agents
  - ▶ Intravenous or subcutaneous fluids
- **Nasogastric or gastric tube drainage**
  - ▶ Increased risk of aspiration
  - ▶ Consider a limited trial only if other measures fail to reduce vomiting
- **Total parenteral nutrition (TPN)**
  - ▶ Consider only if there is expected improvement of quality of life and life expectancy of months to years

#### REASSESSMENT

##### Acceptable outcomes:

- Adequate management of malignant bowel obstruction symptoms
- Reduction of patient/family/caregiver distress
- Decreased caregiver burden

Continue to treat and monitor symptoms and quality of life

If unacceptable

- Re-evaluate palliative care interventions and intensify as possible
- Consult or refer to specialized palliative care services or hospice

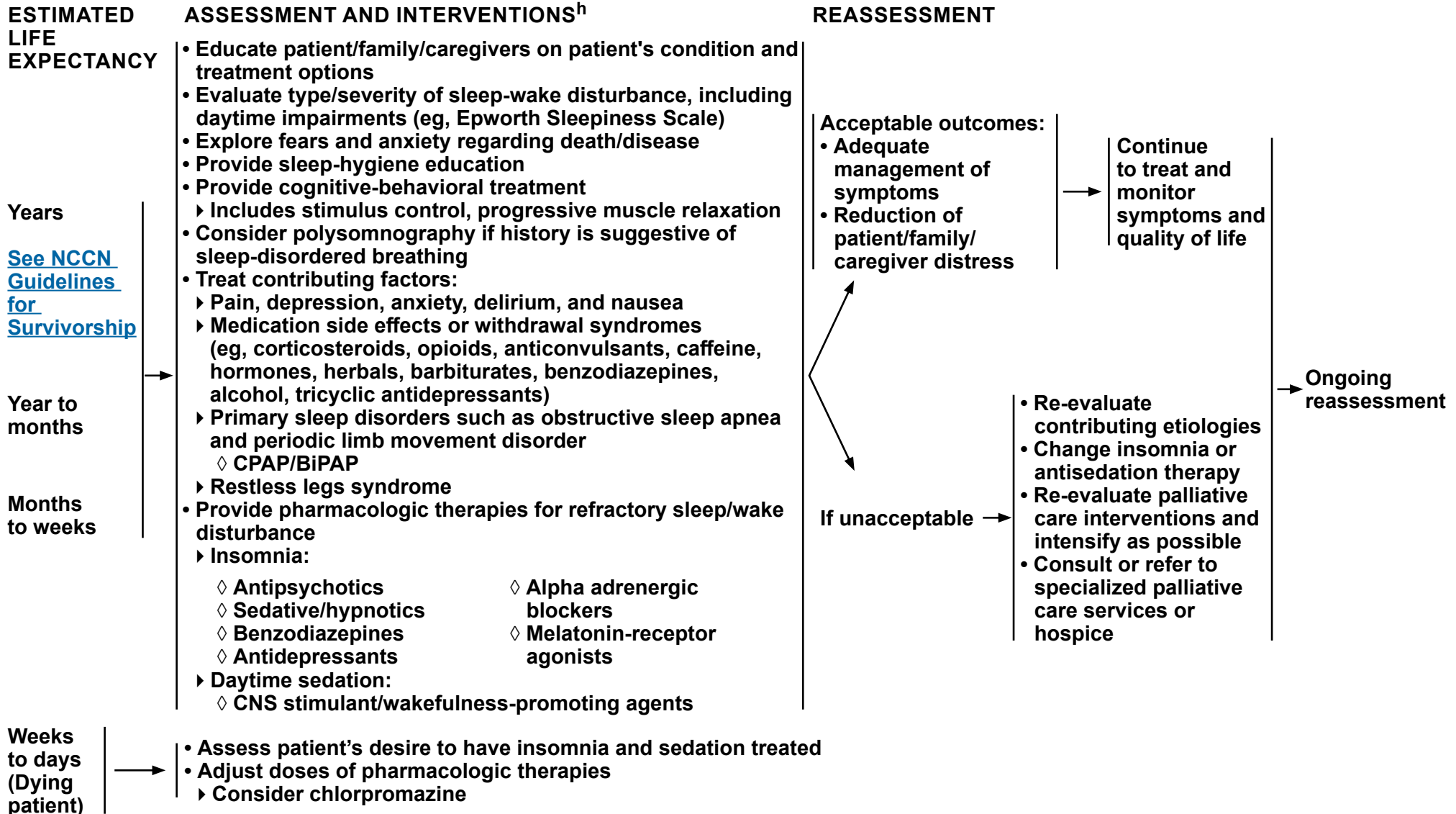
Ongoing reassessment

<sup>h</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### SLEEP/WAKE DISTURBANCES INCLUDING INSOMNIA AND SEDATION

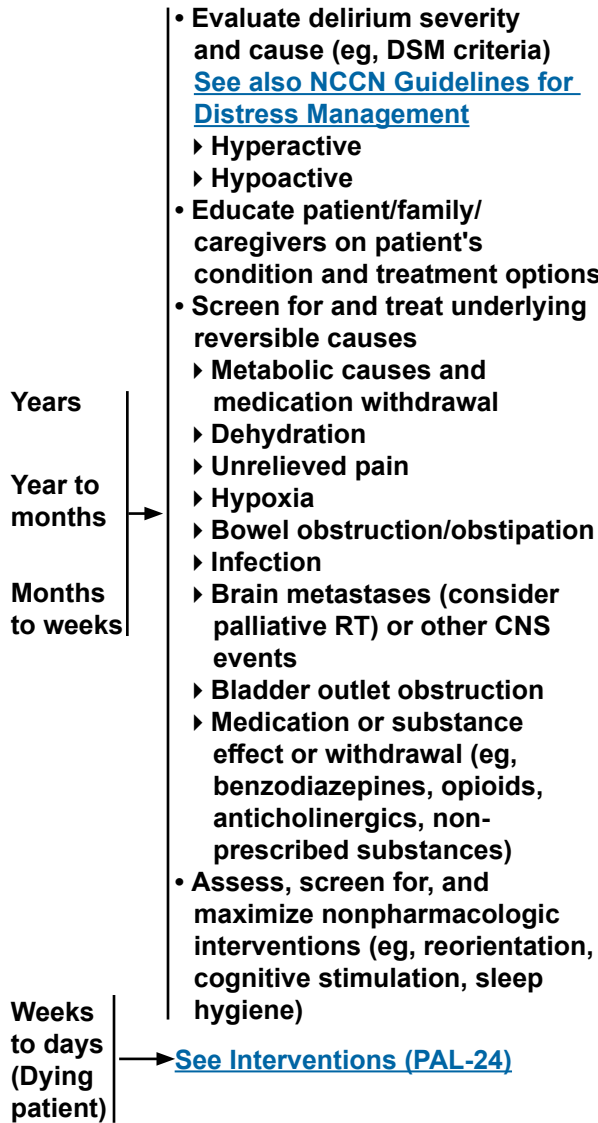


<sup>h</sup>See Drug Appendix (PAL-A) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

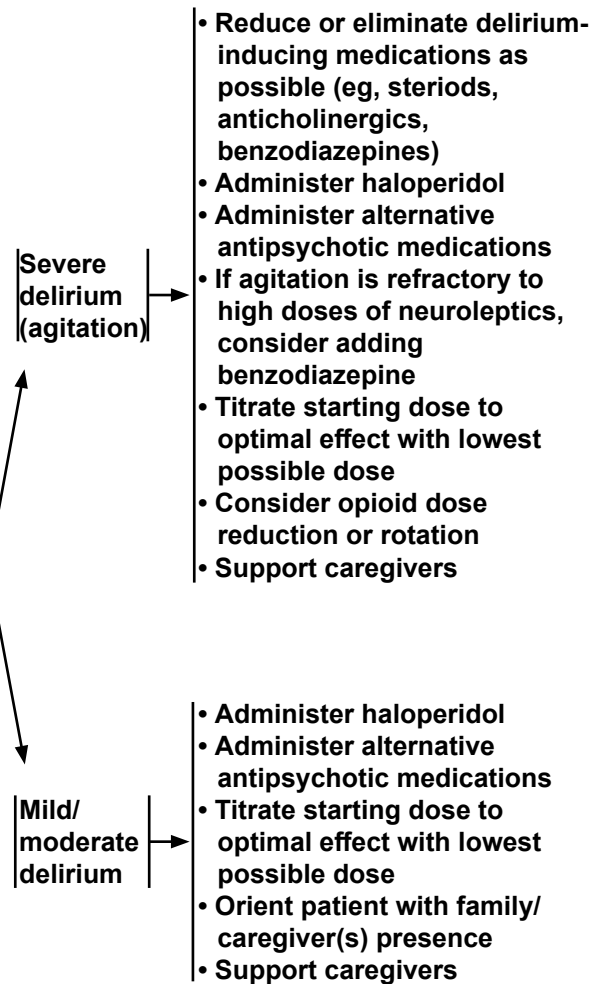


### ESTIMATED LIFE EXPECTANCY

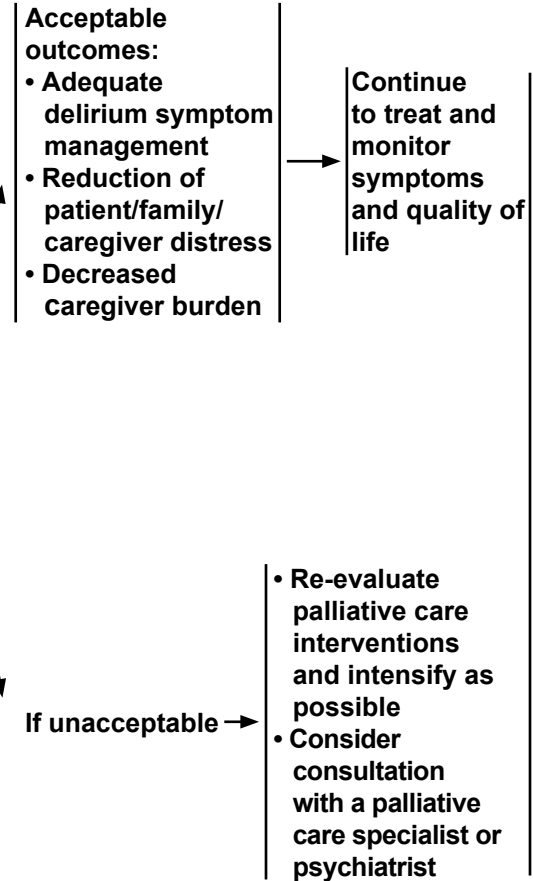


### DELIRIUM

#### INTERVENTIONS<sup>h</sup>



#### REASSESSMENT



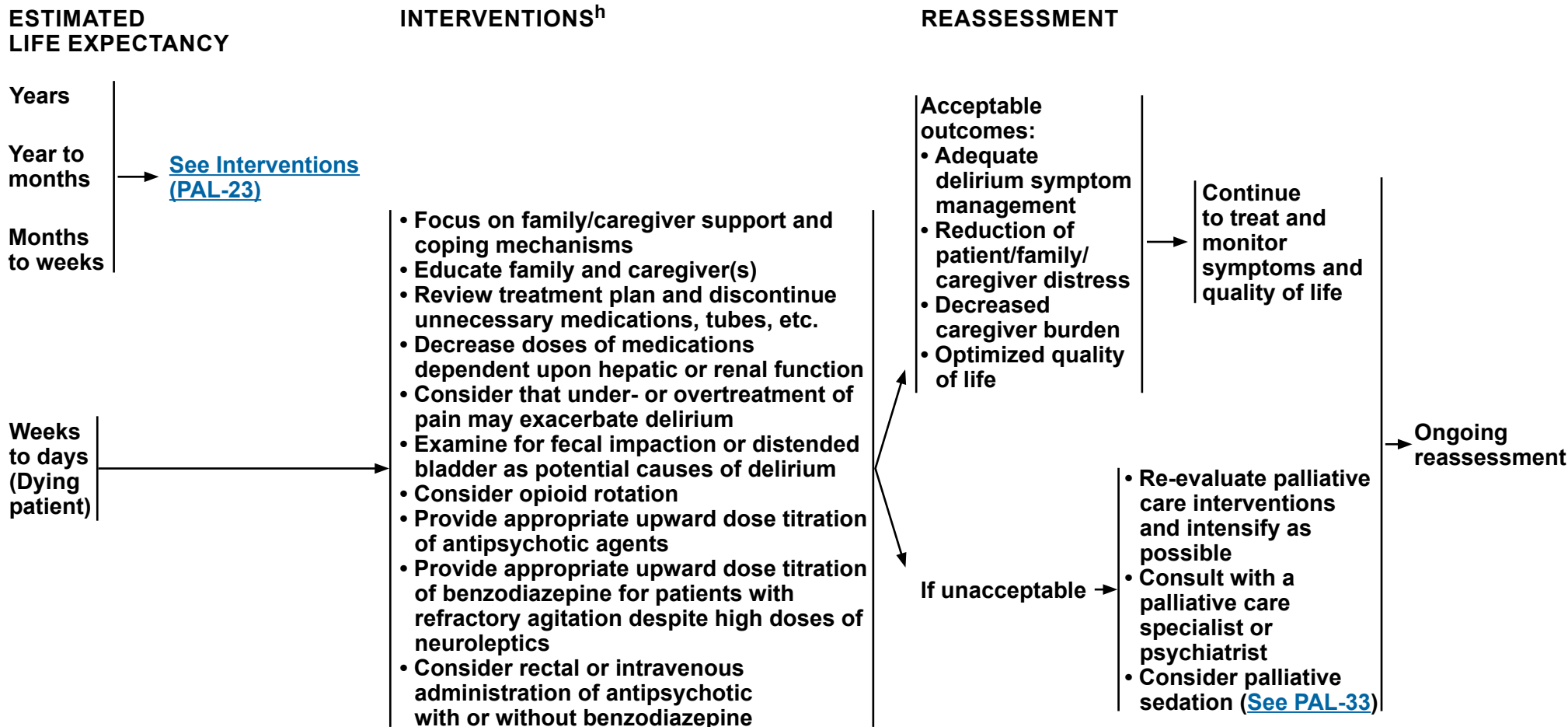
→ Ongoing reassessment

<sup>h</sup>[See Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



### DELIRIUM

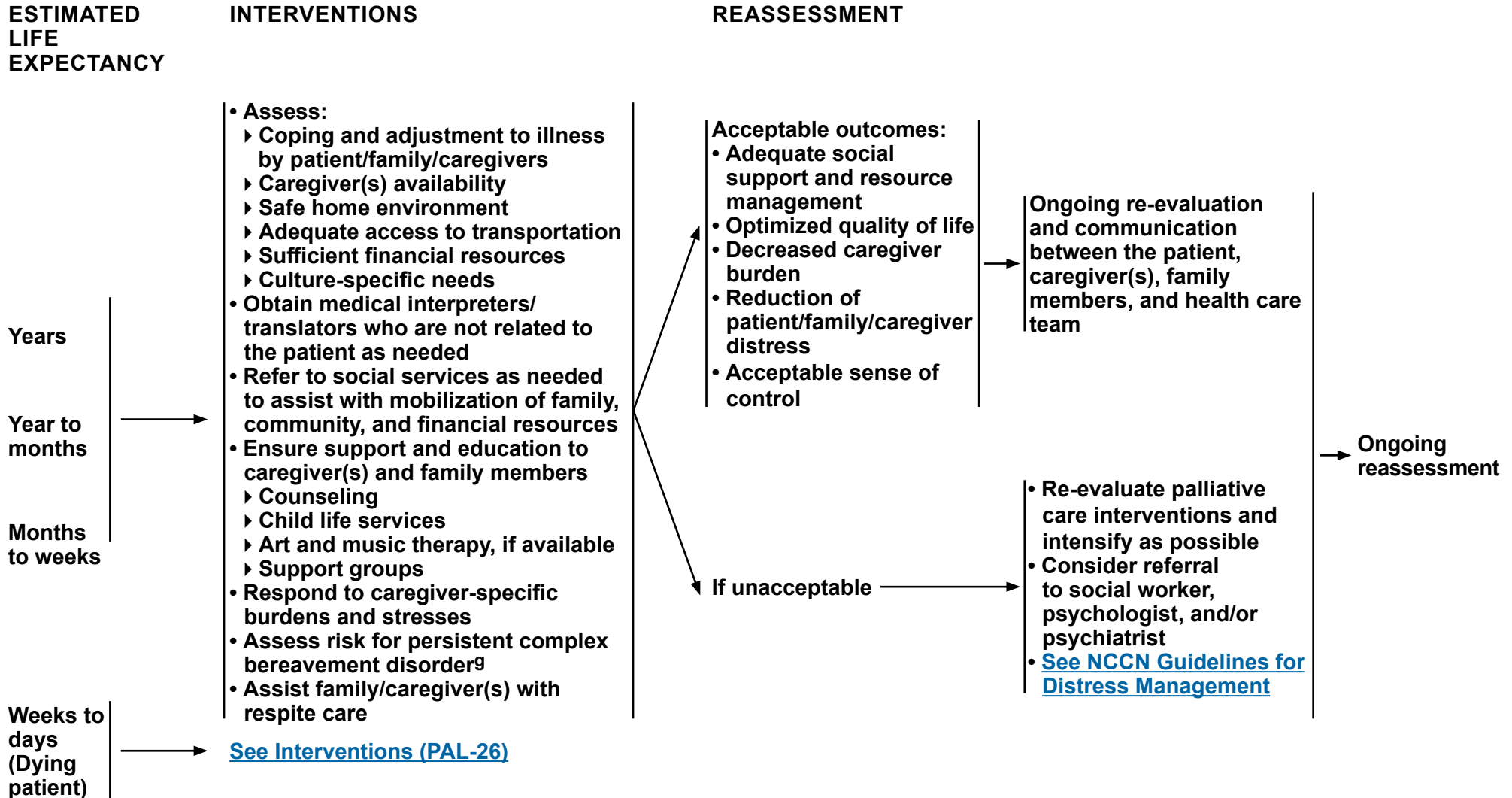


<sup>h</sup>See [Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

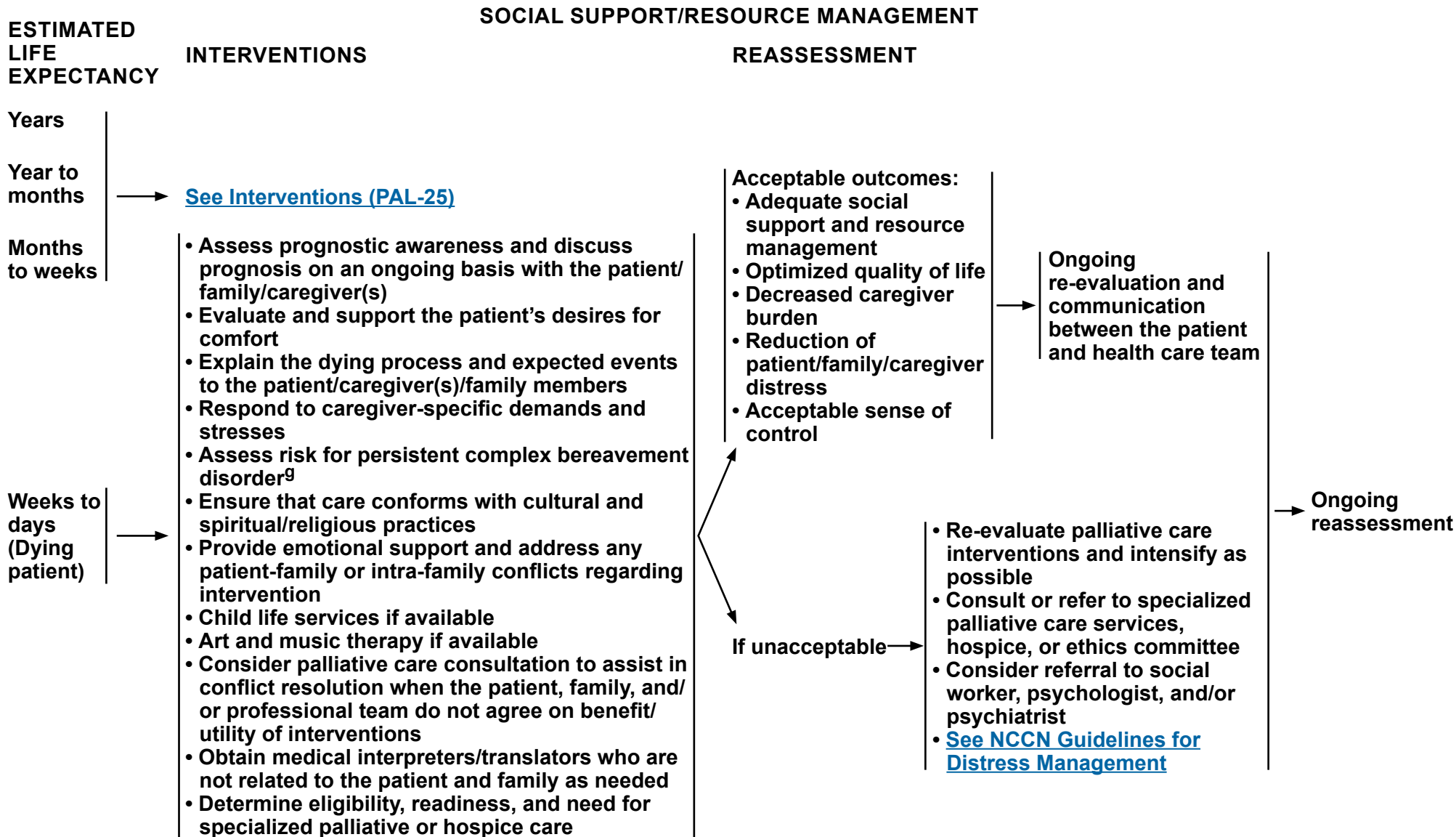


### SOCIAL SUPPORT/RESOURCE MANAGEMENT



<sup>9</sup>Persistent complex bereavement disorder is a chronic heightened state of mourning that significantly impairs functioning.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



<sup>9</sup>Persistent complex bereavement disorder is a chronic heightened state of mourning that significantly impairs functioning.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.





### PREPARING PATIENTS/FAMILIES/CAREGIVERS FOR END-OF-LIFE AND TRANSITION TO HOSPICE CARE

**ESTIMATED  
LIFE  
EXPECTANCY**

**ASSESSMENT/INTERVENTIONS**

**REASSESSMENT**

Years  
Year to  
months  
Months  
to weeks

- Assess prognostic awareness and patient/family/caregiver understanding of the expected course of disease
- Provide clear, consistent discussion with the patient/family/caregiver about prognosis and anticipated care needs on an ongoing basis
- Facilitate advance care planning ([See PAL-29](#))
  - ▶ Assess for decision-making capacity and need for a surrogate decision maker
  - ▶ Elicit values and preferences with respect to quality of life
- Determine need for specialized palliative care or eligibility and readiness for hospice care

**Acceptable outcomes:**

- Reduction of patient/family/caregiver distress
- Acceptable sense of control
- Decreased caregiver burden
- Strengthened relationships
- Optimized quality of life
- Personal growth and enhanced meaning

**If unacceptable:**

- Re-evaluate palliative care interventions and intensify as possible

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

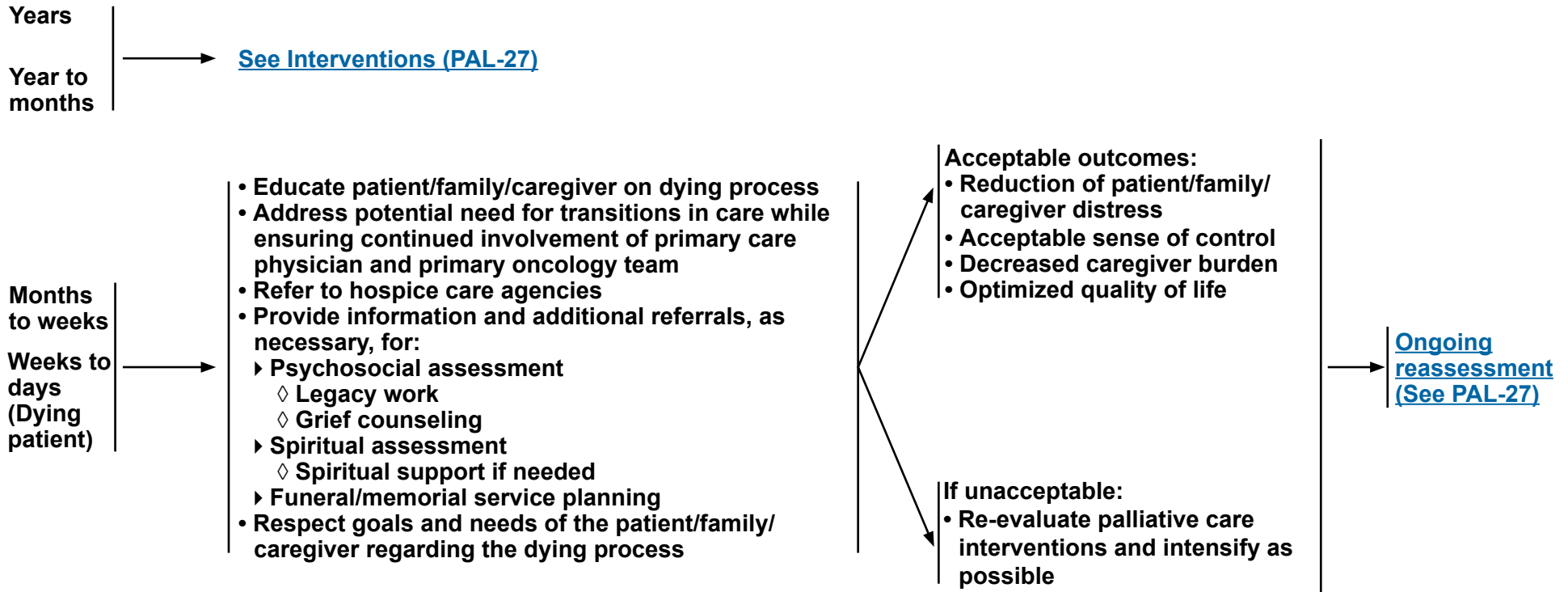


### PREPARING PATIENTS/FAMILIES/CAREGIVERS FOR END-OF-LIFE AND TRANSITION TO HOSPICE CARE

**ESTIMATED  
LIFE  
EXPECTANCY**

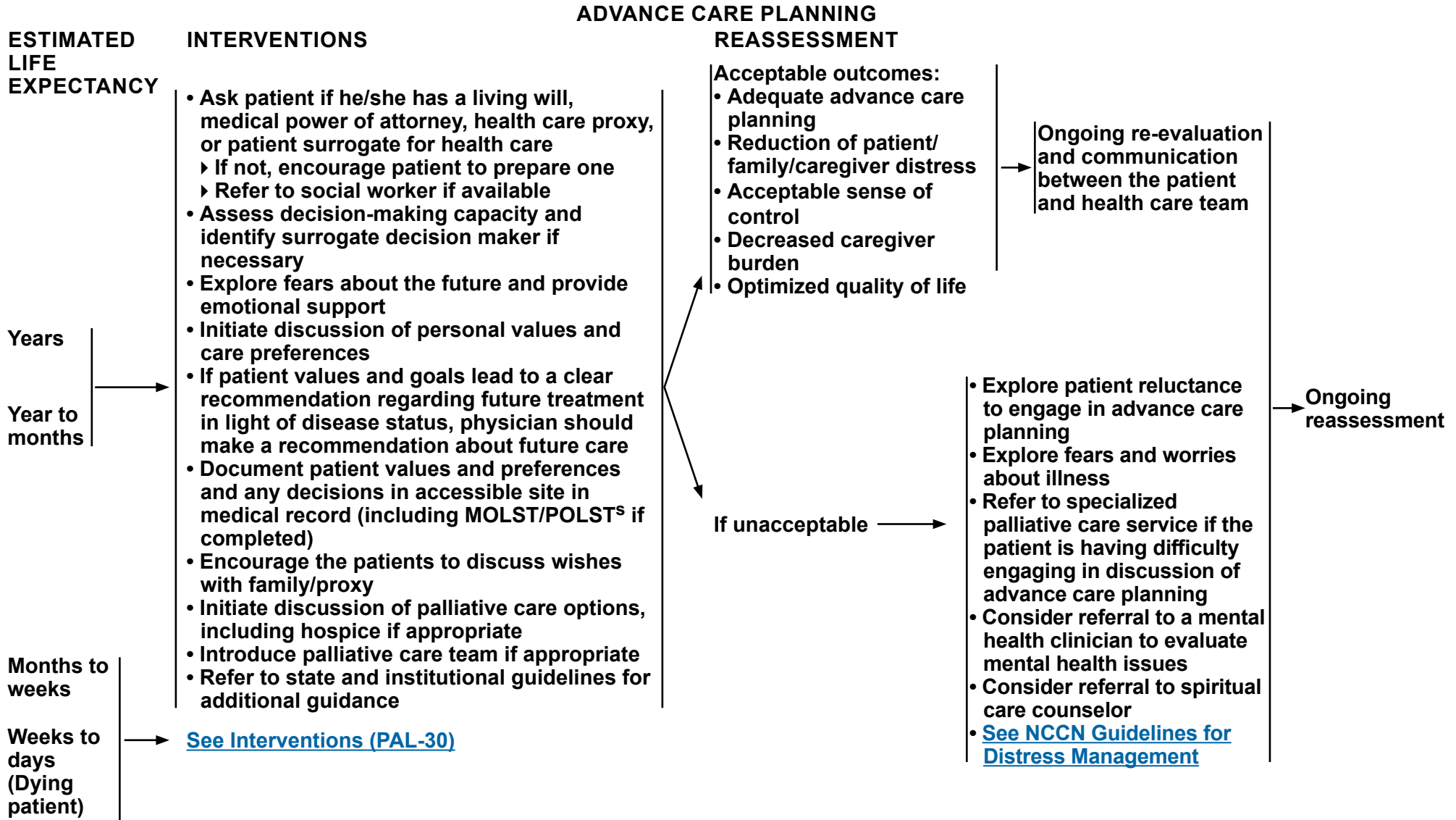
**ASSESSMENT/INTERVENTIONS**

**REASSESSMENT**



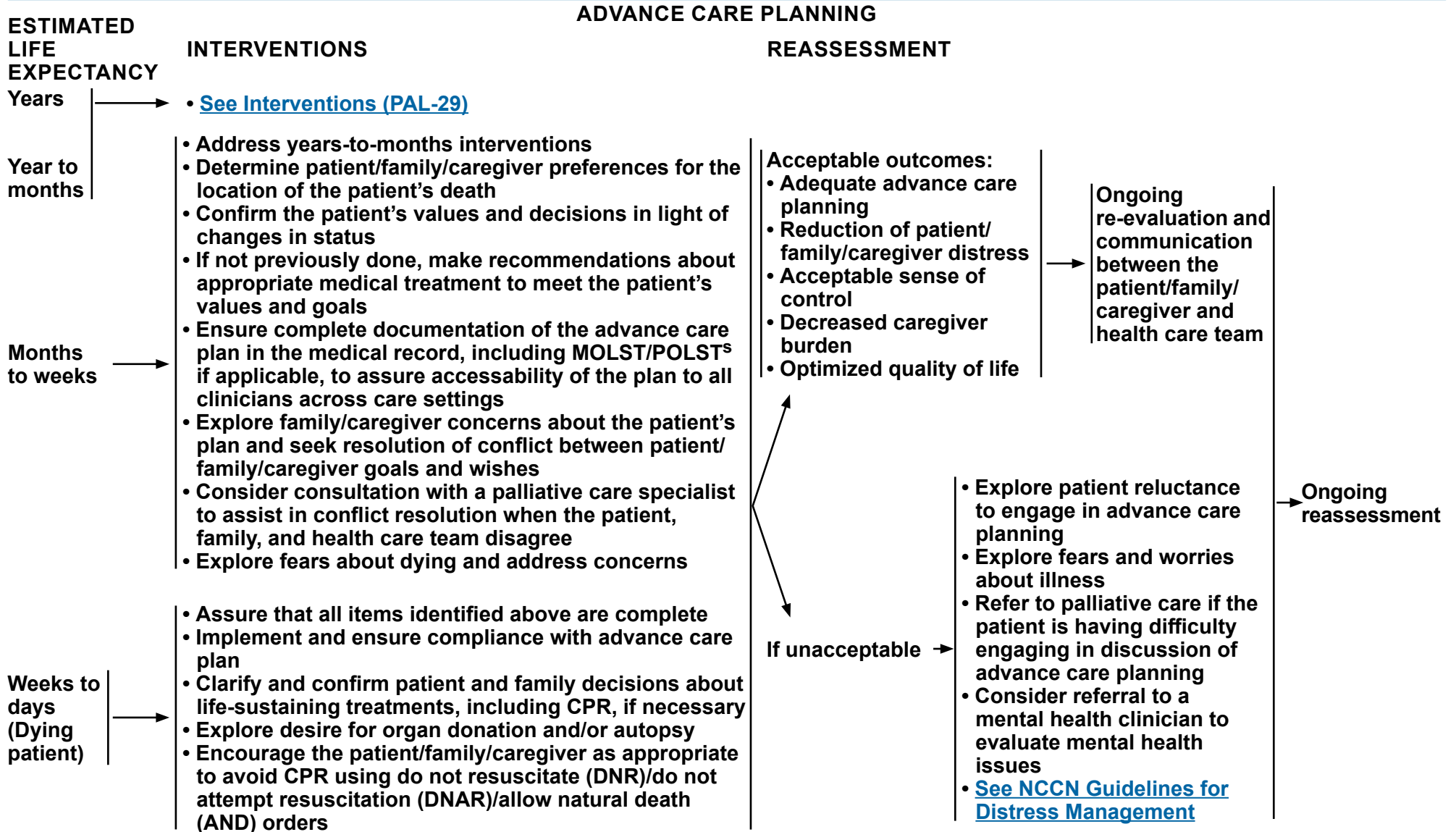
**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



<sup>s</sup>Patient's values and preferences and any decisions should be documented in the medical record, including MOLST/POLST (Medical Orders for Life-Sustaining Treatment or Physician Orders for Life-Sustaining Treatment).

**Note: All recommendations are category 2A unless otherwise indicated.**  
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**



<sup>s</sup>Patient's values and preferences and any decisions should be documented in the medical record, including MOLST/POLST (Medical Orders for Life-Sustaining Treatment or Physician Orders for Life-Sustaining Treatment).

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

### RESPONSE TO REQUESTS FOR HASTENED DEATH (PHYSICIAN-ASSISTED DYING)

- We believe that a request for hastened death often has important meanings that require exploration. The most appropriate initial response to a request for hastened death is to intensify palliative care. Patients making such a request should be referred to a palliative care specialist. However, evaluating a patient's request for hastened death is an important skill, even for clinicians who feel this practice is never morally acceptable. Clarifying these meanings may enlarge the range of useful therapeutic options and might reduce the patient's wish to die.
- Explore the reasons for the request for a hastened death, and find out "why now" in a joint discussion with the patient, family, and caregivers.
  - ▶ Reassess symptom management.
  - ▶ Reassess psychological/psychiatric issues, especially depression, anxiety, grief, psychosis, delirium, and dementia.
  - ▶ Ask about the patient's relationship to family or other important people.
  - ▶ Ask about individual values and personal views of spiritual/existential suffering and consider spiritual care consultation for further exploration and intervention.
  - ▶ Assess for fears of caregiver burden and abandonment and re-emphasize physician commitment to the patient.
- Address the request explicitly. If a patient uses a euphemism for death or refers to it indirectly, ask for clarification. Do not assume that a wish for death to come soon is a wish for a lethal prescription.
- Distinguish wishing not to live in the patient's current state from wishing for a hastened death.
- Request a consult with a mental health professional to evaluate and treat reversible causes of psychological suffering.
- Offer information about the natural history of the disease and explain the process of dying.
- Discuss the differences between withdrawal of life-sustaining nutrition/hydration, voluntary cessation of eating or drinking, and/or sedation for refractory symptoms.
- Address the role of medical caregivers, including hospice if appropriate.
- Know the local legal status of hastened death. Some patients may be confused about legal/ethical distinctions; treatment withdrawal and aggressive treatments for symptoms, such as pain, are not requests for hastened death. Euthanasia is not legal in any state in the United States.
- Examine your own response as a clinician to a particular patient's request. Requests for hastened death can force clinicians to confront their own personal, professional, moral, and legal responsibilities. Dealing with an individual patient can be quite different from thinking about the issue in abstract circumstances. Consider a consultation with an ethics committee, specialized palliative care service, or experienced colleague. These cases are usually complex and often benefit from consideration of multiple perspectives.
- Clarify the care plan. Requests for hastened death should prompt ongoing discussion and active attempts to ameliorate physical, psychosocial, and spiritual distress. Re-emphasize your own commitment to providing continuing care for the patient. Re-evaluate and maintain medications for symptom management.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**CARE OF THE IMMINENTLY DYING HOSPITALIZED PATIENT**

For an imminently dying patient, consider using an end-of-life care order set, which may contain physical, psychosocial, and practical interventions, including the following:

- **Physical**
  - ▶ Obtain hospice evaluation, if available
  - ▶ Intensify comfort measures
    - ◊ Implement skin safety protocol according to risk assessment:
      - Regularly reposition the patient for comfort as indicated
      - Reassess and premedicate for wound care as needed
      - Use a pressure-relieving mattress, if available
      - Provide eye and mouth care to maintain moisture
      - Treat for urinary retention and fecal impaction
  - ▶ Ensure deactivation of implanted defibrillator
  - ▶ Consider deactivation of implanted pacemaker in select patients
  - ▶ Discontinue unnecessary diagnostic tests and interventions such as transfusions, needle sticks, blood glucose monitoring, oxygen saturation monitoring, and suctioning
  - ▶ Replace check of vital signs with regular (eg, every 4 h) symptom assessments
  - ▶ Switch routes of medication administration when the oral route is no longer feasible
  - ▶ Adjust doses of medications to optimal comfort
    - ◊ Treat pain and fever
  - ▶ Treat unclearable terminal secretions (death rattle) by:
    - ◊ Reducing parenteral and enteral fluids
    - ◊ Repositioning the patient
    - ◊ Avoid deep suctioning
  - ▶ Treat dyspnea by adjusting the dose of medication ([See PAL-11](#))
  - ▶ Treat delirium ([See PAL-24](#))
  - ▶ Consider palliative sedation for refractory restlessness and agitation ([See PAL-33](#))
  - ▶ Be prepared to discuss a request for organ donation and autopsy
- **Psychosocial**
  - ▶ Help support the patient/family/caregiver to accept discontinuation of TPN and transfusions, dialysis, IV hydration, and medications that will not add to the patient's comfort
  - ▶ Consider social work and chaplain consults
  - ▶ Ensure that the family/caregiver understands the signs and symptoms of imminent death and that they are supported throughout the dying process
  - ▶ Offer anticipatory bereavement support
  - ▶ Provide support to children and grandchildren and provide education to parents on age-appropriate grieving process
  - ▶ Encourage visits by children if consistent with family values
  - ▶ Support cultural practices
  - ▶ Ensure that caregivers understand and will honor advance directives
  - ▶ Promote healthy grieving
- **Practical**
  - ▶ Mobilize in-hospital end-of-life care policies and procedures
  - ▶ Ensure that the patient's advance directives are documented and implemented
  - ▶ Discuss and document patient/family/caregiver wishes for resuscitation. In the event that CPR is unlikely to be effective, recommend other options such as DNR/DNAR/AND orders and promote comfort care.
  - ▶ Provide the patient/family/caregiver with respectful space and uninterrupted time together
  - ▶ Provide information on funeral planning, if desired

[See After-Death Interventions \(PAL-34\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.





## PALLIATIVE SEDATION

- Palliative sedation to unconsciousness, in which the intended effect is deep sedation, remains controversial.<sup>t</sup>
- Refractory symptoms are symptoms that cannot be adequately managed despite comprehensive, interdisciplinary palliative care that does not compromise consciousness.
- Confirm that the patient has refractory symptoms and is imminently dying.
  - ▶ Imminently dying patients have a prognosis of hours to days. If palliative sedation is being considered, prognosis should be confirmed by two physicians.
- Obtain informed consent for sedation from the patient and/or surrogate/family.
  - ▶ Discuss the patient's disease status, treatment goals, prognosis, and expected outcomes with the patient and/or surrogate.
  - ▶ Clarify that sedation will consist of the continuous administration of medications that will render the patient unconscious.
  - ▶ Review the ethical justification of the use of sedation with the patient/surrogate/family and members of the health care team.
    - ◊ An ethics consult may be considered in accordance with institutional guidelines and state regulations.
  - ▶ Discontinuation of life-prolonging therapies (eg, artificial hydration/nutrition and/or withholding of cardiopulmonary resuscitation) often accompanies palliative sedation.
- Support reassignment of health care professionals who cannot provide sedation due to personal or professional values and beliefs as long as patient care can be safely transferred to the care of another health care professional.
- Select an appropriate sedative treatment plan based on the patient's response to recent and current medications.<sup>h</sup>

Typical sedatives used for palliative sedation parenteral infusions include:

  - ▶ Midazolam
  - ▶ Propofol
- Continue current pain and symptom management interventions and titrate as needed.
- Monitor patient symptoms regularly, titrate sedatives and other medications, and reassess the need for ongoing palliative sedation based on response and drug/drug interactions to establish and maintain a level of sedation that relieves the patient's refractory symptoms.
- Provide ongoing psychosocial and spiritual support for the patient's surrogate, family, and health care professionals.

<sup>h</sup>See [Drug Appendix \(PAL-A\)](#) for specific recommendations for medical management of symptoms.

<sup>t</sup>Ten Have H, Welie JV. Palliative sedation versus euthanasia: an ethical assessment. *J Pain Symptom Manage* 2014;47(1):123-136. <https://www.ncbi.nlm.nih.gov/pubmed/23742736>.

**Note:** All recommendations are category 2A unless otherwise indicated.

**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



DEATH	ASSESSMENT	AFTER-DEATH INTERVENTIONS
<p>Death →</p>	<p>A “peaceful death”:</p> <ul style="list-style-type: none"> <li>• Free from avoidable distress and suffering for the patient, family, and caregiver(s)</li> <li>• In general accord with the patient’s and family’s wishes</li> <li>• Consistent with clinical, cultural, and ethical standards</li> </ul>	<p><b>For family and caregiver(s)</b></p> <ul style="list-style-type: none"> <li>• Immediate after-death care:                             <ul style="list-style-type: none"> <li>▶ Inform family (if not present) of death</li> <li>▶ Offer condolences</li> <li>▶ Provide the family time with the body</li> <li>▶ Involve chaplain to assess family’s desire for religious ritual or spiritual support</li> <li>▶ Remove tubes, drains, lines, and the foley catheter unless an autopsy is planned</li> <li>▶ Ensure culturally sensitive, respectful treatment of the body</li> <li>▶ Address survivor concerns about organ donation and/or autopsy</li> <li>▶ File the death certificate, complete forms, and provide necessary information for the funeral director and family as appropriate</li> <li>▶ Inform other involved health care professionals of the patient’s death</li> </ul> </li> <li>• Bereavement support:                             <ul style="list-style-type: none"> <li>▶ Formally express condolences on the patient’s death (eg, card, call, letter)</li> <li>▶ Refer to appropriate bereavement services within the institution or in the community</li> <li>▶ Attend a debriefing meeting with the family if they desire one</li> </ul> </li> <li>• Identify family members at risk for persistent complex bereavement disorder<sup>9</sup></li> </ul> <p><b>For health care professionals</b></p> <ul style="list-style-type: none"> <li>• General support:                             <ul style="list-style-type: none"> <li>▶ Legitimize discussion of personal issues that impact patient care</li> <li>▶ Create a climate of safety for discussion of patient deaths</li> <li>▶ Provide regular opportunities for reflection and remembering for staff through a memorial ritual</li> </ul> </li> <li>• After-death support:                             <ul style="list-style-type: none"> <li>▶ Review medical issues related to the patient’s death                                     <ul style="list-style-type: none"> <li>◇ Explore concerns and questions regarding quality of patient care</li> </ul> </li> <li>▶ Review the family’s emotional responses to the patient’s death</li> <li>▶ Review the staff’s emotional responses to the patient’s death                                     <ul style="list-style-type: none"> <li>◇ Identify health care professionals at risk for persistent complex bereavement disorder,<sup>9</sup> moral distress, or compassion fatigue</li> <li>◇ Include nurses, nursing assistants, physician team members (including medical students, residents, and fellows), social workers, and chaplaincy, as appropriate</li> <li>◇ Consider a bereavement ritual for staff (eg, brief reading, moment of quiet)</li> </ul> </li> </ul> </li> </ul>

<sup>9</sup>Persistent complex bereavement disorder is a chronic heightened state of mourning that significantly impairs functioning.

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



**PALLIATIVE CARE DRUG APPENDIX**

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
<b>Dyspnea</b> ( <a href="#">PAL-11</a> )	<b>Life Expectancy: Years; Year to Months; and Months to Weeks</b> • <b>General:</b> Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN for opioid naïve, increase dose by 25% for non-opioid naïve ▶ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • <b>Anxiety:</b> Lorazepam, 0.25–1 mg PO q4h PRN for benzodiazepine naïve
<b>Dyspnea</b> ( <a href="#">PAL-12</a> )	<b>Life Expectancy: Weeks to Days (dying patient)</b> • <b>General:</b> Morphine, 2.5–10 mg PO q2h PRN or 1–3 mg IV q2h PRN if opioid naïve, increase dose by 25% for non-opioid naïve ▶ For acute progressive dyspnea, or for patients who are not opioid naïve, more aggressive titration may be required • <b>Anxiety:</b> Lorazepam, 0.25–1 mg PO q4h PRN if benzodiazepine naïve • <b>Fluid overload:</b> Furosemide
<b>Secretions</b> ( <a href="#">PAL-12</a> )	• <b>Excessive secretions:</b> Scopolamine, 0.4 mg SC q4h PRN/1.5 mg patches, 1–3 patches q 72 h OR atropine, 1% ophthalmic solution 1–2 drops SL q4h PRN OR glycopyrrolate, 0.2–0.4 mg IV or SC q4h PRN
<b>Anorexia/ Cachexia</b> ( <a href="#">PAL-13</a> )	<b>Life Expectancy: Years; Year to Months</b> • <b>Depression/anorexia:</b> Mirtazapine, 7.5–30 mg PO QHS • <b>Gastroparesis (early satiety):</b> Metoclopramide 5–10 mg PO QID 30 min before meals and at bedtime • <b>Low/no appetite:</b> Megestrol acetate, 400–800 mg/d PO
<b>Anorexia/ Cachexia</b> ( <a href="#">PAL-14</a> )	<b>Life Expectancy: Months to Weeks; Weeks to Days (dying patient)</b> • <b>Offer education to patient</b> • <b>Low/no appetite:</b> Megestrol acetate, 400–800 mg/d PO OR olanzapine, 5 mg/d PO OR dexamethasone, 4–8 mg/d PO OR consider cannabinoid • <b>Depression:</b> Mirtazapine, 7.5–30 mg PO QHS

[See key for abbreviations PAL-A \(5 of 5\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)

**PALLIATIVE CARE DRUG APPENDIX**

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
<b>Nausea and Vomiting (NV)- Initial Treatment (<a href="#">PAL-15</a>)</b>	<p><b>Life Expectancy: Years; Year to Months; Months to Weeks; and Weeks to Days (dying patient)</b></p> <ul style="list-style-type: none"> <li>• See <a href="#">NCCN Guidelines for Antiemesis</a> for chemotherapy/radiation-induced NV</li> <li>• <b>Gastroparesis:</b> Metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime</li> <li>• <b>CNS involvement:</b> Dexamethasone, 4–8 mg PO BID-TID</li> <li>• <b>Gastric outlet obstructions:</b> Dexamethasone, 4–8 mg/d PO; proton pump inhibitor; metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime</li> <li>• <b>Gastritis/GERD:</b> Proton pump inhibitor OR H2 blocker</li> <li>• <b>Medication-induced gastropathy:</b> Proton pump inhibitor OR metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime</li> </ul> <p><b>Nonspecific NV</b></p> <ul style="list-style-type: none"> <li>• <b>Dopamine receptor antagonists or 5HT3 receptor antagonists</b> <ul style="list-style-type: none"> <li>▸ Haloperidol, 0.5 mg PO TID OR metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime OR prochlorperazine, 5–10 mg PO 3–4 times/d, maximum 40 mg/d OR olanzapine, 5–10 mg PO 2–3 times/d OR ondansetron, 4 mg PO q4h or 8 mg PO q8h</li> </ul> </li> <li>• <b>Contributing anxiety:</b> Lorazepam, 0.5–1 mg PO q4h PRN</li> <li>• <b>Vertiginous component:</b> Anticholinergic AND/OR antihistamine</li> </ul>
<b>Nausea and Vomiting (NV)- Initial Treatment (<a href="#">PAL-16</a>)</b>	<p><b>Life Expectancy: Years; Year to Months; Months to Weeks; and Weeks to Days (dying patient)</b></p> <ul style="list-style-type: none"> <li>• <b>Consider appropriate route of administration</b> <ul style="list-style-type: none"> <li>▸ 1) Prescribe oral, sublingual, or rectal agent and titrate to maximum benefit</li> <li>▸ 2) If NV persists, provide PRN, scheduled, or continuous parenteral infusion as necessary</li> <li>▸ 3) Consider subcutaneous administration as an alternative</li> </ul> </li> <li>• <b>Titrate to maximum benefit and tolerance:</b> olanzapine, prochlorperazine, haloperidol, or metoclopramide</li> <li>• <b>For continued NV, consider additional agents:</b> <ul style="list-style-type: none"> <li>▸ Dexamethasone, 4–8 mg/d PO; ondansetron, 4–8 mg PO every 6 h; scopolamine (patch or IV); meclizine, 25–100 mg/d PO; oral cannabinoid</li> </ul> </li> </ul>
<b>Constipation (<a href="#">PAL 17</a>)</b>	<p><b>Life Expectancy: Years; Year to Months; Months to Weeks; and Weeks to Days (dying patient)</b></p> <ul style="list-style-type: none"> <li>• <b>Prophylaxis:</b> Titrate the senna and add polyethylene glycol, recommend starting with polyethylene glycol if the patient is not on opioids and can tolerate the volume of liquid</li> <li>• <b>General:</b> Add bisacodyl, titrate to 10–15 mg PO daily-TID with a goal of 1 non-forced bowel movement (BM) every 1–2 days</li> <li>• <b>Persistent constipation:</b> bisacodyl suppository, one rectally daily-BID; polyethylene glycol, 1 capful/8 oz water PO BID; lactulose, 30–60 mL PO BID-QID; sorbitol, 30 mL PO q2h x 3, then PRN; magnesium hydroxide, 30–60 mL PO daily-BID; or magnesium citrate, 8 oz PO daily</li> <li>• <b>Opioid-induced constipation:</b> Consider methylnaltrexone, 8 or 12 mg/dose SC, no more than once a day; linaclotide, 72–145 mcg/d PO; naloxegol, 12.5–25 mg/d PO <ul style="list-style-type: none"> <li>▸ Not for post-op ileus and mechanical bowel obstruction</li> </ul> </li> </ul>

[See key for abbreviations PAL-A \(5 of 5\)](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.[Continued](#)PAL-A  
2 OF 5



### PALLIATIVE CARE DRUG APPENDIX

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
<b>Diarrhea</b> <a href="#">(PAL-19)</a>	<p><b>Life Expectancy: Years; Year to Months; and Months to Weeks</b></p> <p><b>Grade 1</b></p> <ul style="list-style-type: none"> <li>• General: Loperamide, 4 mg PO x 1 then 2 mg PO after each loose stool, up to 16 mg/d</li> <li>• If not on opioids: Diphenoxylate/atropine 1–2 tabs PO q6h PRN, maximum 8 tabs/d</li> </ul> <p><b>Grade 2</b></p> <ul style="list-style-type: none"> <li>• Initiate/continue loperamide, 4 mg PO x 1 then 2 mg PO after each loose stool, up to 16 mg/d</li> <li>• If not on opioids: Diphenoxylate/atropine 1–2 tabs PO q6h PRN, maximum 8 tabs/d</li> <li>• Consider hyoscyamine, 0.125 mg PO/ODT/SL q4h PRN, max: 1.5 mg/d; atropine 0.5–1 mg SC/IM/IV/SL q 4–6h PRN</li> <li>• C. diff-induced: Metronidazole, 500 mg PO/IV QID x 10–14 days; vancomycin, 125–500 mg PO QID x 10–14 days</li> <li>• Non-C. diff infection: Treat appropriately based on culture findings</li> <li>• Immunotherapy-related: Dexamethasone, 4–8 mg/d; infliximab, 5 mg/kg q 2–6 weeks</li> </ul> <p><b>Grades 3/4 (Inpatient hospitalization w/ICU for Grade 4)</b></p> <ul style="list-style-type: none"> <li>• Initiate/continue loperamide, 4 mg PO x 1 then 2 mg PO after each loose stool, up to 16 mg/d</li> <li>• If not on opioids: Diphenoxylate/atropine, 1–2 tabs PO q6h PRN, maximum 8 tabs/d</li> <li>• Consider hyoscyamine, 0.125 mg PO/ODT/SL q4h PRN, max: 1.5 mg/d; atropine 0.5–1 mg SC/IM/IV/SL q 4–6 h PRN</li> <li>• Consider octreotide, 100–200 mcg/d SC, q8h or by continuous infusion</li> </ul>
<b>Diarrhea</b> <a href="#">(PAL-19)</a>	<p><b>Life Expectancy: Weeks to Days (dying patient)</b></p> <ul style="list-style-type: none"> <li>• Reevaluate ongoing antidiarrheal, anticholinergic agents</li> <li>• Initiate or increase dose of around-the-clock opioid</li> <li>• Atropine 0.5–1 mg SC/IV/SL q 4–6h PRN</li> <li>• Consider octreotide, 100–200 microgram SC q8h</li> <li>• Consider glycopyrrolate, 0.2–0.4 mg IV q4h PRN</li> </ul>
<b>Malignant Bowel Obstruction</b> <a href="#">(PAL-20)</a>	<p><b>Life Expectancy: Years; Year to Months; Months to Weeks; and Weeks to Days (dying patient)</b></p> <p><b>Goal to Maintain Gut Function</b></p> <ul style="list-style-type: none"> <li>• Reduce opioid dose or rotate opioid</li> <li>• Metoclopramide, 5–10 mg PO QID 30 min before meals and at bedtime</li> <li>• Dexamethasone, 4–12 mg IV daily, discontinue if no improvement in 3–5 days</li> </ul> <p><b>Gut Function Cannot be Maintained</b></p> <ul style="list-style-type: none"> <li>• Scopolamine (patch or IV); hyoscyamine, 0.125 mg PO/ODT/SL q4h PRN; glycopyrrolate, 0.2–0.4 mg IV q4h PRN</li> <li>• Octreotide, 100–300 mcg SC BID-TID or 10–40 mcg/h continuous SC/IV infusion; if prognosis &gt;8 weeks, consider long-acting release (LAR) or depot injection</li> </ul>

[See key for abbreviations PAL-A \(5 of 5\)](#)

**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

[Continued](#)

**PALLIATIVE CARE DRUG APPENDIX**

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
<b>Sleep/Wake Disturbance</b> <a href="#">(PAL-22)</a>	<b>Life Expectancy: Years; Year to Months; and Months to Weeks</b> <u>Insomnia</u> <ul style="list-style-type: none"> <li>• Trazodone, 25–100 mg PO at bedtime</li> <li>• Olanzapine, 2.5–5 mg PO at bedtime</li> <li>• Zolpidem, 5 mg PO at bedtime</li> <li>• Mirtazapine, 7.5–30 mg PO at bedtime</li> <li>• Chlorpromazine, 25–50 mg PO at bedtime</li> <li>• Quetiapine, 12.5–25 mg PO at bedtime</li> <li>• Lorazepam, 0.5–1 mg PO at bedtime</li> <li>• For phase shift disorder consider ramelteon (8 mg PO 30 min before bedtime) or melatonin (30 min before bedtime; dosage may vary by formulation)</li> </ul> <u>Daytime Sedation</u> <ul style="list-style-type: none"> <li>• Caffeine, 100–200 mg PO q 6 h, last dose 4 PM</li> <li>• Methylphenidate, start with 2.5–20 mg PO BID, second dose no later than 6 h before bedtime</li> <li>• Dextroamphetamine, 2.5–10 mg PO BID, second dose no later than 12 h before bedtime</li> <li>• Modafinil, 100–400 mg PO each morning</li> </ul> <u>Restless Legs Syndrome</u> <ul style="list-style-type: none"> <li>• Ropinirole, 0.25 mg PO 1–3 h before bedtime</li> <li>• Pramipexole, starting dose 0.125 mg PO at bedtime, may require titration</li> <li>• May also consider pregabalin, carbidopa-levodopa, or low-dose methadone with dopamine agonist; however, all of these medications are off-label for RLS</li> </ul>
<b>Sleep/Wake Disturbance</b> <a href="#">(PAL-22)</a>	<b>Life expectancy: Weeks to Days (dying patient)</b> <ul style="list-style-type: none"> <li>• Titrate dose of existing pharmacotherapy</li> <li>• Consider chlorpromazine, 25–100 mg PO/PR at bedtime</li> </ul>

[See key for abbreviations PAL-A \(5 of 5\)](#)**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**[Continued](#)**PAL-A**  
**4 OF 5**



**PALLIATIVE CARE DRUG APPENDIX**

Condition	Recommended Agents and Dosage by Estimated Life Expectancy and Symptom Etiology
<b>Delirium (PAL-23)</b>	<p><b>Life Expectancy: Years; Year to Months; and Months to Weeks</b></p> <p><b>Mild/Moderate Delirium</b></p> <ul style="list-style-type: none"> <li>• Haloperidol, 0.5–2 mg PO BID/TID</li> <li>• Alternatives: risperidone, 0.5–1 mg PO BID; olanzapine, 5–20 mg PO daily; or quetiapine fumarate, 25–200 mg PO/SL BID</li> </ul> <p><b>Severe Delirium (agitation)</b></p> <ul style="list-style-type: none"> <li>• Haloperidol, 0.5–2 mg IV q1–4h PRN</li> <li>• Alternatives: olanzapine, 2.5–7.5 mg PO/SL q2–4h PRN (maximum = 30 mg/d); chlorpromazine, 25–100 mg PO/PR/IV q4h PRN for bedbound patients</li> <li>• High-dose neuroleptic-refractory: Consider adding lorazepam, 0.5–2 mg SC/IV q4h</li> </ul>
<b>Delirium (PAL-24)</b>	<p><b>Life Expectancy: Weeks to Days (dying patient)</b></p> <ul style="list-style-type: none"> <li>• Upward titrate haloperidol, risperidone, olanzapine</li> <li>• High-dose neuroleptic-refractory: Upward titrate lorazepam</li> <li>• Consider rectal or IV haloperidol</li> <li>• Consider chlorpromazine, 25–100 mg PO/PR at bedtime with or without lorazepam, 0.5–2 mg SC/IV q4h</li> </ul>
<b>Palliative Sedation (PAL-33)</b>	<p><b>Imminently dying patient</b></p> <ul style="list-style-type: none"> <li>• Midazolam, continuous infusion</li> <li>• Propofol, continuous infusion</li> </ul>

**Abbreviations Key**

Timing: q (every); h (hour); d (day); BID (twice a day); TID (three times per day); QID (four times per day); QHS (at bedtime); PRN (as needed)  
Route of administration: IM (intramuscular); IV (intravenous); ODT (orally disintegrating tablet); PO (oral); PR (rectal); SC (subcutaneous); SL (sublingual)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 1.2019 Palliative Care

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

## Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 06/01/17

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

## Table of Contents

Overview.....	2
Literature Search Criteria and Guidelines Update Methodology.....	2
Palliative Care in Oncology.....	3
Impact of Palliative Care.....	3
Role of Hospice Care.....	5
Palliative Care Standards & Research.....	6
Trial Design.....	7
Barriers to Timely Provision of Palliative Care.....	7
Training in Palliative Care.....	8
Communication Skills Training.....	8
NCCN Guidelines for Palliative Care.....	9
Palliative Care Screening.....	9
Palliative Care Assessment.....	10
Assessment for Benefits and Burdens of Anticancer Therapy.....	10

Assessment of Patient and Family Goals, Values, Expectations, and Priorities.....	10
Assessment of Physical Symptoms.....	10
Assessment of Psychosocial Distress.....	10
Assessment of Educational and Informational Needs and Cultural Factors Affecting Care.....	11
Criteria for Consultation with Palliative Care.....	11
Palliative Care Interventions.....	11
Anticancer Therapy.....	13
Symptom Management.....	14
Pain.....	14
Dyspnea.....	14
Anorexia/Cachexia.....	15
Nausea and Vomiting.....	17
Constipation.....	18
Diarrhea.....	19
Malignant Bowel Obstruction.....	19
Fatigue/Weakness/Asthenia.....	20
Sleep/Wake Disturbances.....	20
Delirium.....	21
Psychosocial Distress – Social Support/Resource Management.....	22
Palliative Care Reassessment.....	22
End-of-Life Care Issues.....	23
Preparing Patients and Families for End-of-Life and Transition to Hospice Care.....	23
Advance Care Planning.....	23
Requests for Hastened Death.....	25
Care of the Imminently Dying Hospitalized Patient.....	25
Palliative Sedation.....	26
A Peaceful Death.....	26
After-Death Care Interventions.....	27
Putting Palliative Care Guidelines into Practice.....	27
Psychosocial Support for Palliative Care Providers.....	28
Conclusion.....	29
Table 1: Palliative Care Internet Resources for Clinicians <sup>a</sup> .....	30
References.....	31

### Overview

The aim of the NCCN Guidelines for Palliative Care is to help assure that each patient with cancer experiences the best quality of life possible throughout the illness trajectory by providing guidance for the primary oncology team. The NCCN Palliative Care Panel is an interdisciplinary group of representatives from NCCN Member Institutions, consisting of medical oncologists, hematologists and hematologic oncologists, pediatric oncologists, neurologists and neuro-oncologists, anesthesiologists, psychiatrists and psychologists, internists, palliative care and pain management specialists, and geriatric medicine specialists. These guidelines were developed and are updated annually by the collaborative efforts of these experts based on their clinical experience and available scientific evidence.

More than 1.68 million people are expected to be diagnosed with cancer in the United States in 2017, and 600,920 people are expected to die of the disease.<sup>1</sup> Global cancer rates are increasing, with an associated rise in the number of cancer survivors living with symptoms and disabilities as a result of their disease and/or its treatment (see the [NCCN Guidelines for Survivorship](#)).<sup>1-3</sup> More than one-third of patients with cancer in a large observational cohort study reported moderate to severe symptoms in the majority of categories (pain, nausea, anxiety, depression, shortness of breath, drowsiness, well-being, loss of appetite, and tiredness) in the last weeks of life.<sup>4</sup> Greater access to palliative care may help to address the challenges faced by oncology patients and their families.

The Center to Advance Palliative Care (CAPC; [www.capc.org](http://www.capc.org)) describes an optimal approach in which care is “provided by a team of palliative care doctors, nurses, and other specialists who work together with a patient’s other doctors to provide an extra layer of support. It is appropriate at any age and at any stage in a serious illness and can be provided along with

curative treatment”.<sup>5</sup> During the past 20 years, increasing attention has been paid to quality-of-life issues in oncology throughout the disease trajectory.<sup>3,6-11</sup> Palliative care in oncology began as hospice and end-of-life care, but it has developed into an integral part of comprehensive cancer care.<sup>3,12-16</sup>

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Palliative Care, an electronic search of the PubMed database was performed to obtain key literature in palliative care published between June 2015 and May 2017, using the following search terms: (palliative care AND cancer) OR (palliative care AND oncology) OR (hospice AND cancer) OR (hospice AND oncology) OR (“end of life” AND cancer) OR (“end of life” AND oncology). The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 589 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

### Palliative Care in Oncology

These guidelines define palliative care as a special kind of patient- and family-centered health care that focuses on effective management of pain and other distressing symptoms, while incorporating psychosocial and spiritual care according to patient/family needs, values, beliefs, and culture(s). The goals of palliative care are to anticipate, prevent, and reduce suffering and to support the best possible quality of life for patients and their families, regardless of the stage of the disease or the need for other therapies.<sup>17</sup> Palliative care begins at diagnosis and should be delivered concurrently with disease-directed, life-prolonging therapies and should facilitate patient autonomy, access to information, and choice. While palliative care previously focused on end-of-life care, the idea that palliative care needs to be integrated earlier into the continuum of cancer care is increasingly understood.<sup>18-22</sup> Palliative care becomes the main focus of care when disease-directed, life-prolonging therapies are no longer effective, appropriate, or desired, or when symptoms predominate.

Palliative care should be initiated by the primary oncology team (including physicians, nurses, social workers, other mental health professionals, chaplains, physician assistants, pharmacists, and dietitians) and then augmented by collaboration with an interdisciplinary team of palliative care experts to address intractable symptoms and/or complex psychosocial issues. Additionally, palliative care efforts should reach beyond the patient to family and caregivers. When further anti-cancer therapy is likely to do more harm than good, palliative care becomes the predominant care offered to patients with advanced cancer. When possible, inpatient palliative care can facilitate transfer to hospice care at home or in a care facility. For patients too unstable for transfer out of the inpatient setting, palliative care and hospice may provide end-of-life care for patients in the

hospital. Palliative care should continue even after the patient's death in the form of bereavement support for the patient's family and caretakers. Several groups have described their ideas and approaches for, experience and outcomes with, and barriers to developing successful programs that integrate palliative care into routine oncologic care.<sup>21-35</sup>

### Impact of Palliative Care

In February 2012, ASCO published a provisional clinical opinion based on 7 randomized controlled trials and expert consensus.<sup>36</sup> The ASCO panel stated that there is substantial evidence to show that “palliative care—when combined with standard cancer care or as the main focus of care—leads to better patient and caregiver outcomes”. The ASCO panel concluded that strong consideration should be given to the integration of palliative care with standard oncology care early in the course of illness for patients with metastatic cancer and/or high symptom burden. In 2014, a dynamic service model for integrating palliative care into the continuum of oncology care was presented at an ASCO leadership conference.<sup>34</sup>

In 2016, ASCO updated their guidelines to state – based on multiple randomized trials – that palliative care should be standard for all advanced cancer patients. Systematic review of the palliative care in oncology data supported best outcomes with care provided by an interdisciplinary palliative care team initiated within eight weeks of diagnosis.<sup>37</sup> In the existing trial data, oncologist-alone care served as the standard and inferior arms, and the data were unable to demonstrate that oncologists alone were able to adequately provide both the oncologic and palliative aspects of care. The principal investigators of several of these major trials support implementation of the TEAM approach (*T*ime, an extra hour a month; *E*ducation, especially about prognostic awareness, achievable goals, and advance care planning; *A*ssessments done formally for symptoms, spiritual needs, and distress/coping; and *M*anagement, by and



interdisciplinary team) as a structured way for oncology offices to design their care.<sup>38</sup>

Studies show that early integration of palliative care into the cancer care continuum results in improved patient outcomes.<sup>39-41</sup> A remarkable study showed that early introduction of palliative care can not only improve quality of life for patients with advanced cancer but can also improve survival.<sup>42</sup> A secondary analysis of this study further showed that patients receiving early palliative care were less likely to receive intravenous chemotherapy in the last 60 days of life (odds ratio, 0.47; 95% CI, 0.23–0.99;  $P = .05$ ),<sup>43</sup> likely because these patients had a more accurate understanding of their prognosis, which impacted decisions about their care.<sup>44</sup> Another study demonstrated significant improvement in multiple symptoms within one day of a palliative care consultation, highlighting the potential benefit of palliative care even during brief hospital stays.<sup>45</sup>

A recent prospective study showed that early integration of palliative care facilitated the discontinuation of anticancer regimens and improved measures of quality of life for patients with advanced breast or gynecologic cancers. Further, palliative care consultation was a positive prognostic factor for overall survival.<sup>40</sup> Similarly, a retrospective analysis of 609 patients with terminal cancer suggested that increased duration of palliative care services was positively correlated with survival time.<sup>46</sup> Home-based palliative care was associated an equal or longer survival compared to inpatient palliative care in patients with cancer.<sup>47</sup>

Results were recently reported from the ENABLE III trial, which examined outcomes after early versus delayed initiation of palliative care in patients with advanced cancer. Patients in the early palliative care group had significantly higher Kaplan-Meier 1-year survival rates than the delayed palliative care group (63% vs. 48%,  $P = .038$ ).<sup>41</sup> The timing of interventions for caregivers was also examined in this trial, suggesting that earlier

provision of palliative care for caregivers lessened their depression and stress burden scores.<sup>48</sup>

In a study comparing standard care with ongoing palliative care in patients with advanced cancer who had a prognosis of 6 to 24 months to live, palliative care resulted in improved patient quality of life, satisfaction with care, and decreased symptom severity.<sup>39</sup> A recent retrospective analysis of patients with advanced cancer highlighted the importance of early palliative care consultations (>3 months before death) and revealed an association between outpatient palliative care and decreased aggressiveness of end-of-life care.<sup>49</sup>

A 2015 systematic review of studies on early integration of outpatient/home palliative care revealed numerous trials demonstrating the positive impact of early palliative care, but also highlighted the lack of standard methodology across trials to assess outcomes.<sup>50</sup> Overall, research suggests that successful integration of palliative care early in the continuum of care reduces morbidity for patients with cancer and enhances patient and family/caregiver satisfaction (reviewed by Rocque and Cleary<sup>51</sup> and Khan et al<sup>52</sup>).

Earlier palliative care has also been shown to affect end-of-life care trajectories. Palliative care consultations in patients with advanced cancers have also been shown to reduce the quantity and intensity of life-prolonging care received towards the end of life. Likewise, the lack of palliative care team consultation has been shown to be a predisposing factor for futile life-sustaining treatments at the end of life.<sup>53</sup> An observational study suggested that inpatient palliative care led to stabilized end-of-life care trajectories after discharge.<sup>54</sup>

Studies have also demonstrated the potential for community-based or home-based palliative care services to positively influence patient care. These services have been associated with reduced need for end-of-life

emergency department visits, reduced length and frequency of hospitalization, as well as fewer ICU admissions and in-hospital deaths.<sup>55-</sup>

<sup>59</sup> Palliative care has been shown to reduce symptom burden, improve quality of life, and increase the odds of dying at home. Similarly, a 2013 Cochrane Database systematic review that analyzed home palliative care in patients with advanced illness demonstrated reliable reduction of symptom burden and increased likelihood of dying at home without a negative impact on caregiver grief.<sup>60</sup>

Palliative care has also been linked to cost-savings as well. Earlier palliative care consultations have been associated with decreased health care costs for patients with advanced cancer, including those with multiple comorbidities.<sup>61,62</sup> According to recent data, dedicated palliative care units and programs can be cost effective and favorably impact health systems finances.<sup>63,64</sup>

### Role of Hospice Care

Hospice is the most established model of palliative care for patients with a prognosis of less than 6 months and is eligible for coverage by third-party payers and Medicare. Enrollment in hospice has been shown to reduce hospitalization and receipt of high-intensity non-hospice care at the end of life. According to the National Home and Hospice Care Survey, the number of adult patients with cancer using hospice care tripled during 1991 through 1992 to 1999 through 2000.<sup>65</sup> The 2013 edition of *NHPCO Facts and Figures: Hospice Care in America* states that 43.3% of Medicare decedents with a cancer diagnosis accessed  $\geq 3$  days of hospice in 2007, increasing from 36.6% in 2001.<sup>66</sup> However, the median length of stay (LOS) in hospice service was just under 19 days in 2012,<sup>66</sup> and recent studies suggest continued underuse of hospice services among eligible patients.<sup>67,68</sup> Most patients who receive hospice care in this country are referred too late for hospice care to exert its full benefit, and many patients are never referred at all.<sup>69,70</sup> A recent study of Medicare patients with

advanced lung cancer supports this, revealing that over 75% of patient deaths occurred without enrollment in hospice.<sup>71</sup>

An analysis of the SEER database revealed that men with advanced prostate cancer who were enrolled in hospice were less likely to receive high-intensity care, including ICU admission and inpatient stays, at the end of life.<sup>69</sup> Moreover, a study of 207 deceased patients with cancer who had stopped cancer treatment showed reduced emergency department visits, hospitalizations, and other noncancer clinic visits for those enrolled in hospice.<sup>72</sup> Additionally, analyses of data from 3069 deceased patients more than 50 years of age (extracted from the Health and Retirement Study) revealed that hospice enrollment significantly decreased hospitalization, non-hospice health care utilization, and cost of care.<sup>73</sup>

End-of-life care can often be more aggressive than what is supported by current evidence. Generally, Medicare patients with poor-prognosis cancer received highly intensive end-of-life-care.<sup>74</sup> Furthermore, administration of chemotherapy late in the course of cancer care, including in the last days of life, is growing more common,<sup>75,76</sup> and oncologists have reported that they have found hospice regulations and reimbursement limitations too restrictive.<sup>77</sup> Overall, provision of end-of-life care was inconsistent and varied widely across regions, even among comprehensive cancer centers.<sup>74,78</sup>

One study at an academic medical center revealed marked and unwarranted variation in hospice LOS within divisions and by doctor. For instance, in thoracic oncology, several oncologists had an average LOS of 36 days while others were clustered around 4 days for the same patient population. However, oncologists were receptive to feedback and training<sup>79</sup> By establishing hospice referrals as a quality improvement measure, one health system reported that LOS in hospice doubled within a year of implementation.<sup>80</sup> Similarly, another recent study revealed that educational outreach and implementation of specific triggers for palliative



care consultation were associated with increased hospice referrals and LOS.<sup>81</sup>

### Palliative Care Standards & Research

Assessing outcomes and evaluating palliative cancer care is essential to ensure high-quality, evidence-based care. However, systematic reviews of the data often suggest that many aspects of palliative care lack high-quality evidence, and there is a general lack of standard methodology in palliative care trials.<sup>50,82-84</sup>

The third edition of the Clinical Practice Guidelines for Quality Palliative Care by the National Consensus Project was published in 2013,<sup>85</sup> and the National Quality Forum has developed a national quality framework for evaluating palliative care programs, extending beyond terminally ill patients with cancer to include a broad spectrum of patients with multiple illnesses.<sup>86</sup> These guidelines provide an in-depth assessment of many issues surrounding palliative care (eg, cultural, ethical, legal, physical, psychological, social, spiritual, and existential aspects of care).

ASCO recently published a statement on individualized care for patients with advanced cancer.<sup>9</sup> While significant improvements over the past decade were noted (eg, improvements in palliative care education and training for oncologists; an increase in hospital-based palliative care programs and community-based hospice organizations), the statement points out that conversations with patients about their palliative needs are still happening too late in the progression of their disease. Some of the key elements of individualized care listed in the report state that patients should be given:

- enough information to enable them to make informed choices regarding their treatment;
- encouragement to focus on symptom-directed palliative care when disease-directed therapies fail;

- the opportunity to participate in clinical trials that may improve their outcome or that of future patients; and
- the opportunity to die with dignity and peace of mind.

In August 2011, the Commission on Cancer (CoC) of the American College of Surgeons (ACS) released new accreditation standards for hospital cancer programs (<http://www.facs.org/news/2011/coc-standards0811.html>).<sup>87</sup> Their patient-centered focus requires that patients have access to palliative and hospice care, psychosocial support, and pain management—either onsite or by referral. The standards also state that palliative care should be provided by an interdisciplinary team of medical and mental health professionals, social workers, and spiritual counselors and should be available beginning at the time of diagnosis and continuously throughout treatment, surveillance, and bereavement.

In 2014, the Institute of Medicine (IOM) released a consensus report entitled “Dying in America- Improving Quality and Honoring Individual Preferences Near the End of Life,” in which experts highlighted the need for improved end-of-life care. Key findings and recommendations for improved quality of care focused on person-centered, family-oriented care; clinician-patient communication and advance care planning; professional education and development; policies and payment systems; and public education and engagement.<sup>88</sup>

Implementation of standardized patient-centered outcome measures (PCOMs) in palliative care has been shown to impact processes of care, improving symptom recognition, promoting discussion of quality of life, and increasing referrals based on PCOM-generated information.<sup>35</sup> Similarly, a study by Kamal and colleagues showed that provider conformance with supportive care quality measures significantly improved quality of life for patients with cancer who were receiving palliative care.<sup>89</sup>

### Trial Design

The evidence base for the treatment recommendations for physical and psychosocial symptoms in patients with cancer is generally weak.<sup>83,84</sup> Clinical trials in palliative oncology face many challenges, including recruitment difficulties, high attrition rates, and insufficient funding.<sup>90-92</sup> Several groups have recommended considerations for the design of future palliative care clinical trials, including standardization of reporting and supportive care measures, the integration of technology for data collection, the use of validated outcome measures, and the use of trial designs other than the randomized controlled trial.<sup>35,93-100</sup> In addition, formal feasibility studies can help ensure the success of subsequent larger trials.<sup>94,101</sup>

A 2015 systematic review of studies on early integration of outpatient/home palliative care revealed numerous trials demonstrating the positive impact of early palliative care, but also highlighted the lack of standard methodology across trials to assess outcomes.<sup>50</sup> Despite the challenges associated with conducting large-scale palliative care research studies, several notable studies have examined the impact of palliative care efforts on patient and family/caregiver outcomes.<sup>83</sup> Ongoing studies continue to evaluate improved methods for early integration of palliative care into oncologic treatment.<sup>102</sup>

### Barriers to Timely Provision of Palliative Care

The major reasons for delayed referral to palliative care are professional reluctance and public confusion about the definition of palliative care. Despite the growth of clinical and academic palliative care over the past two decades and the efforts of most palliative care organizations to clarify that palliative care should be given at the time of diagnosis or when there are poorly managed symptoms regardless of prognosis, many people think that palliative care still refers only to care given at the end of life, leading to an inappropriate association of palliative care with death.<sup>103-106</sup> Supportive care has been suggested as an alternative name, to help break

this association and facilitate earlier use of palliative care for patients in need. Supportive care in cancer initially focused on the support of patients receiving active cancer therapy with antiemetics, antibiotics, bone marrow stimulants, and transfusions.<sup>107</sup> However, some studies suggest that patients and providers may prefer supportive care terminology to refer to palliative care services.<sup>108,109</sup> At MD Anderson Cancer Center, a switch in the service name from “Palliative Care” to “Supportive Care” was associated with increased patient referrals, referrals at an increased interval before death, and referrals earlier in the course of disease.<sup>110</sup> Regardless of the terminology, patients and families should be informed that palliative care is an integral part of their comprehensive cancer care.<sup>103,111,112</sup>

A retrospective review of patients with advanced cancer seen at MD Anderson Cancer Center found that only 45% of patients had a palliative care consultation before death, and many of those occurred close to death.<sup>113</sup> Similarly, a retrospective study of 6076 patients with advanced pancreatic cancer revealed that only 52% of patients received a palliative care consultation.<sup>114</sup> Data from the Nationwide Inpatient Sample on patients with incurable head and neck cancers revealed a palliative care consultation rate of only 5%.<sup>115</sup> Interestingly, in a recent survey only 37% of physicians reported that they had access to a specialized palliative care service that accepted patients on chemotherapy.<sup>116</sup> Despite the 6-month prognosis eligibility, the median length of service for hospice patients in 2012 was 18.7 days. Approximately 36% of hospice patients died or were discharged within 7 days of admission to hospice care.<sup>66</sup> Thus, barriers to early referrals still exist (reviewed by Davis et al<sup>22</sup>).

The American Academy of Hospice and Palliative Medicine ([www.aahpm.org](http://www.aahpm.org)), founded in 1988, and the CAPC ([www.capc.org](http://www.capc.org)), established in 1999, are organizations dedicated to advancing the discipline of hospice and palliative medicine. These organizations seek to

expand access to quality palliative care services in hospitals and other health care settings for people with advanced illness.

### Training in Palliative Care

Educational programs should be provided to all health care professionals and trainees so they can develop effective palliative care knowledge, skills, and attitudes. The number of palliative care programs in the United States is rapidly increasing. The establishment of hospice and palliative medicine as a medical subspecialty in 2008 received support from at least 10 cosponsoring American Board of Medical Specialties (ABMS; [www.abms.org](http://www.abms.org)) boards, including Anesthesiology, Family Medicine, Internal Medicine, Physical Medicine and Rehabilitation, Psychiatry and Neurology, Surgery, and Pediatrics. Support for expansion of palliative medicine education has been offered by the Liaison Committee on Medical Education (LCME; [www.lcme.org](http://www.lcme.org)), which has mandated palliative medicine education for medical schools. In addition, the Accreditation Council for Graduate Medical Education (ACGME; [www.acgme.org](http://www.acgme.org)) now requires training in palliative medicine for oncology fellows, including training in pain, psychosocial care, personal awareness, and hospice care.

Researchers at a large urban teaching hospital demonstrated the effectiveness of education on palliative care and referral criteria for increasing overall referrals to palliative care services and enhanced referrals for the purpose of pain management.<sup>117</sup> Effective training in palliative care can also positively impact provider, patient, and caregiver quality of life. One study suggested that an online palliative care education intervention for primary care physicians led to measurable improvements in patient outcomes such as pain, symptoms, and quality of life.<sup>118</sup> In a survey study, oncology fellows reported that training on end-of-life issues and goal-of-care discussions mitigated burnout and distress.<sup>119</sup>

Provider education and training in palliative care can positively impact providers and patients. The OPTIM (Outreach Palliative Care trial of Integrated Regional Model) study is a multiregional, mixed-methods study that examined the effects of a palliative care intervention implemented across 4 regions of Japan.<sup>120</sup> The intervention consisted of provider education and training; education and awareness initiatives for the general public/patients; establishment of community-based palliative care teams to instruct community health care institutions; and establishment of regional palliative care centers to coordinate multidisciplinary community resources. Surveys were provided to patients, bereaved family members, physicians, and nurses both before and after the intervention. The results indicated an increased percentage of patients receiving palliative care and dying at home, increased patient- and family-reported quality of care, and decreased physician- and nurse-reported difficulties in providing palliative care.

Palliative care resources that may be useful for clinicians are listed in Table 1, below.

### Communication Skills Training

Provider communication skills play a particularly important role for palliative care in oncology. However, several studies have revealed gaps in patient-centered communication with regard to patient prognosis and understanding of the intent of treatment. Valuable insight has been garnered regarding provider communication and patient understanding from the Cancer Care Outcomes Research and Surveillance (CanCORS) study of approximately 10,000 patients with lung or colorectal cancer. A survey of 1193 patients from CanCORS found that 69% of patients with advanced lung cancer and 81% of those with advanced colorectal cancer thought that their palliative chemotherapy could cure them.<sup>121</sup> While it is unclear whether these patients were told their prognosis, if they did not understand or choose to understand the information, or if they merely



answered the survey with a high degree of optimism,<sup>122</sup> this result demonstrates a clear need for improvement in the area of physician-patient communication. Additional analyses of 722 patients with stage IV lung or colorectal cancer showed that only 33% of patients recognized that their chemotherapy regimens were “not at all” likely to cure their cancer.<sup>123</sup> Similar misconceptions also apply to palliative radiation therapy. In a study of 384 patients with inoperable lung cancer, 64% of patients did not understand that their radiation therapy was not curative.<sup>124</sup> Notably, in a cohort of 686 patients with metastatic lung or colorectal cancer from CanCORS, only 16.5% were able to correctly state their prognosis.<sup>125</sup>

Survey and observational data have revealed that many doctors are hesitant to have honest discussions with their patients, in part because these discussions can be very difficult and emotionally draining for the physicians.<sup>126-128</sup> Oncologists revealed a high level of perceived burden regarding discussions about discontinuing anticancer treatments, and study results have indicated a desire on the part of providers for additional communication skills training.<sup>127,128</sup> Training in communication has been shown to improve clinician-patient communication<sup>129-133</sup> and to possibly decrease physician burnout and improve physician empathy and mood.<sup>134</sup> For example, a recent randomized controlled trial showed that an 11-hour communication skills training workshop for oncologists was effective at improving communication skills, including those specific to the transition to palliative care.<sup>135</sup> Additionally, the VOICE cluster randomized controlled trial recently demonstrated the effectiveness of a patient-centered communication training for physicians caring for patients with advanced cancer.<sup>133</sup>

Clear, consistent, and empathetic communication with the patient and family about the natural history of the cancer and its prognosis is at the core of effective palliative care.<sup>136-140</sup> It is important to assess and reassess patient goals and preferences regarding communication of difficult news

over the course of disease.<sup>141</sup> When patients understand the goals of treatment, they can make choices that are consistent with their life goals. A multicenter observational study revealed that prognostic disclosure from physicians resulted in more realistic patient expectations regarding life expectancy without harming measures of emotional wellbeing or patient ratings of their physician relationship.<sup>142</sup> In addition, effective patient-physician communication has been shown to decrease patient stress, increase adherence to treatment, and improve outcomes.<sup>143,144</sup> Open communication with relatives or caregivers of patients with cancer is also critical, particularly when patients near the end of life.<sup>139,145</sup>

### NCCN Guidelines for Palliative Care

The NCCN Guidelines for Palliative Care were developed to facilitate the appropriate integration of palliative care into oncology practice. The guidelines outline procedures for screening, assessment, palliative care interventions, reassessment, and after-death care. The panel initially focused on the needs of patients in their last 12 months of life. The panel chose this period to distill the content of textbooks and curricula into guidelines that could facilitate clinical decision-making in the same way that NCCN disease-oriented and symptom-oriented guidelines have. More recent versions of these guidelines have expanded the focus to all patients and family experiencing cancer throughout the disease trajectory, consistent with the Provisional Clinical Opinion from ASCO.<sup>36</sup>

### Palliative Care Screening

The primary oncology team should screen all patients at every visit for one of more of the following: 1) unmanaged symptoms; 2) moderate to severe distress related to cancer diagnosis and therapy; 3) serious comorbid physical, psychiatric, and psychosocial conditions; 4) potentially life-limiting disease; 5) metastatic solid tumors; 6) patient or family concerns about the course of disease and decision-making; 7) patient or family requests for palliative care; and/or patient request for hastened death.

Patients who meet these screening criteria and those who make a specific request for palliative care should undergo a full palliative care assessment.

Patients who do not meet these screening criteria should be re-screened at the next visit. In addition, the oncology team should inform patients and their family members about palliative care services. Anticipation of palliative care needs and prevention of symptoms should also be discussed, and conversations regarding advance care planning should be initiated.

### Palliative Care Assessment

Patients who meet screening criteria (see above) should undergo a comprehensive palliative care assessment by their primary oncology team evaluating the benefits and burdens of anticancer therapy; physical symptoms; psychosocial or spiritual distress; personal goals, values, and expectations; educational and informational needs; and cultural factors affecting care.<sup>6-8</sup>

#### **Assessment for Benefits and Burdens of Anticancer Therapy**

Many cancer symptoms can be relieved by control of the cancer with anticancer therapy. Assessment of the benefits and burdens of anticancer therapy for each individual is based on the existing NCCN disease-specific guidelines (the most recent version of all guidelines can be found on the NCCN website at [www.NCCN.org](http://www.NCCN.org)). Special attention should be given to the natural history of the specific tumor; the potential for response to further treatment; the meaning of anticancer therapy to the patient and family; the potential for treatment-related toxicities including impairment of vital organs and performance status; and serious comorbid conditions. Specific recommendations regarding anticancer therapy for patients with various life expectancies are discussed in *Palliative Care Interventions*, below.

#### **Assessment of Patient and Family Goals, Values, Expectations, and Priorities**

Patients and their families should also be asked about their personal goals, values, expectations, and priorities. Shared decision-making with patient and family is important. A 2015 systematic review of quantitative studies identified the following elements of palliative care that were ranked as most important by patients and their families: effective communication and shared decision-making; expert care; respectful and compassionate care; and trust and confidence in clinicians.<sup>140</sup>

The patients' priorities for palliative care, including goals, the perceived meanings of both anticancer therapy and quality of life, should be assessed. Goals and expectations that might be better met by the hospice model of palliative care should be identified. When appropriate, it is important to determine the patients' understanding of the incurability of their disease and whether patients wish to know survival statistics.

#### **Assessment of Physical Symptoms**

The most common symptoms that need to be assessed are pain, dyspnea, anorexia, cachexia, nausea, vomiting, constipation, malignant bowel obstruction, fatigue, weakness, asthenia, insomnia, daytime sedation, and delirium.<sup>146</sup> Palliative interventions for these symptoms are discussed individually below.

#### **Assessment of Psychosocial Distress**

Assessment of psychosocial distress should focus on illness-related distress and psychosocial, spiritual, or existential needs according to the [NCCN Guidelines for Distress Management](#). Special problems with social support and resources (ie, home, family, community, or financial issues) must also be assessed. Recommendations for the management of psychosocial distress can be found below and in the NCCN Guidelines for Distress Management.

### **Assessment of Educational and Informational Needs and Cultural Factors Affecting Care**

The values and preferences of patients and families about information and communication should also be assessed. The oncology team should inquire about cultural factors affecting care and perceptions of the patient/family regarding the patient's disease status.<sup>147</sup>

### **Criteria for Consultation with Palliative Care**

Criteria for consultation with a palliative care specialist are based on patient characteristics, social circumstances, and anticipatory bereavement issues. The oncology team should consider consultation for patients with a life-limiting cancer diagnosis or limited anticancer treatment options due to advanced disease process, multiple/severe comorbid conditions, and/or rapidly progressive functional decline or persistently poor performance status. Additional criteria include high symptom burden, especially non-pain symptoms resistant to conventional management; history of multiple allergies or adverse effects; frequent emergency department visits or hospital admissions; need for ICU-level care; need for palliative stenting/gastrostomy; a high distress score (eg,  $\geq 4$  on the Distress Thermometer; see the [NCCN Guidelines for Distress Management](#)); cognitive impairment; or communication barriers. In addition, consultation with palliative care specialists should be considered for those needing clarification of the goals of care; patient/family or provider dissatisfaction with the care plan; those at high risk for poor pain management; those who make a request for hastened death; and/or those who are resistant to engaging in advance care planning.

Difficult social circumstances or a high risk for complicated grief reactions indicate a need for referral for consultation with a palliative care specialist. These may include family/caregiver limitations, inadequate social support, financial limitations, limited access to care, family discord, intensely dependent relationships, financial limitations, limited access to care, patient's concern regarding care of dependents, spiritual or existential

distress, unresolved or multiple prior losses, and/or children younger than 18 years of age living in the household.

Palliative care consultation should also be considered when complex care coordination issues exist among multiple care teams, or if staff issues such as compassion fatigue, moral distress, or burnout are present. For more information regarding psychosocial issues affecting care providers, see the section on *Psychosocial Support for Palliative Care Providers*.

### **Palliative Care Interventions**

The oncology team should initiate palliative treatments following the specific recommendations described in these guidelines for common symptoms. Comorbid physical and psychosocial conditions should be treated by appropriate clinicians. Consultation or collaboration with palliative care specialists or teams is recommended for patients with more complex problems to improve their quality of life and survival.<sup>36,41,42,47</sup> Referrals should be made as needed to mental health and social services, pastoral care, health care interpreters, hospice services, or other specialists. Finally, the oncology team can be helpful in mobilizing community support through religious organizations, schools, or community agencies.

The panel divided patients into 3 groups to address the effect of life expectancy on the delivery of palliative care interventions: 1) patients with years to months to live; 2) patients with months to weeks to live; and 3) dying patients in their final weeks to days. Patients in their final hours of life are referred to as *imminently dying* and may require special interventions. The panel recognizes the lack of precision in estimating life expectancy but believes that this delineation will be useful for the delivery of appropriate palliative care interventions. The patient and family's personal, spiritual and existential, cultural, and religious goals, values, and expectations may change throughout these timeframes. Optimal provision



of palliative care requires ongoing reassessment and modification of strategies, as well as ongoing communication between the patient, family, and health care team.

Indicators that patients are in their last 6 months of life include decreased performance status (ECOG score  $\geq 3$ ; KPS score  $\leq 50$ ), persistent hypercalcemia, central nervous system metastases, delirium, superior vena cava syndrome, spinal cord compression, cachexia, malignant effusions, liver failure, kidney failure, or other serious comorbid conditions. Many patients with stage IV cancers, especially those with metastatic lung cancer, pancreatic cancer, and glioblastoma multiforme, would benefit from palliative care beginning at diagnosis, because expected survival is limited.<sup>148-150</sup>

For patients whose life expectancy is “years to months” or “months to weeks,” it is important to determine how much information a patient wishes to know and how much of that information should be shared with the patient’s family. In patients queried regarding preferences about receiving prognostic information and detailed information on their disease, studies show that the majority express a desire to receive this information.<sup>151-154</sup> Patients will also require answers to any questions about what to expect in the next few months and anticipatory guidance on the dying process. In addition, determining the decision-making styles of patients and their families helps facilitate congruence of a patient’s goals, values, and expectations with those of the family. Clinicians should also determine the patient’s assessment of the relative importance of quality of life compared with length of life. Patients should be assisted in reviewing and revising their life priorities, resolving their unfinished business, and putting their financial and personal affairs in order.

Dying patients may wish to prepare for death and to help prepare family members to go on without them. Both patients and families benefit from education on the dying process. Families should be guided through their

anticipatory grief, and arrangements should be made to ensure that the patient’s and family’s needs and goals regarding the dying process are respected. Planning to ensure continuing care and referrals to appropriate care is important. Arrangements should be available to ensure that the patient does not die alone unless that is the patient’s preference.

Clinicians should discuss the prognosis with patients and their families clearly and consistently to help them develop realistic expectations. Assessment and confirmation of understanding of prognosis is important and may guide treatment decisions. Information about the natural history of the specific tumor and the realistic outcomes of anticancer therapy should be included in the discussion. Many investigators have shown that seriously ill middle-aged and older patients tend to be more optimistic and less accurate about their prognosis than their physicians; such misunderstanding of the situation can affect their preferences for cardiopulmonary resuscitation and for life-extending measures.<sup>155</sup> Spiritual, existential, and cultural issues are often best addressed through collaboration with pastoral care counselors, professional translators, the patient’s personal clergy, and representatives from the patient’s cultural community. Religious and cultural issues surrounding the beliefs and practices near the time of death must be anticipated and carefully managed.<sup>147,156</sup> Finally, social and spiritual support and resource management interventions should be provided to ensure a safe end-of-life care environment, a competent primary caregiver, and access to necessary medications and treatments. Providers must be sensitive to cultural values that may influence the best way for this information to be presented and discussed.

Palliative care interventions for managing specific symptoms and the benefits and burdens of anticancer therapy are discussed below as outlined in the algorithm. Additional palliative care interventions for other symptoms will be developed as deemed necessary.

### Anticancer Therapy

A recent IOM report, *Communicating with Patients on Health Care Evidence*, found that 90% of Americans surveyed want to know their options for tests and treatments and to be involved in decision making for their health, with almost 50% wanting to discuss the option of forgoing anticancer therapy and continuing non-chemotherapy palliative care.<sup>157,158</sup> However, the report also found that far fewer respondents had such discussions with their physicians.

Patients who have years to months to live and a good performance status are likely to be interested in continuing anticancer therapy to prolong survival and reduce cancer-related symptoms.<sup>159-162</sup> Anticancer therapy may be conventional evidence-based treatment as outlined in the NCCN disease-specific guidelines (available at [www.NCCN.org](http://www.NCCN.org)) or treatment in the context of a clinical trial. In some of the advanced-stage cancers, chemotherapy may be superior to best supportive care and may prolong survival.<sup>163,164</sup> Palliative RT also plays an important role in the management of patients with advanced cancer.<sup>165</sup> Furthermore, patients with advanced cancer who are not eligible for systemic chemotherapy may benefit from molecular targeted therapies that may be effective for relieving symptoms, maintaining stable disease, and improving quality of life without the adverse events that may be associated with cytotoxic cancer therapies.<sup>166,167</sup> Physicians, patients, and their families should discuss prognosis, intent and goals of therapy (palliative or curative), range of choices, benefits and burdens of anticancer therapy, and possible effects on quality of life. In addition, the oncology team should prepare the patient psychologically for possible disease progression.

Anticancer therapy should be in line with stated patient goals and priorities and be accompanied by appropriate prevention/management of side effects as well as palliative care. A recent longitudinal cohort study evaluated the impact of palliative chemotherapy on quality of life near

death as a function of patient performance status. In patients with progressive metastatic cancer, palliative chemotherapy failed to improve quality of life near death for those with moderate or poor performance status and worsened quality of life for those with initially good performance status.<sup>168</sup> Anticancer therapy may at times go beyond what is evidence-based. A CanCORS study of 1574 patients with metastatic non-small cell lung cancer suggested that many patients received higher doses and a greater number of palliative radiation treatments than what is supported by current evidence.<sup>169</sup> Additionally, a study of patients with metastatic colorectal cancer revealed that more than 90% of patients consulted with a medical oncologist, and 82% of these patients received chemotherapy.<sup>170</sup>

Patients with months to weeks to live should be provided with guidance regarding the anticipated course of the disease. Physicians should confirm patients' understanding of goals of therapy and preferences regarding prognostic information. These patients are typically tired of therapy, homebound, and more concerned about the side effects of more treatment. The focus of treatment for these patients shifts from prolonging life towards maintaining quality of life. These patients should consider potential discontinuation of anticancer treatment that is not directly addressing a symptom complex and be offered best supportive care, including referral to palliative care or hospice.<sup>167,168,171-173</sup> To avoid demeaning the value of end-of-life care, palliative care and/or hospice care should not be described as "giving up," but instead reframed as "fighting" for better quality of life.

In general, patients with weeks to days to live (ie, dying patients) should discontinue all treatments not directly contributing to patient comfort. Intensive palliative care focusing on symptom management should be provided in addition to preparation for the dying process. Refer to hospice when possible.

### Symptom Management

Special considerations in the implementation of these guidelines based on life expectancy are delineated in the algorithm. The major focus of these special considerations is the withholding and withdrawal of aggressive interventions; prevention and elimination of side effects associated with pharmacologic pain management; the acceptance of loss of function for the sake of relief of symptoms; and the treatment of the unique symptoms of patients in their final hours of life.

With regard to symptoms, the management of pain, dyspnea, anorexia/cachexia, nausea and vomiting, constipation, diarrhea, malignant bowel obstruction, fatigue, delirium, and psychological distress is fundamental<sup>174-176</sup> and discussed in detail below. As a general principle, if/when appropriate, providers should try to use palliative interventions that may address multiple symptoms.

#### Pain

See the [NCCN Guidelines for Adult Cancer Pain](#). In addition, it is important to note that dying patients in their last weeks of life have several specific requirements. For instance, opioid dose should not be reduced solely for decreased blood pressure, respiration rate, or level of consciousness when opioid is necessary for adequate management of dyspnea and pain. In fact, opioids can be titrated aggressively for moderate/severe acute/chronic pain.<sup>177</sup> In addition, palliative sedation can be considered for refractory pain (see below) following consultation with pain management/palliative care specialists. Palliative RT may be used to address pain associated with bone metastases.<sup>178,179</sup>

#### Dyspnea

Dyspnea is one of the most common symptoms in patients with advanced lung cancer.<sup>180</sup> The American Thoracic Society consensus statement

defines dyspnea as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity”.<sup>181</sup>

Symptom intensity should first be assessed in all patients. In non-communicative patients with weeks to days to live, symptom intensity should be assessed using physical signs of dyspnea. Underlying causes or comorbid conditions should be treated using chemotherapy or radiation therapy; therapeutic procedures for cardiac, pleural, or abdominal fluid<sup>182-184</sup>; bronchoscopic therapy; or bronchodilators, diuretics, steroids, antibiotics, transfusions, or anticoagulants for pulmonary emboli.

Both pharmacologic and non-pharmacologic interventions have been investigated in the management of dyspnea. A review concluded that little definitive data evaluating the effectiveness of dyspnea interventions exist and that randomized controlled trials are needed.<sup>185,186</sup> Other reviews have determined that there are sufficient data to make treatment recommendations.<sup>183,187</sup> Pharmacologic interventions may include opioids with or without benzodiazepines.<sup>183,185,186,188-191</sup> Benzodiazepines can be tried for treatment of dyspnea if it is associated with anxiety; the beneficial effect of benzodiazepines on dyspnea in patients with advanced cancer is small.<sup>185</sup>

Of the opioids, morphine has undergone the most extensive investigation for treating dyspnea in patients with cancer, but recent studies have also looked at opioids such as fentanyl and oxycodone. A single-institution trial of nebulized fentanyl in patients with cancer with dyspnea showed improved oxygenation and reduced tachypnea, and 79% of patients said it improved their breathing.<sup>192</sup> An attempted randomized, placebo-controlled trial at the same institution was not successful, because the practice had already diffused widely with over 1000 doses being prescribed.<sup>193</sup> Multiple case reports give promising data about fentanyl, but further research is needed.<sup>194</sup> In a small randomized controlled trial, prophylactic subcutaneous fentanyl was effective for improving dyspnea and fatigue at



rest and following a 6-minute walk test.<sup>195</sup> A study revealed that nebulized fentanyl reduced intensity and unpleasantness of dyspnea in patients with chronic obstructive pulmonary disease (COPD).<sup>196</sup> Nebulized fentanyl has not yet been studied in patients with cancer, but it can be considered in patients who do not respond well to the other interventions in these guidelines. Additionally, an observational study of 136 patients with terminal cancer also suggested that continuous infusion of subcutaneous oxycodone may provide relief of dyspnea in addition to relief of pain.<sup>197</sup> For patients receiving chronic opioids, the panel recommends consideration of a 25% dose increase to manage dyspnea.

Scopolamine, atropine, hyoscyamine, and glycopyrrolate are options to reduce excessive secretions associated with dyspnea.<sup>198-202</sup> Glycopyrrolate does not effectively cross the blood–brain barrier and is less likely than the other drug options to cause delirium, but this agent can produce anticholinergic side effects.<sup>203-205</sup> Scopolamine can be administered subcutaneously or transdermally; physicians should be aware that the onset of benefit for transdermal scopolamine patches is about 12 hours,<sup>206</sup> and they are thus not an appropriate choice for imminently dying patients. A subcutaneous injection of scopolamine can be administered when the patch is applied or if management of secretions is inadequate.

Palliative RT can be considered for patients with SVC syndrome or those who have respiratory obstruction by tumor mass.<sup>165,207</sup>

Non-pharmacologic interventions include the use of handheld fans directed at the face, supplemental oxygen, and time-limited trials of noninvasive mechanical ventilation. A randomized, controlled, crossover trial demonstrated that breathlessness was reduced in patients when they directed a handheld fan toward their faces.<sup>208</sup> Another randomized controlled trial examined the effects of room air versus palliative oxygen delivered via nasal cannula in patients with refractory dyspnea. Dyspnea

scores were no different among patients receiving palliative oxygen versus room air, encouraging the use of less burdensome interventions.<sup>209</sup>

High-flow nasal oxygen and noninvasive mechanical ventilation are not available outside of the hospital setting, but may provide temporary improvements in hypoxemia and dyspnea. In a recent feasibility study of 200 patients with solid tumors randomized to receive either noninvasive positive-pressure ventilation (biphasic positive airway pressure, BiPAP) or oxygen therapy, patients in the ventilation group had greater improvements in dyspnea symptoms and required lower doses of opiates than patients in the oxygen group.<sup>210</sup> However, a smaller phase II randomized trial comparing high-flow oxygen to BiPAP for persistent dyspnea in patients with advanced cancer revealed no significant differences between the two approaches.<sup>211</sup>

As life expectancy decreases, the role of mechanical ventilation and oxygen diminishes, and the role of opioids, benzodiazepines, glycopyrrolate, and scopolamine increases. If fluid overload is a contributing factor, enteral and parenteral fluids should be decreased or discontinued, and low-dose diuretics can be considered.

### **Anorexia/Cachexia**

Cachexia is physical wasting with loss of skeletal and visceral muscle mass and is very common among patients with cancer.<sup>212,213</sup> Many patients with cancer lose the desire to eat (anorexia), which contributes to cachexia. Cachexia can also occur independently from anorexia, as proinflammatory cytokines and tumor-derived factors directly lead to muscle proteolysis.<sup>212,213</sup> Cachexia leads to asthenia (weakness), hypoalbuminemia, emaciation, immune system impairment, metabolic dysfunction, and autonomic failure. Cancer-related cachexia has also been associated with failure of anti-cancer treatment, increased treatment toxicity, delayed treatment initiation, early treatment termination, shorter survival, and psychosocial distress.<sup>212-214</sup> A recent study that examined

cancer cachexia in a cohort of 1473 patients across all weight ranges showed that muscle depletion conveys a similarly poor prognosis as involuntary weight loss, regardless of body mass index.<sup>215</sup>

Reversible causes of anorexia, such as oropharyngeal candidiasis and depression, should be addressed. Treatment includes the relief of symptoms that interfere with food intake (eg, pain, constipation, nausea/vomiting), as well as metoclopramide for early satiety.<sup>183,187,216</sup>

For patients with months-to-weeks or weeks-to-days life expectancy, consider the use of appetite stimulants (eg, megestrol acetate, dexamethasone, olanzapine) if increased appetite is an important aspect of quality of life.<sup>217-221</sup> A recent systematic review and meta-analysis of megestrol acetate revealed improved appetite and slight improvements in weight gain when using this drug to treat anorexia/cachexia in patients with cancer.<sup>218</sup> While one in four patients treated with megestrol acetate will have an increase in appetite and 1 in 12 will have an increase in weight, clinicians need to know that 1 in 6 will develop thromboembolic phenomena and 1 in 23 will die due to the drug.<sup>218</sup>

A combination therapy approach may yield the best possible outcomes for patients with cancer cachexia. A randomized phase III trial in 332 patients with cancer-related anorexia/cachexia revealed superior outcomes for patients receiving a combination regimen that included medroxyprogesterone, megestrol acetate, eicosapentaenoic acid and L-carnitine supplementation, and thalidomide, versus therapy with any of the above single agents.<sup>222</sup> Another phase III trial of 104 patients with advanced gynecologic cancers and cachexia supported the merits of combination therapy; compared with megestrol acetate alone, patients receiving megestrol acetate plus L-carnitine, celecoxib, and antioxidants had improved lean body mass, appetite, and quality of life.<sup>223</sup>

Although cannabinoid-based interventions (eg, dronabinol, cannabis) have some demonstrated efficacy for treating chemotherapy-induced nausea and vomiting and AIDS-related anorexia, the data to support cannabinoid-based interventions for treating anorexia/cachexia in patients with cancer are very limited, in part due to legal constraints within this field of research.<sup>224</sup> A randomized clinical trial of cannabis extract and delta-9-tetrahydrocannabinol in patients with cancer-related anorexia-cachexia syndrome did not demonstrate a benefit of these agents over placebo on appetite and quality of life.<sup>225</sup> Another randomized trial comparing megestrol acetate to dronabinol in treating cancer-associated anorexia revealed megestrol acetate to be superior for promoting weight gain (75% vs. 49% of patients) and appetite (11% vs. 3%) in patients with advanced cancer.<sup>226</sup> However, to a lesser extent, dronabinol did improve appetite and weight gain in some study patients. Ultimately, for some patients with cancer-related anorexia, cannabinoids could be helpful. However, it is important to note that cannabinoid administration in elderly patients may induce delirium, and providers should be aware of the local state rules and regulations regarding medicinal cannabinoid use.

Nutrition consultation should also be considered, because calorie-dense, high-protein supplementation has demonstrated some efficacy for weight stabilization,<sup>183,212,227-229</sup> although some studies show nutritional interventions to be ineffective.<sup>230</sup> A meta-analysis found that while nutritional intervention does not significantly affect weight gain or energy intake, it can improve some aspects of quality of life, including emotional functioning, dyspnea, and hunger.<sup>231</sup> Nutritional support, including enteral and parenteral feeding as appropriate, should also be considered when the disease or treatment affects the ability to eat and/or absorb nutrients and the patient's life expectancy is months to years.<sup>232</sup> The goals and intensity of nutritional support change as life expectancy is reduced to weeks to days. Overly aggressive enteral or parenteral nutrition therapies can actually increase the suffering of dying patients.<sup>232-235</sup> In addition, a

recent randomized controlled trial of patients with cancer enrolled in hospice found that parenteral hydration had no effect on dehydration symptoms such as fatigue and hallucination and had no effect on quality of life or survival.<sup>236</sup> Therefore, instead of artificial hydration and nutrition, palliative care in the final weeks of life focuses on treating dry mouth and thirst, and providing education and support to the patient and family regarding the emotional aspects of withdrawal of nutritional support. Family members should be informed of alternate ways to care for dying patients.

### ***Nausea and Vomiting***

Chemotherapy-induced nausea and vomiting has a major impact on a patient's quality of life.<sup>237</sup> Nausea and vomiting induced by chemotherapy or radiation therapy should be managed as outlined in the [NCCN Guidelines for Antiemesis](#). Patients can also experience nausea and vomiting unrelated to chemotherapy and radiation, resulting from gastric outlet obstruction, bowel obstruction, constipation, opioid use, or hypercalcemia.<sup>238</sup> These causes should be identified and treated. Consider palliative RT for nausea and vomiting related to brain metastases.<sup>165,239,240</sup> Proton pump inhibitors and histamine-2 (H2) receptor antagonists can be used to manage gastritis or gastroesophageal reflux. Gastric outlet obstruction may benefit from treatment with corticosteroids; alternative treatment options include endoscopic stenting or insertion of a decompressing G-tube. Many medications can also cause nausea and vomiting, and blood levels of possible culprits, such as digoxin, phenytoin, carbamazepine, and tricyclic antidepressants, should be checked.<sup>241,242</sup>

Non-specific nausea and vomiting are often managed with dopamine- or 5-HT<sub>3</sub> (5-hydroxytryptamine 3)-receptor antagonists (eg, prochlorperazine, haloperidol, metoclopramide, olanzapine). However, experts have debated the quality and strength of the evidence to support specific agents in the management of nonspecific nausea and vomiting in

palliative care.<sup>243,244</sup> A systematic review assessed the level of evidence for antiemesis unrelated to chemotherapy, concluding that antiemetic recommendations have moderate to weak evidence at best; the strongest evidence supported the use of metoclopramide.<sup>244</sup> For anxiety-related nausea, the addition of benzodiazepines can be considered. If a vertiginous component to the nausea and vomiting exists, anticholinergic/antihistamine agents may be appropriate.

Titrate dopamine receptor antagonists to maximum benefit and tolerance.<sup>245-249</sup> In the setting of continued nausea and vomiting, consider additional drug classes with potential antiemetic properties: corticosteroids,<sup>250,251</sup> 5-HT<sub>3</sub> receptor antagonists,<sup>252-254</sup> anticholinergic agents and/or antihistamines,<sup>251</sup> or oral cannabinoids.<sup>255</sup> Agents that target the cannabinoid system may offer some efficacy in treating refractory chemotherapy-induced nausea and vomiting.<sup>256</sup> Dronabinol and nabilone are two cannabinoid agents approved for treating chemotherapy-induced nausea and vomiting that is refractory to standard antiemetic therapies. Alternative therapies (eg, acupuncture, hypnosis, cognitive behavioral therapy) can also be considered.<sup>257-259</sup> Palliative sedation (see below) can be considered as a last resort if intensified efforts by specialized palliative care or hospice services fail.

For persistent nausea and vomiting, consider the appropriate route of administration. First, prescribe oral agent and titrate to maximum benefit and consider opioid rotation.<sup>260</sup> If nausea and vomiting is persistent, provide IV administration as needed. For continued persistent symptoms, provide scheduled IV administration or continuous infusion of antiemetics. An around-the-clock dosing schedule may provide the most consistent benefit to the patient. Continuous intravenous or subcutaneous infusions of different antiemetics may be necessary for the management of intractable NV.



### Constipation

Constipation occurs in approximately 50% of patients with advanced cancer and most patients treated with opioids.<sup>261</sup> Although several drugs including antacids, anticholinergic drugs (antidepressants, antispasmodics, phenothiazines, and haloperidol), and antiemetics are known to cause constipation,<sup>262</sup> opioid analgesics are most commonly associated with constipation. Providers should discontinue any nonessential constipating medications. In addition to physical discomfort, constipation in patients with advanced cancer can cause psychological distress and anxiety regarding continued opioid use.<sup>263</sup> Opioid-induced constipation (OIC) should be anticipated and treated prophylactically with a stimulating laxative to increase bowel motility with or without stool softeners.<sup>264</sup> While there is little evidence on which is the best initial bowel regimen in patients with cancer<sup>265</sup> one small study compared the use of senna alone versus a senna-docusate combination. The results demonstrated that the addition of the stool softener docusate was not necessary.<sup>266</sup> Increasing intake of fluid and physical activity should also be encouraged, when appropriate. Added dietary fiber may be considered for patients with adequate fluid intake.

If constipation is present, the cause and severity must be assessed. Impaction, obstruction, and other treatable causes, such as hypercalcemia, hypokalemia, hypothyroidism, and diabetes mellitus, should be assessed and treated. Constipation may also be treated by adding bisacodyl 10 to 15 mg, 2 to 3 times daily with a goal of 1 non-forced bowel movement every 1 to 2 days. If impaction is observed, glycerine suppositories (with or without mineral oil retention enema) may be administered or manual disimpaction may be performed. Use suppository and enema with caution in patients receiving chemotherapy due to risk of cytopenia.

If constipation persists, adding other laxatives may be considered, such as rectal bisacodyl once daily or oral polyethylene glycol, lactulose, magnesium hydroxide, or magnesium citrate.<sup>265</sup> If gastroparesis is suspected, the addition of a prokinetic agent, such as metoclopramide, may be considered.

Peripherally acting  $\mu$ -opioid receptor antagonists may help to relieve OIC while maintaining pain management. Recent studies have shown that methylnaltrexone provided effective relief of OIC while preserving opioid-mediated analgesia.<sup>267,268</sup> Naloxegol, a similar peripherally acting  $\mu$ -opioid receptor antagonist, has also been studied for treating OIC in patients receiving chronic opioids for noncancer pain.<sup>269,270</sup> Gastrointestinal specialists have reported some success using erythromycin for constipation symptoms that do not respond to peripherally-acting  $\mu$ -opioid receptor antagonists such as methylnaltrexone.

Several newer agents have also been examined for treating constipation. Lubiprostone is an orally active prostaglandin analog that activates select chloride channels to enhance intestinal fluid secretion.<sup>271,272</sup> This agent was shown to be effective for treating OIC in patients with chronic noncancer pain. Lubiprostone could be used in combination with a peripherally acting  $\mu$ -opioid receptor antagonist such as methylnaltrexone. Linaclotide is a selective agonist of guanylate cyclase-C receptors in the intestines to enhance intestinal secretions, and has been effective in the treatment of constipation associated with irritable bowel syndrome and chronic idiopathic constipation.<sup>273,274</sup> The American Gastroenterological Association includes lubiprostone and linaclotide as recommended options for treating constipation associated with irritable bowel disorder.<sup>275</sup>

Based on these results, the NCCN Palliative Care Panel recommends considering 0.15 mg per kilogram of body weight of methylnaltrexone every other day (no more than once a day) for patients experiencing constipation that has not responded to standard laxative therapy.

Methylnaltrexone should not be used in patients with a postoperative ileus or mechanical bowel obstruction.

### **Diarrhea**

In patients with cancer, diarrhea can be caused by a number of potential factors, including anticancer treatment-related side effects, infection, antibiotic use, dietary changes, or fecal impaction.<sup>276</sup> Diarrhea is a common side effect of various chemotherapeutics (eg, fluorouracil and irinotecan), as well tyrosine kinase inhibitors and certain biologic agents (eg, ipilimumab, cetuximab, panitumumab).<sup>277-280</sup> Abdominal and pelvic radiation therapy (alone or as part of chemoradiation regimens) can also induce gastrointestinal toxicity resulting in diarrhea.<sup>278,279</sup>

The National Cancer Institute Common Toxicity Criteria are typically used for measuring diarrhea in this patient population.<sup>276</sup> The panel recommends that patients be screened to determine the grade of diarrhea. Providers should provide immediate intervention for dehydration based on grade and assess for potential cause(s).

For patients with years, years to months, or months to weeks of estimated life expectancy who have grade 1 or 2 diarrhea, recommendations include hydration and electrolyte replacement (oral or IV fluids as appropriate), antidiarrheal medications, and a bland/BRAT (Bread, Rice, Applesauce, Toast) or clear liquid diet. If chemotherapy-related, decrease dose or discontinue therapy. For treating grade 2 diarrhea, anticholinergic agents such as hyoscyamine or atropine can be considered. Infection-induced diarrhea should be treated with the appropriate antibiotic. Immunotherapy-related diarrhea can be treated with corticosteroids, infliximab, and/or probiotics. Patients with grade 3 or 4 diarrhea should receive inpatient treatment (intensive care for Grade 4 diarrhea if consistent with patient goals). In addition to fluid replacement, antidiarrheal therapy, and anticholinergics, octreotide can also be considered. For graft-versus-host disease (GVHD) diarrhea, consider limiting diet, administering steroids,

and IV nutrition. In the home setting, subcutaneous hydration can be considered.

For patients with weeks to days of estimated life expectancy, the above interventions can be considered as consistent with the goals of care. At-home IV hydration may be considered in addition to scopolamine or hyoscyamine. If diarrhea persists, consider octreotide or glycopyrrolate. Patients should begin around-the-clock opioids or receive an increased dose of ongoing opioid regimens.

### **Malignant Bowel Obstruction**

Malignant bowel obstructions are usually diagnosed clinically and confirmed with radiography. For patients with years to months to live, surgery following CT scan is the primary treatment option. While surgery can lead to improvements in quality of life, surgical risks should be discussed with patients and families, including risk of mortality, morbidity, and re-obstruction.<sup>281</sup> Also take into account prognosis and relative invasiveness of the intervention proposed. Although surgery is the primary treatment for malignant obstruction, some patients with advanced disease or patients in generally poor condition are unfit for surgery and require alternative management to relieve distressing symptoms. Risk factors for poor surgical outcome include ascites, carcinomatosis, palpable intra-abdominal masses, multiple bowel obstructions, previous abdominal radiation, advanced disease, and poor overall clinical status.<sup>282</sup> In these patients, medical management can include pharmacologic measures, parenteral fluids, endoscopic management, and enteral tube drainage (silicone tubing may offer superior comfort over vinyl).

Pharmacologic management of malignant bowel obstruction can be separated into two groups of patients: those for whom the goal is to maintain gut function and those for whom gut function is no longer possible. When the goal is maintaining gut function, patients can be treated with opioids, antiemetics, and corticosteroids, alone or in

combination. When gut function is no longer considered possible, pharmacologic options also include somatostatin analogs (eg, octreotide) and/or anticholinergics.<sup>283-288</sup> If octreotide is helpful and the patient has a life expectancy of at least 1 month, it may be beneficial to consider a depot form of octreotide once an optimal dose is established. Antiemetics that increase gastrointestinal mobility such as metoclopramide should not be used in patients with complete obstruction, but may be beneficial when obstruction is partial. Use of octreotide is recommended early in the diagnosis because of its efficacy and tolerability.<sup>289,290</sup> Despite positive findings from several smaller randomized trials, a recent phase III trial of octreotide in 86 patients with malignant bowel obstruction failed to demonstrate a significant effect of this drug on days free of vomiting, number of vomiting episodes, symptom management, and other secondary endpoints.<sup>291</sup>

A venting gastrostomy tube (inserted by interventional radiology, endoscopy, or surgery) or an endoscopically placed stent can also palliate symptoms of malignant bowel obstruction.<sup>292,293</sup> Total parenteral nutrition can be considered to improve quality of life in patients with a life expectancy of years to months. These interventions have been shown to have little positive impact on survival time, but may improve quality of life.<sup>148,149</sup>

### **Fatigue/Weakness/Asthenia**

The data on methylphenidate for treating cancer-related fatigue have been mixed.<sup>294</sup> While some trials have suggested a dose-dependent benefit of this agent on fatigue symptoms,<sup>295,296</sup> other studies have failed to produce positive results.<sup>297</sup> Phase III randomized trials of modafinil for treating cancer-related fatigue suggested that modafinil had a modest efficacy and was most effective for those with severe fatigue.<sup>298,299</sup> For more information, see the [NCCN Guidelines for Cancer-Related Fatigue](#).

### **Sleep/Wake Disturbances**

Patients with cancer often suffer from insomnia or daytime sedation.<sup>300-302</sup> In a recent study of 442 patients with advanced cancer, 330 (75%) patients were assessed as having baseline sleep disturbance as assessed by the Edmonton Symptom Assessment System (ESAS) sleep item.<sup>303</sup> Patients should first be evaluated for sleep/wake disturbances using, for example, the Epworth Sleepiness Scale.<sup>304</sup> If patients have a history of sleep-disordered breathing (eg, excessive snoring, gasping for air, observed apneas, frequent arousals, sudden involuntary movement of arm or legs during sleep, unexplained daytime drowsiness), polysomnography should be considered. Polysomnography should also be considered for patients with head and neck cancers, because obstructive sleep apnea (OSA) is prevalent in patients with this disease.<sup>305,306</sup> Primary sleep disorders, such as OSA and periodic limb movement disorder, should be treated with continuous positive airway pressure (CPAP) or BiPAP.<sup>307</sup> Restless leg syndrome, if present, can be treated with ropinirole, pramipexole with pregabalin, or carbidopa-levodopa.<sup>308-316</sup> Fears and anxiety regarding death and disease should be explored, and other contributing factors to sleep/wake disturbances should be treated, including pain, depression, anxiety, delirium, and nausea. Cognitive behavioral therapy may be effective in treating sleep/wake disturbances in patients with cancer.<sup>187,317-321</sup>

For refractory insomnia, pharmacologic management includes the short-acting benzodiazepine lorazepam; the non-benzodiazepine zolpidem; antipsychotic medications such as chlorpromazine, quetiapine, and olanzapine; and sedating antidepressants such as trazodone and mirtazapine.<sup>322</sup> The panel suggests that mirtazapine may be especially effective in patients with depression and anorexia. Benzodiazepines should be avoided in older patients and in patients with cognitive impairment, because they have been shown to cause decreased cognitive performance.<sup>323</sup> Caution should be exercised when administering zolpidem



due to the known risk of next-morning impairment. In 2013, the U.S. Food and Drug Administration (FDA) required lower recommended doses of zolpidem (ie, from 10 mg to 5 mg for immediate-release products and from 12.5 mg to 6.25 mg for extended-release formulations).<sup>324</sup>

For refractory daytime sedation, the guidelines suggest several options. The central nervous system stimulants methylphenidate or dextroamphetamine should be given with a starting dose of 2.5 to 5 mg orally (PO) with breakfast. If the effect of the drug does not last through lunch, a second dose can be given at lunch, preferably no later than 2:00 PM. Doses can be escalated as needed.<sup>325</sup> Another option for refractory daytime sedation is the psychostimulant modafinil, which has been approved in adults for excessive sleepiness associated with OSA/hypopnea syndrome (OSAHS), shift work sleep disorder, and narcolepsy.<sup>326</sup> The panel also recommends caffeine and dextroamphetamine as additional options for refractory daytime sedation. The last dose of caffeine should be given no later than 4:00 PM.

Dying patients should be assessed for their desire to have their insomnia or sedation treated. The doses of their pharmacologic therapies can be adjusted as appropriate. The addition of an anti-psychotic drug (chlorpromazine or quetiapine) can be considered in patients whose insomnia is refractory.

Please also see the [NCCN Guidelines for Adult Cancer Pain](#) and the [NCCN Guidelines for Cancer-Related Fatigue](#) for their discussions on sleep/wake disturbances.

### **Delirium**

Delirium should be assessed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria.<sup>327</sup> Reversible causes should be identified and treated appropriately.<sup>328</sup> Delirium may present as either a hypoactive or a hyperactive subtype.<sup>329</sup> Recent studies

have suggested that hypoactive delirium was the most prevalent subtype in palliative care patients and that this condition is often underdiagnosed due to its presentation.<sup>330,331</sup>

Two comprehensive reviews describe the evidence base for recommended pharmacologic and non-pharmacologic treatments for delirium in patients with cancer.<sup>187,332</sup> Non-pharmacologic interventions (eg, reorientation, cognitive stimulation, sleep hygiene) should be maximized before pharmacologic interventions are used. Delirium-inducing medications (ie, steroids, anticholinergics) should be reduced or eliminated as much as possible.<sup>333</sup> Benzodiazepines should not be used as initial treatment for delirium in patients not already taking them.

The symptoms of moderate delirium can be managed with oral haloperidol, risperidone, olanzapine, or quetiapine fumarate.<sup>334-336</sup> The symptoms of severe delirium (ie, agitation) should be managed with antipsychotic, neuroleptic drugs such as haloperidol, olanzapine, or chlorpromazine.<sup>337</sup> Because of its hypotensive side effect, intravenous chlorpromazine should only be used in bed-bound patients. A benzodiazepine, such as lorazepam, may be added for agitation that is refractory to high doses of neuroleptics.<sup>338</sup> The presence of therapeutic levels of neuroleptics usually prevents the paradoxical excitation sometimes seen when delirious patients are given lorazepam. The dosages of these symptom-management medications should be titrated to optimal relief. Opioid dose reduction or rotation can also be considered for patients with severe delirium. RT can be considered for patients with delirium due to brain metastases, however there are currently no data demonstrating improvement, and palliative efforts should be intensified with the awareness that delirium is a marker for “days not weeks” prognosis.<sup>339-341</sup> Caregivers should be supported in caring for their loved one and coping with this distressing condition.

Delirium in patients with advanced cancer and limited life expectancy and/or shortened prognosis.<sup>339-342</sup> In these patients, iatrogenic causes should be eliminated whenever possible. Opioid rotation can be considered (see [NCCN Guidelines for Adult Cancer Pain](#)) if the delirium is believed to be caused by neurotoxicity of the current opioid. If delirium is a result of disease progression, palliative care must be focused on symptom management and family support. Neuroleptic and benzodiazepine medications should have their dose increased and/or their route of administration changed to ensure adequate delirium symptom management.<sup>343</sup> Unnecessary medications and tubes should be removed. For refractory delirium in dying patients, palliative sedation can be considered following consultation with a palliative care specialist and/or psychiatrist (see below).

Please also see the [NCCN Guidelines for Distress Management](#) for further discussion of delirium in patients with cancer.

### **Psychosocial Distress – Social Support/Resource Management**

For distress related to psychological or psychiatric complications and spiritual or existential crisis, please see the [NCCN Guidelines for Distress Management](#).

For best outcomes, psychosocial care should be integrated into routine cancer care across all disease stages and in both the inpatient and outpatient settings.<sup>32,344</sup> A recent systematic review of patients with advanced cancer identified psychosocial resources among the factors that promoted personal growth during the experience of cancer.<sup>345</sup>

For patients with estimated life expectancy ranging from years to months experiencing psychosocial distress, social support/resource management should be offered. Assess prognostic awareness and discuss on an ongoing basis with patient, family, and caregivers. Patients should be cared for in a safe environment with available caregivers. In addition, it is

important to ensure that the patient has adequate financial resources and refers to social services (social worker, psychologist, and/or psychiatrist) as needed. Support and education should be provided to the caregivers and family members.<sup>346-348</sup> Personal, spiritual, or cultural issues related to the patient's illness and prognosis should be discussed.<sup>349</sup> Bereavement risk should be assessed. If language is a barrier, a professional health care interpreter, who is not related to the patient or family, should be available for patients, caregivers, and families as needed.

In a dying patient with an estimated life expectancy of weeks to days, the patient's desires for comfort should be evaluated and supported. The process of dying and the expected events should be explained to the patient, caregivers, and family members. Bereavement risk should be reassessed. Patients and family members should be provided with emotional support to address any intra-family conflict regarding palliative care interventions. Eligibility and readiness for specialized palliative/hospice care should be determined.

### **Palliative Care Reassessment**

The outcome measures for these guidelines are much more difficult to define than those for NCCN disease-specific guidelines. The panel reviewed end-of-life care outcomes from several surveys of North American citizens.<sup>103,350-352</sup> The panel chose a modified version of Singer's outcomes until more precise outcome measures are available. Acceptable palliative care should provide the following: 1) adequate pain and symptom management; 2) reduction of patient and family distress; 3) acceptable sense of control; 4) relief of caregiver burden; 5) strengthened relationships; and 6) optimized quality of life, personal growth, and enhanced meaning. The panel added "having an advance care plan in progress" as part of the criteria for acceptable outcome. Research is ongoing regarding better ways to measure "dying well."<sup>353</sup>

All patients should be reassessed regularly, and effective communication and information sharing must exist between the patient, caregivers, and health care providers. Patients and family members benefit most from ongoing discussions about the natural history of the disease and prognosis in clear, consistent language. If the interventions are unacceptable upon reassessment, the oncology or palliative care team should intensify palliative care and reassess the patient and family situation. The oncology team should also consult specialized palliative care services, hospice, or an ethics committee. Referral to a psychiatrist or psychologist to evaluate and treat undiagnosed psychiatric disorders, substance abuse, and inadequate coping mechanisms should be considered. If psychosocial distress persists, palliative care options should be intensified, and the patients should be managed according to the NCCN Guidelines for Distress Management.

Patients' treatment goals and expectations may change and evolve as disease progresses. Reassessment should be ongoing, with continuation or modification of life-expectancy-guided palliative care until the patient's death or survivorship.

### End-of-Life Care Issues

#### Preparing Patients and Families for End-of-Life and Transition to Hospice Care

For patients with an estimated life expectancy of years or years to months, providers should engage in clear, consistent discussion with the patient and family about prognosis and anticipated care needs on an ongoing basis. Facilitate advance care planning and assess decision-making capacity and need for a surrogate decision maker. Elicit values and preferences with respect to quality of life and determine need for specialized palliative care or eligibility and readiness for hospice care. When the patient's functional status indicates 6-12 months prognosis, a dedicated "hospice information" visit with the oncologist may ease the

transition to hospice care for the patient and family and ensure that the oncologist remains involved.

Patients with an estimated life expectancy of months to weeks or weeks to days should be referred to hospice agencies. Assess patient/family understanding of the dying process and provide education as needed. Providers should address potential need for transitions in care while ensuring continued involvement of the primary care physician and primary oncology team. Patients should receive information and additional referrals, as necessary, for psychosocial assessment, legacy work, grief counselling, spiritual support, and funeral/memorial service planning.

Respect goals and needs of the patient and family regarding the dying process and promote that patient does not die alone unless this is an established preference of patient.

#### Advance Care Planning

The oncology team should initiate discussions of personal values and preferences for end-of-life care while patients have a life expectancy of years to months. Recent studies have shown that these discussions frequently happen too late in the trajectory of disease, often during acute hospital care and often with health professionals other than the primary oncologist.<sup>354-356</sup> Further, earlier end-of-life care discussions have been associated with less aggressive care and increased use of hospice,<sup>357,358</sup> while less aggressive care has been associated with an improved quality of life.<sup>359</sup> Studies suggest that most patients with cancer would prefer to die at home,<sup>360,361</sup> but lack of timely advance care planning can render this impossible.

ASCO has developed a booklet to help patients and their families understand and discuss the cancer diagnosis and treatment options (<http://www.cancer.net/coping/advanced-cancer-care-planning>). A recent randomized controlled trial found that a video decision support tool



increased the likelihood that patients would choose to forgo resuscitation.<sup>362</sup> A randomized controlled trial of a structured intervention to facilitate end-of-life discussions (consisting of an information pamphlet and provider discussion) led to earlier designation of do-not-resuscitate orders and decreased the likelihood of patients dying in the hospital.<sup>363</sup> In addition, a recent study showed that electronic prompts and email reminders to doctors could increase rates of documentation of code status in patients with advanced lung cancer.<sup>364</sup> A 2015 systematic review summarizes the evidence base from randomized trials of interventions designed to promote shared decision making and advance care planning in patients with serious illness.<sup>365</sup>

Advance care planning should include an open discussion about palliative care options, such as hospice; personal values and preferences for end-of-life care; the congruence between the patient's wishes/expectations and those of the family/health care team; and information about advance directives. It may be helpful to determine the patient and family's prior experience(s) with end-of-life care. Patients should be asked if they have completed any advance care planning such as living wills, powers of attorney, or delineation of specific limitations regarding life-sustaining treatments including cardiopulmonary resuscitation, mechanical ventilation, and artificial nutrition/hydration. The patient's values and preferences and any decisions should be documented in the medical record, including MOLST or POLST (Medical Orders for Life-Sustaining Treatment or Physician Orders for Life-Sustaining Treatment) if completed.<sup>366</sup>

When the patient's life expectancy is reduced to months to weeks, the oncology team should actively facilitate completion of appropriate advance directives and ensure their availability in all care settings. MOLST/POLST should be documented and accessible to all providers across care settings. The team should also confirm the patient's values and decisions

in light of changes in status. Palliative care consultation can be considered to assist in conflict resolution when the patient, family, and/or medical professional team do not agree on the benefit/efficacy of interventions.

The patient's preferred location for receiving end-of-life care should be determined. Most patients with cancer would prefer to spend one's remaining time at home,<sup>360,361</sup> but sometimes their care needs or support system at home cannot support their care. Some patients request to receive end-of-life care in a skilled nursing facility or an in-patient hospice facility.<sup>361,367</sup> A prospective study showed that patients dying in an ICU had higher levels of physical and emotional distress compared with patients dying at home or in hospice. Additionally, caregivers of these patients had a greater incidence of prolonged grief disorder.<sup>368</sup> Providing palliative care services has been shown to decrease deaths in ICUs.<sup>367</sup> A recent retrospective cohort study showed that patients who wanted to be at home at the end of life were more likely to do so if they had daily hospice visits, if they were married, if they had advance directives, if they did not have moderate or severe pain, or if they had good performance status.<sup>361</sup> A second retrospective study suggested that referral to specialist palliative care at a greater interval of time prior to death increased the likelihood of patients dying at home or in hospice rather than in the hospital.<sup>369</sup> If advance care plans have not been completed, the oncology team should explore the patient's reluctance to engage in advance care planning and refer to palliative care if needed.

In patients with a life expectancy of only weeks to days, the patient's decision regarding cardiopulmonary resuscitation and other life-sustaining treatments must be clarified and confirmed. Providers should facilitate continued involvement of the primary care physician and primary oncology team. The desire for organ donation and/or autopsy must also be explored with the patient. Overall, the oncology team must implement and ensure compliance with the patient's advance care plan.

### Requests for Hastened Death

Special palliative care interventions include responses to requests for hastened death (ie, physician-assisted dying). The most appropriate initial response to a request for hastened death is to intensify palliative care. All such patients should be referred to a palliative care specialist. A request for hastened death often has important meanings that require exploration. Open exploration of the patient's request for hastened death may identify unmet needs and new palliative care interventions that may be helpful. Concerns related to the withdrawal of life-sustaining treatment, voluntary cessation of eating and drinking, and/or sedation should be discussed with patients and families. Psychiatric consultation to evaluate and treat reversible causes of psychological suffering should be requested. Patients should be assured that their health care team is committed to providing continuing care. Although physician-assisted suicide, under specified conditions, is legal in the states of California, Oregon, Montana, Vermont, and Washington, euthanasia is not legal in any of the United States.<sup>370-374</sup> It is important for physicians to know the local legal status of physician-assisted suicide, as other states have pending legislation regarding either prohibiting or permitting physician-assisted suicide. Several organizations have released position statements and/or helpful websites on the issue of physician aid-in-dying (see Table 1).

### Care of the Imminently Dying Hospitalized Patient

An imminently dying patient is defined as one within hours of death who is not stable enough for transport.<sup>375</sup> Caring for an imminently dying patient is intense for the patient, family, and health care team. A recent international qualitative study described many of the common non-pharmacologic palliative care activities provided in the last days of life.<sup>376</sup> An end-of-life care order set that includes physical, practical, and psychosocial interventions may be beneficial for practitioners to use for imminently dying patients. If not already done, obtaining a hospice evaluation may also be helpful.

The physical aspects of care for an imminently dying patient focus on adequate symptom management and comfort, keeping in mind the patient's wishes and values. Approaches may include intensifying ongoing care; adjusting medication doses for optimal comfort; discontinuing unnecessary interventions (eg, diagnostic tests, transfusions, artificial nutrition, hydration, dialysis, needle sticks); ensuring access to symptom-relief medication through alternate routes if oral administration is difficult; improving physical comfort by providing a pressure-relieving mattress and regular repositioning; eye and mouth care to maintain moisture; treating urinary retention and fecal impaction; managing terminal restlessness and agitation with palliative sedation; reducing death rattle/terminal secretion (eg, repositioning patient; reducing parenteral and enteral fluids; adding medications such as scopolamine, hyoscyamine, atropine, or glycopyrrolate)<sup>202,377</sup>; and preparing for patient and family requests for autopsy and/or organ donation. Physicians may also wish to consider deactivating implanted pacemakers in select patients.<sup>378</sup>

The psychosocial aspects of care for an imminently dying patient take into account individual and family goals, preferences, cultures, and religious beliefs. Open communication should occur between the patient, family, and care team regarding the physical and psychological aspects of the dying process and the importance of honoring any advance directives. The care plan may also include consultation with social workers or chaplains to meet social and spiritual needs; counseling to promote healthy grieving; support for children/grandchildren and education for parents on age-appropriate grieving processes. Patients who are actively dying in their final hours of life should be allowed to spend uninterrupted time with family, if they wish to do so.

The practical aspects of care for an imminently dying patient in the hospital include: mobilizing in-hospital end-of-life care policy and procedures; ensuring that the patient's advance directive is documented

and implemented and a do-not-attempt-resuscitation (DNAR) or allow natural death (AND) order is written and followed; securing a private room for the patient; and enabling family presence around-the-clock. Discuss and document patient/family wishes for resuscitation. In the event that CPR is unlikely to be effective, recommend other options such as AND or promoting comfort care. If the patient and family have not documented a DNAR order, patient/family education and counseling should be intensified to try to help them accept this level of care to prevent harm to the patient from futile attempts at cardiopulmonary resuscitation. Providers should be aware that policies regarding resuscitation may differ based on treatment setting. A patient with a documented inpatient DNAR order may also require DNAR orders for out-of-hospital settings (eg, dialysis care, ambulance transport). In states where the MOLST/POLST is honored across all treatment settings, it will protect the patient.

### Palliative Sedation

Palliative sedation may be considered for imminently dying patients (life expectancy of hours to days) with refractory symptoms that persist despite comprehensive, interdisciplinary palliative care. If palliative sedation is being considered, a prognosis of imminent death should be confirmed. Informed consent must be obtained from the patient and/or a surrogate or family member following discussions of the patient's disease status, treatment goals, prognosis, and expected outcomes. Consent for palliative sedation must be accompanied by consent for discontinuation of life-prolonging therapies (such as artificial hydration/nutrition) and withholding of cardiopulmonary resuscitation, as these therapies would only serve to increase suffering in this case.

Palliative sedation has its ethical justification in the Doctrine of Double Effect,<sup>379-384</sup> which provides guidance in situations where an attempt to do good also produces harm (eg, providing medication for the relief of suffering that also causes respiratory depression). Several studies have

investigated whether palliative sedation shortens survival. Results obtained from systematic reviews did not reveal a clear impact of palliative sedation on survival time, although many of the included studies lacked high-quality data.<sup>385,386</sup> A large prospective study in 2426 patients with advanced cancer provided additional evidence that continuous deep sedation provided by palliative care specialists did not significantly shorten survival time.<sup>387</sup> Prior to initiating palliative sedation, an ethics consult should be considered in accordance with institutional guidelines and state regulations.

Palliative sedation is best performed by palliative care experts.<sup>388</sup> The most common sedatives used for palliative sedation are midazolam and propofol by parenteral infusions.<sup>382</sup> Recent studies suggested that palliative sedation may also be feasible in the home setting and could be utilized in patients who wish to die at home.<sup>389,390</sup>

### A Peaceful Death

These NCCN Guidelines are the first to include death as an expected outcome and after-death care for the family as an essential part of the continuum of cancer care. Many studies have attempted to define a “good death” or a “peaceful death” from the perspective of clinicians, patients, and families.<sup>391-394</sup> Interestingly, one study found that patients, families, and physicians had very similar ideas of what constitutes a peaceful death: freedom from pain, being at spiritual peace, and being with family ranking among the top three considerations by all three groups.<sup>394</sup> End-of-life care should be flexible enough to ensure that the death is viewed as a peaceful death by those involved.<sup>394</sup> The definition of a “peaceful death” used by the NCCN Palliative Care Panel is “one that is free from avoidable distress and suffering for patients, families, and caregivers; in general accord with patient's and family's wishes; and consistent with clinical, cultural, and ethical standards.”<sup>395</sup>



Final results of the prospective, longitudinal cohort Coping With Cancer study of 396 patients with advanced cancer and their caregivers were recently reported. The study found a higher quality of life in the last weeks of life in patients who avoided visits to the ICU and feeding tubes, did not die in the hospital, worried less, prayed or meditated, were visited by a pastor in the hospital or clinic, and felt a strong therapeutic alliance with their physicians.<sup>359</sup>

### After-Death Care Interventions

Comprehensive palliative care for the patient's family and caregivers continues after the patient's death. Immediate issues include informing the family (if not present), offering condolences, and providing family time with the body. Chaplain involvement to assess family's desire for religious ritual or spiritual support may be helpful. Additional concerns include ensuring culturally sensitive and respectful treatment of the body, including removal of tubes, drains, lines, and the Foley catheter (unless an autopsy is planned); addressing concerns about organ donation or autopsy; facilitating funeral arrangements through completion of necessary paperwork; and informing insurance companies and other health care professionals of the patient's death.

Bereavement support should be offered, beginning with a personal visit or telephone call from the patient's primary oncology team, followed by a condolence letter. Family members at risk for complicated grief should be identified and offered support and treatment.<sup>396-398</sup> Children of patients with cancer represent a uniquely at-risk population for psychosocial dysfunction. Additionally, a recent study suggested that certain predictors of prolonged grief could be identified in family caregivers at the time of the patient's entry to palliative care; these factors include severity of pre-death symptoms; condition of the caregiver's relationship to the patient; impact of caregiving duties on the caregiver's schedule; quality of family functioning; and level of optimism, especially if low.<sup>399</sup>

Bereavement care is often best provided by an experienced hospice team or a skilled mental health care professional. The family may request a debriefing meeting from the medical team and may require assistance in identifying community bereavement resources. A well-supported end-of-life care experience will facilitate the family's acceptance of appropriate referrals for cancer risk assessment and risk modification. If not already recommended, providers should direct family members towards genetic screening, especially if the deceased patient was positive for known genetic markers that confer risk. For more information, see the NCCN Guidelines for [Genetic/Familial High-Risk Assessment: Breast and Ovarian](#) and [Genetic/Familial High-Risk Assessment: Colorectal](#).

### Putting Palliative Care Guidelines into Practice

Institutions should develop processes for integrating palliative care into cancer care, both as part of usual oncology care and for patients with specialty palliative care needs. Many approaches to this have been described, but there is no single best practice.<sup>23-31,400</sup>

Patients and families should be informed that palliative care is an integral part of their comprehensive cancer care. Educational programs should be provided to all health care professionals and trainees so that they can develop effective palliative care knowledge, skills, and attitudes. Skilled palliative care specialists and interdisciplinary palliative care teams, including board-certified palliative care physicians, advanced practice nurses, and physician assistants, should be readily available to provide consultative or direct care to patients and families who request or require the expertise. Finally, the quality of palliative care should be monitored by institutional quality improvement programs.

The experiences of patients with cancer begin with the diagnosis, and many palliative care questions should be considered early in the comprehensive cancer care plan. As the cancer progresses and the value

of further anticancer therapy diminishes, palliative measures should be intensified. Clear and consistent discussion of goals, values, preferences, prognostic information, and therapeutic options can help patients, families, and providers make appropriate decisions in a shared manner.

Undergoing anticancer therapy should not preclude addressing end-of-life issues. Collaborating with palliative care experts on such matters extends oncologists' therapeutic repertoire and diminishes the stress of caring for patients who have incurable disease. Increasing emphasis on palliative care in oncology should improve patient outcomes and provide new avenues for clinical research and professional satisfaction. Timely introduction of members of the institutional or community palliative care team allows patients to meet the individuals who will help them and their families through their experience. Because the diagnosis of cancer and impending death is such a frightening experience, oncologists must work to alleviate those fears by assuring patients that the members of the oncology and palliative care teams will work with them and their families regardless of what happens. Additionally, oncologists must discuss prognosis with both the family and the palliative care team in order to anticipate and manage problems commonly associated with the diagnosis and treatment of cancer.

As the disease progresses, many patients and families need help coping with the implications of increasing disease burden. Some patients and families have great difficulty accepting a poor prognosis and, as a result, do not engage in advance care planning.<sup>401,402</sup> This may be a sign of imperfect understanding of the disease and should be addressed directly and compassionately.<sup>402</sup> Palliative care supports ongoing education to help patients and families better understand and prepare for disease progression.

Oncologists should encourage advance care planning early in the disease trajectory in order to create a care plan that is consistent with the patients'

wishes. In addition, advance care planning can lessen the burden of making difficult end-of-life decisions. The combined efforts of the oncology team and the hospice/palliative care team can improve the overall outcome for patients and their families.

### Psychosocial Support for Palliative Care Providers

After the loss of a patient, psychosocial support should be available for providers who have been involved in the patient's care. A bereavement or memorial ritual, such as a brief reading or moment of quiet, can be considered. Funeral attendance by health care professionals may also be considered. Health care professionals should review medical issues related to patient death, explore concerns and questions about quality of patient care, and review emotional responses of family and staff to the patient's death.

Oncology and palliative care teams commonly encounter patient loss and deal with grief, and over time the resultant emotional distress can lead to provider burnout, compassion fatigue, and/or moral distress.<sup>403-406</sup> These syndromes can manifest as symptoms of depression, anxiety, fatigue, and low mental quality of life.<sup>407</sup> Personnel experiencing such symptoms should be identified and assisted. Considerable research has been dedicated to evaluating patterns of patient, family, and caregiver grief, and interventions to mediate this distress. Far less attention has been devoted to similar issues among health care providers and teams; further research is needed. For a summary of the literature on compassion fatigue and burnout among oncology providers, see reviews by Najjar and colleagues (2009),<sup>403</sup> Shanafelt and Dyrbye (2012),<sup>407</sup> and Sherman and colleagues (2006).<sup>408</sup>

Although limited in quantity, most studies on compassion fatigue are derived from the oncology nursing literature. A large survey of hospice and palliative care providers (ie, clinical, administrative, allied health workers)

revealed a strong correlation between burnout and compassion fatigue, and revealed the need for enhanced support of individuals in this field.<sup>409</sup> Additionally, a cross-sectional survey of nurses, medical assistants, and radiology technicians at a comprehensive cancer center revealed concerning levels of burnout and compassion fatigue in both inpatient and outpatient care settings.<sup>410</sup> A resiliency program was piloted and eventually scaled hospital-wide to educate providers on these issues and provide interventional strategies. Improvements in burnout and secondary traumatic stress were observed.<sup>410,411</sup> Several studies from the Mayo Clinic demonstrated that mindfulness training through the Stress Management and Resiliency Training (SMART) program was able to improve anxiety, stress, quality of life, and mindfulness among providers.<sup>412-414</sup> A recent meta-analysis of efficacy data on meditative interventions for health professionals demonstrated a small to moderate benefit according to measures of emotional exhaustion (effect size 0.37, 95% CI, 0.04–0.70), sense of personal accomplishment (effect size 1.18, 95% CI, 0.10–2.25), and life satisfaction (effect size 0.48, 95% CI, 0.15–0.81).<sup>415</sup>

Qualitative research on compassion fatigue interventions reveals that oncology clinicians rated the following resources as helpful: educational interventions, support programs or resources in the workplace, retreats, and self-care measures.<sup>403,416</sup> Unfortunately, despite the reported desire for such interventions, access can be limited. In a nationwide survey of oncology nurses, only 60% of survey respondents reported access to an employee assistance program, 45% reported no offerings of education addressing workplace coping, and 82% of respondents reported no off-site programs such as retreats.<sup>416</sup>

Generally, evidence-based interventions for compassion fatigue, moral distress, and burnout in physicians are lacking. When asked to provide useful preventative measures and coping strategies, palliative care specialists recommended emphasizing the rewarding aspects of their work

and strategies for “enhanced meaning-making”.<sup>417</sup> Experts in the field have also highlighted the importance of self-awareness and self-care measures for oncologists and palliative care specialists to decrease levels of compassion fatigue.<sup>418</sup> To this end, self-care was established as a core competency area for fellows in hospice and palliative medicine.<sup>418</sup> Examples and evidence for additional preventative strategies and solutions for oncologist burnout are reviewed by Shanafelt and Dyrbye.<sup>407</sup>

### Conclusion

These guidelines are intended to help oncology teams incorporate palliative care into their practice and thereby provide the best and most comprehensive cancer treatment possible for patients with incurable cancer. Patients with advanced disease may be overly optimistic about their chances of cure and survival, and this can have a negative effect on their quality of life. One study found that those who overestimated their survival were more likely to die a bad death.<sup>155</sup> Using a decision aid, Smith et al found that most patients want honest information, even if it is bad news.<sup>419</sup> Although use of the decision aid typically took 20 minutes and was challenging for oncologists, it did not cause patients to give up hope or become distressed. Physician-led discussion of disease progression and death can improve quality of care and quality of life for both patients and families.<sup>420</sup> Providing information in a collaborative manner protects the autonomy of patients to make informed decisions based on potential treatment outcomes.<sup>421</sup> Palliative care can help patients and families set realistic expectations and meet short- and longer-term goals, such as important life-cycle events. Much of the care outlined in these guidelines is geared toward a different hope than that for cure of the disease itself.<sup>125,419,422</sup> Even when cure is no longer possible, hope remains: hope for dignity, comfort, and closure and for growth at the end of life. It is our hope that these guidelines will help oncology and palliative care professionals together create a better future for patients, families, and providers.





# NCCN Guidelines Version 1.2019 Palliative Care

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

## Table 1: Palliative Care Internet Resources for Clinicians<sup>a</sup>

### Palliative Care Clinical Competencies

[www.epec.net](http://www.epec.net)

Education in Palliative and End-of-life Care (EPEC): Comprehensive curriculum covering fundamentals of palliative medicine; teaching guides

[www.StopPain.org](http://www.StopPain.org)

Department of Pain Medicine and Palliative Care at Beth Israel Medical Center: Online education for physicians, nurses, and pharmacists

### Clinical, Educational, Professional, and Public Resources

[www.palliativedrugs.com](http://www.palliativedrugs.com)

Palliativedrugs.com: Extensive information on pharmacologic symptom management

[www.aahpm.org](http://www.aahpm.org)

American Academy of Hospice and Palliative Medicine: Physician membership organization; board review courses; publications

[www.abim.org](http://www.abim.org)

The American Board of Internal Medicine: Physician Board Certification

[www.nhpco.org/](http://www.nhpco.org/)

National Hospice and Palliative Care Organization: Nonprofit membership organization representing hospice and palliative care programs and professionals in the United States

[www.hpna.org/](http://www.hpna.org/)

Hospice & Palliative Nurses Association: Specialty nursing organization with evidence-based educational tools for the nursing team

[www.hms.harvard.edu/cdi/pallcare](http://www.hms.harvard.edu/cdi/pallcare)

Center for Palliative Care at Harvard Medical School: Faculty development courses, other educational programs

[www.nationalconsensusproject.org/](http://www.nationalconsensusproject.org/)

National Consensus Project for Quality Palliative Care: Clinical practice guidelines

[www.americangeriatrics.org/](http://www.americangeriatrics.org/)

American Geriatrics Society: Clinical guidelines and continuing education

### Palliative Care Program Development

[www.capc.org](http://www.capc.org)

Center to Advance Palliative Care: Technical assistance for clinicians and hospitals seeking to establish or strengthen a palliative care program

[www.capc.org/palliative-care-leadership-centers/](http://www.capc.org/palliative-care-leadership-centers/)

Palliative Care Leadership Centers: Eight exemplary palliative care programs providing site visits, hands-on training, and technical assistance to support new palliative care clinicians and programs nationwide

### Physician-Assisted Dying

Statement on Physician-Assisted Dying approved by the AAHPM Board of Directors on June 24, 2016: <http://aahpm.org/positions/pad>

<sup>a</sup> All websites accessed May 2017.

Adapted with permission from Meier DE et al. *Oncology* 2005;19. Available at <http://www.cancernetwork.com/display/article/10165/104428>.

### References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28055103>.
2. Cancer survivors--United States, 2007. *MMWR Morb Mortal Wkly Rep* 2011;60:269-272. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21389929>.
3. Ferris FD, Bruera E, Cherny N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps -- from the American Society of Clinical Oncology. *J Clin Oncol* 2009;27:3052-3058. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19451437>.
4. Seow H, Barbera L, Sutradhar R, et al. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. *J Clin Oncol* 2011;29:1151-1158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21300920>.
5. About Palliative Care. Center to Advance Palliative Care; Available at: <https://www.capc.org/about/palliative-care/>. Accessed August 21, 2015.
6. Berger A, Portenoy R, Weissman D, eds. *Practice and Principles of Supportive Oncology*. Philadelphia: Lippincott-Raven; 1998.
7. Doyle D, Hanks G, MacDonald Ne, eds. *Oxford Textbook of Palliative Medicine*. Oxford: Oxford University; 1998.
8. Emanuel L, von Gunten C, FD F, eds. *The Education for Physicians on End-of-Life Care (EPEC) Curriculum*. Princeton: The Robert Wood Johnson Foundation; 1999.
9. Peppercorn JM, Smith TJ, Helft PR, et al. American society of clinical oncology statement: toward individualized care for patients with advanced cancer. *J Clin Oncol* 2011;29:755-760. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21263086>.
10. Smith TJ, Schnipper LJ. The American Society of Clinical Oncology program to improve end-of-life care. *J Palliat Med* 1998;1:221-230. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15859832>.
11. Hui D, Kim YJ, Park JC, et al. Integration of oncology and palliative care: a systematic review. *Oncologist* 2015;20:77-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25480826>.
12. Cancer pain relief and palliative care. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1990;804:1-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1702248>.
13. Levy MH. Living with cancer: hospice/palliative care. *J Natl Cancer Inst* 1993;85:1283-1287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7688053>.
14. Levy MH. Supportive oncology: forward. *Semin Oncol* 1994;21:699-700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7527594>.
15. MacDonald N. Palliative care--the fourth phase of cancer prevention. *Cancer Detect Prev* 1991;15:253-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1711926>.
16. Elsayem A, Swint K, Fisch MJ, et al. Palliative care inpatient service in a comprehensive cancer center: clinical and financial outcomes. *J Clin Oncol* 2004;22:2008-2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15143094>.
17. WHO Definition of Palliative Care. World Health Organization; 2015. Available at: <http://www.who.int/cancer/palliative/definition/en/>. Accessed November 9, 2015.
18. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA* 1995;274:1591-1598. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7474243>.

19. Malin JL. Bridging the divide: integrating cancer-directed therapy and palliative care. *J Clin Oncol* 2004;22:3438-3440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15277538>.
20. Meyers FJ, Linder J. Simultaneous care: disease treatment and palliative care throughout illness. *J Clin Oncol* 2003;21:1412-1415. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12663735>.
21. Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard oncology care for patients with advanced cancer. *CA Cancer J Clin* 2013;63:349-363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23856954>.
22. Davis MP, Bruera E, Morganstern D. Early integration of palliative and supportive care in the cancer continuum: challenges and opportunities. *Am Soc Clin Oncol Educ Book* 2013;33:144-150. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23714482>.
23. Abrahm JL. Integrating palliative care into comprehensive cancer care. *J Natl Compr Canc Netw* 2012;10:1192-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23054873>.
24. Alesi ER, Fletcher D, Muir C, et al. Palliative care and oncology partnerships in real practice. *Oncology (Williston Park)* 2011;25:1287-1290, 1292-1283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22272501>.
25. Bruera E, Yennurajalingam S. Palliative care in advanced cancer patients: how and when? *Oncologist* 2012;17:267-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22252934>.
26. Dennis K, Librach SL, Chow E. Palliative care and oncology: integration leads to better care. *Oncology (Williston Park)* 2011;25:1271-1275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22272495>.
27. Marchetti P, Voltz R, Rubio C, et al. Provision of palliative care and pain management services for oncology patients. *J Natl Compr Canc Netw* 2013;11 Suppl 1:S17-27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23520182>.
28. Quill TE, Abernethy AP. Generalist plus specialist palliative care--creating a more sustainable model. *N Engl J Med* 2013;368:1173-1175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23465068>.
29. Ramchandran K, Von Roenn JH. Palliative care always. *Oncology (Williston Park)* 2013;27:13-16, 27-30, 32-14 passim. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23461040>.
30. Von Roenn JH, Voltz R, Serrie A. Barriers and approaches to the successful integration of palliative care and oncology practice. *J Natl Compr Canc Netw* 2013;11 Suppl 1:S11-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23520181>.
31. Rangachari D, Smith TJ. Integrating palliative care in oncology: the oncologist as a primary palliative care provider. *Cancer J* 2013;19:373-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24051609>.
32. Fann JR, Ell K, Sharpe M. Integrating psychosocial care into cancer services. *J Clin Oncol* 2012;30:1178-1186. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412139>.
33. Vergo MT, Cullinan AM. Joining together to improve outcomes: integrating specialty palliative care into the care of patients with cancer. *J Natl Compr Canc Netw* 2013;11 Suppl 4:S38-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24158970>.
34. Partridge AH, Seah DS, King T, et al. Developing a service model that integrates palliative care throughout cancer care: the time is now. *J Clin Oncol* 2014;32:3330-3336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25199756>.
35. Etkind SN, Daveson BA, Kwok W, et al. Capture, transfer, and feedback of patient-centered outcomes data in palliative care populations: does it make a difference? A systematic review. *J Pain Symptom Manage* 2015;49:611-624. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25135657>.
36. Smith TJ, Temin S, Alesi ER, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into



standard oncology care. *J Clin Oncol* 2012;30:880-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22312101>.

37. Ferrell BR, Temel JS, Temin S, et al. Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol* 2017;35:96-112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28034065>.

38. Smith CB, Phillips T, Smith TJ. Using the New ASCO Clinical Practice Guideline for Palliative Care Concurrent With Oncology Care Using the TEAM Approach ASCO Annual Meeting. Chicago, IL; 2017. Available at: <http://meetinglibrary.asco.org/record/137931/edbook>.

39. Zimmermann C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24559581>.

40. Rugno FC, Paiva BS, Paiva CE. Early integration of palliative care facilitates the discontinuation of anticancer treatment in women with advanced breast or gynecologic cancers. *Gynecol Oncol* 2014;135:249-254. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25173586>.

41. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25800768>.

42. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20818875>.

43. Greer JA, Pirl WF, Jackson VA, et al. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012;30:394-400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22203758>.

44. Temel JS, Greer JA, Admane S, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell

lung cancer: results of a randomized study of early palliative care. *J Clin Oncol* 2011;29:2319-2326. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21555700>.

45. Lefkowitz C, Teuteberg W, Courtney-Brooks M, et al. Improvement in symptom burden within one day after palliative care consultation in a cohort of gynecologic oncology inpatients. *Gynecol Oncol* 2015;136:424-428. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25546112>.

46. Lee YJ, Yang JH, Lee JW, et al. Association between the duration of palliative care service and survival in terminal cancer patients. *Support Care Cancer* 2015;23:1057-1062. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25281228>.

47. Hamano J, Yamaguchi T, Maeda I, et al. Multicenter cohort study on the survival time of cancer patients dying at home or in a hospital: Does place matter? *Cancer* 2016;122:1453-1460. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27018875>.

48. Dionne-Odom JN, Azuero A, Lyons KD, et al. Benefits of early versus delayed palliative care to informal family caregivers of patients with advanced cancer: outcomes from the ENABLE III randomized controlled trial. *J Clin Oncol* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25800762>.

49. Hui D, Kim SH, Roquemore J, et al. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer* 2014;120:1743-1749. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24967463>.

50. Davis MP, Temel JS, Balboni T, Glare P. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. *Ann Palliat Med* 2015;4:99-121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26231807>.

51. Rocque GB, Cleary JF. Palliative care reduces morbidity and mortality in cancer. *Nat Rev Clin Oncol* 2013;10:80-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23247373>.

52. Khan SA, Gomes B, Higginson IJ. End-of-life care-what do cancer patients want? *Nat Rev Clin Oncol* 2014;11:100-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24281062>.
53. Cruz VM, Camaliente L, Caruso P. Factors associated with futile end-of-life intensive care in a cancer hospital. *Am J Hosp Palliat Care* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24399608>
54. Kotsch F, Stiel S, Heckel M, et al. Care trajectories and survival after discharge from specialized inpatient palliative care--results from an observational follow-up study. *Support Care Cancer* 2015;23:627-634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25142704>.
55. McNamara BA, Rosenwax LK, Murray K, Currow DC. Early admission to community-based palliative care reduces use of emergency departments in the ninety days before death. *J Palliat Med* 2013;16:774-779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23676094>.
56. Seow H, Brazil K, Sussman J, et al. Impact of community based, specialist palliative care teams on hospitalisations and emergency department visits late in life and hospital deaths: a pooled analysis. *BMJ* 2014;348:g3496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24906901>.
57. Henson LA, Gao W, Higginson IJ, et al. Emergency department attendance by patients with cancer in their last month of life: a systematic review and meta-analysis. *J Clin Oncol* 2015;33:370-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25534384>.
58. Jang RW, Krzyzanowska MK, Zimmermann C, et al. Palliative care and the aggressiveness of end-of-life care in patients with advanced pancreatic cancer. *J Natl Cancer Inst* 2015;107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25609233>.
59. Khandelwal N, Kross EK, Engelberg RA, et al. Estimating the effect of palliative care interventions and advance care planning on ICU utilization: a systematic review. *Crit Care Med* 2015;43:1102-1111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25574794>.
60. Gomes B, Calanzani N, Curiale V, et al. Effectiveness and cost-effectiveness of home palliative care services for adults with advanced illness and their caregivers. *Cochrane Database Syst Rev* 2013;6:CD007760. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23744578>.
61. May P, Garrido MM, Cassel JB, et al. Prospective cohort study of hospital palliative care teams for inpatients with advanced cancer: earlier consultation is associated with larger cost-saving effect. *J Clin Oncol* 2015;33:2745-2752. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26056178>.
62. May P, Garrido MM, Cassel JB, et al. Palliative care teams' cost-saving effect is larger for cancer patients with higher numbers of comorbidities. *Health Aff (Millwood)* 2016;35:44-53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26733700>.
63. Isenberg SR, Lu C, McQuade J, et al. Economic Evaluation of a Hospital-Based Palliative Care Program. *J Oncol Pract* 2017;13:e408-e420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28418761>.
64. Isenberg SR, Lu C, McQuade J, et al. Impact of a New Palliative Care Program on Health System Finances: An Analysis of the Palliative Care Program Inpatient Unit and Consultations at Johns Hopkins Medical Institutions. *J Oncol Pract* 2017;13:e421-e430. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28245147>.
65. Han B, Remsburg RE, McAuley WJ, et al. National trends in adult hospice use: 1991-1992 to 1999-2000. *Health Aff (Millwood)* 2006;25:792-799. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16684745>.
66. NHPCO Facts and Figures: Hospice Care in America. Alexandria, VA: National Hospice and Palliative Care Organization; 2013. Available at: [http://www.nhpco.org/sites/default/files/public/Statistics\\_Research/2013\\_Facts\\_Figures.pdf](http://www.nhpco.org/sites/default/files/public/Statistics_Research/2013_Facts_Figures.pdf).
67. Langton JM, Blanch B, Drew AK, et al. Retrospective studies of end-of-life resource utilization and costs in cancer care using health



administrative data: a systematic review. *Palliat Med* 2014;28:1167-1196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24866758>.

68. O'Connor TL, Ngamphaiboon N, Groman A, et al. Hospice utilization and end-of-life care in metastatic breast cancer patients at a comprehensive cancer center. *J Palliat Med* 2015;18:50-55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25353618>.

69. Bergman J, Saigal CS, Lorenz KA, et al. Hospice use and high-intensity care in men dying of prostate cancer. *Arch Intern Med* 2011;171:204-210. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20937914>.

70. NHPCO Facts and Figures: Hospice Care in America. National Hospice and Palliative Care Organization; 2012. Available at: [http://www.nhpc.org/sites/default/files/public/Statistics\\_Research/2012\\_Facts\\_Figures.pdf](http://www.nhpc.org/sites/default/files/public/Statistics_Research/2012_Facts_Figures.pdf). Accessed March 20, 2013.

71. Mack JW, Chen K, Boscoe FP, et al. Underuse of hospice care by Medicaid-insured patients with stage IV lung cancer in New York and California. *J Clin Oncol* 2013;31:2569-2579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23733768>.

72. Breitkopf CR, Stephens EK, Jatoi A. Hospice in end-of-life patients with cancer: Does it lead to changes in nonhospice health care utilization after stopping cancer treatment? *Am J Hosp Palliat Care* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23666617>.

73. Kelley AS, Deb P, Du Q, et al. Hospice enrollment saves money for Medicare and improves care quality across a number of different lengths-of-stay. *Health Aff (Millwood)* 2013;32:552-561. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23459735>.

74. Morden NE, Chang CH, Jacobson JO, et al. End-of-life care for Medicare beneficiaries with cancer is highly intensive overall and varies widely. *Health Aff (Millwood)* 2012;31:786-796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22492896>.

75. Earle CC, Neville BA, Landrum MB, et al. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 2004;22:315-321. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14722041>.

76. Earle CC, Landrum MB, Souza JM, et al. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol* 2008;26:3860-3866. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18688053>.

77. Foley K, Gelband H, eds. *Improving palliative care for cancer*. Washington, DC: National Academy Press; 2001.

78. Goodman D, Morden NE, Chang CH, et al. Trends in Cancer Care Near the End of Life. A Dartmouth Atlas of Health Care Brief: The Dartmouth Institute for Health Policy and Clinical Practice; 2013. Available at: [http://www.dartmouthatlas.org/downloads/reports/Cancer\\_brief\\_090413.pdf](http://www.dartmouthatlas.org/downloads/reports/Cancer_brief_090413.pdf).

79. Wang X, Knight LS, Evans A, et al. Variations Among Physicians in Hospice Referrals of Patients With Advanced Cancer. *J Oncol Pract* 2017;13:e496-e504. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28221897>.

80. Von Gunten CF. A quality improvement approach to oncologist referrals for hospice care. *Journal of Clinical Oncology* 2016;34:45-45. Available at: [http://ascopubs.org/doi/abs/10.1200/jco.2016.34.26\\_suppl.45](http://ascopubs.org/doi/abs/10.1200/jco.2016.34.26_suppl.45).

81. Mullen MM, Divine LM, Porcelli BP, et al. The effect of a multidisciplinary palliative care initiative on end of life care in gynecologic oncology patients [abstract]. Annual Meeting of the Society of Gynecologic Oncology. National Harbor, MD; 2017. Available at: [https://www.sgo.org/wp-content/uploads/2017/03/3a\\_Tuesday-March-14-2017-SGO-Annual-Meeting-on-Womens-Cancer-Abstracts.pdf](https://www.sgo.org/wp-content/uploads/2017/03/3a_Tuesday-March-14-2017-SGO-Annual-Meeting-on-Womens-Cancer-Abstracts.pdf).

82. Lorenz KA, Lynn J, Dy SM, et al. Evidence for improving palliative care at the end of life: a systematic review. *Ann Intern Med* 2008;148:147-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18195339>.
83. El-Jawahri A, Greer JA, Temel JS. Does palliative care improve outcomes for patients with incurable illness? A review of the evidence. *J Support Oncol* 2011;9:87-94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21702398>.
84. Hui D, Arthur J, Dalal S, Bruera E. Quality of the supportive and palliative oncology literature: a focused analysis on randomized controlled trials. *Support Care Cancer* 2012;20:1779-1785. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21935717>.
85. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care, Third Edition*. 2013. Available at: <http://www.nationalconsensusproject.org>.
86. National Quality Forum: A National Framework and Preferred Practices for Palliative and Hospice Care Quality. 2006. Available at: <http://www.qualityforum.org/Home.aspx>.
87. Cancer Program Standards 2012: Ensuring Patient-Centered Care. American College of Surgeons Commission on Cancer; 2012. Available at: <http://www.facs.org/cancer/coc/programstandards2012.html>. Accessed March 20, 2013.
88. Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life Washington, DC: Institute of Medicine; 2014. Available at: <http://iom.nationalacademies.org/Reports/2014/Dying-In-America-Improving-Quality-and-Honoring-Individual-Preferences-Near-the-End-of-Life.aspx>.
89. Kamal AH, Bull J, Stinson CS, et al. Conformance with supportive care quality measures is associated with better quality of life in patients with cancer receiving palliative care. *J Oncol Pract* 2013;9:e73-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23942504>.
90. Gelfman LP, Du Q, Morrison RS. An update: NIH research funding for palliative medicine 2006 to 2010. *J Palliat Med* 2013;16:125-129. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23336358>.
91. Hui D, Glitza I, Chisholm G, et al. Attrition rates, reasons, and predictive factors in supportive care and palliative oncology clinical trials. *Cancer* 2013;119:1098-1105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23132290>.
92. Leblanc TW, Lodato JE, Currow DC, Abernethy AP. Overcoming recruitment challenges in palliative care clinical trials. *J Oncol Pract* 2013;9:277-282. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24130254>.
93. Agar M, Lockett T. Outcome measures for palliative care research. *Curr Opin Support Palliat Care* 2012;6:500-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23080308>.
94. Davis MP, Mitchell GK. Topics in research: structuring studies in palliative care. *Curr Opin Support Palliat Care* 2012;6:483-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23123820>.
95. Kamal AH, Swetz KM, Dy S, et al. Integrating technology into palliative care research. *Curr Opin Support Palliat Care* 2012;6:525-532. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23080307>.
96. LeBlanc TW, Abernethy AP, Currow DC, Kutner JS. Considerations in reporting palliative care clinical trials: standardizing information reported and authorship practices. *Curr Opin Support Palliat Care* 2012;6:494-499. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23080306>.
97. Lodato JE, Aziz N, Bennett RE, et al. Achieving palliative care research efficiency through defining and benchmarking performance metrics. *Curr Opin Support Palliat Care* 2012;6:533-542. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23080309>.
98. Lee RT, Ramchandran K, Sanft T, Von Roenn J. Implementation of supportive care and best supportive care interventions in clinical trials

enrolling patients with cancer dagger. *Ann Oncol* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25922064>.

99. Boland J, Currow DC, Wilcock A, et al. A systematic review of strategies used to increase recruitment of people with cancer or organ failure into clinical trials: implications for palliative care research. *J Pain Symptom Manage* 2015;49:762-772 e765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25546286>.

100. Nipp RD, Currow DC, Cherny NI, et al. Best supportive care in clinical trials: review of the inconsistency in control arm design. *Br J Cancer* 2015;113:6-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26068397>.

101. Hagen NA, Biondo PD, Brasher PM, Stiles CR. Formal feasibility studies in palliative care: why they are important and how to conduct them. *J Pain Symptom Manage* 2011;42:278-289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21444184>.

102. Nordly M, Benthien KS, Von Der Maase H, et al. The DOMUS study protocol: a randomized clinical trial of accelerated transition from oncological treatment to specialized palliative care at home. *BMC Palliat Care* 2014;13:44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25242890>.

103. Levy MH. Supportive oncology-palliative care: what's in a name? *Semin Oncol* 2005;32:131-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15815956>.

104. Von Roenn JH. Optimal cancer care: Concurrent oncology and palliative care. *J Natl Compr Canc Netw* 2013;11 Suppl 1:S1-2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23520180>.

105. Hui D, Mori M, Parsons HA, et al. The lack of standard definitions in the supportive and palliative oncology literature. *J Pain Symptom Manage* 2012;43:582-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22104619>.

106. Hui D, De La Cruz M, Mori M, et al. Concepts and definitions for "supportive care," "best supportive care," "palliative care," and "hospice care" in the published literature, dictionaries, and textbooks. *Support Care Cancer* 2013;21:659-685. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22936493>.

107. Rittenberg CN, Johnson JL, Kuncio GM. An oral history of MASCC, its origin and development from MASCC's beginnings to 2009. *Support Care Cancer* 2010;18:775-784. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20221642>.

108. Maciasz RM, Arnold RM, Chu E, et al. Does it matter what you call it? A randomized trial of language used to describe palliative care services. *Support Care Cancer* 2013;21:3411-3419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23942596>.

109. Fadul N, Elsayem A, Palmer JL, et al. Supportive versus palliative care: what's in a name?: a survey of medical oncologists and midlevel providers at a comprehensive cancer center. *Cancer* 2009;115:2013-2021. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19235253>.

110. Dalal S, Palla S, Hui D, et al. Association between a name change from palliative to supportive care and the timing of patient referrals at a comprehensive cancer center. *Oncologist* 2011;16:105-111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21212438>.

111. Chochinov HM. Dying, dignity, and new horizons in palliative end-of-life care. *CA Cancer J Clin* 2006;56:84-103; quiz 104-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16514136>.

112. Kim A, Fall P, Wang D. Palliative care: optimizing quality of life. *J Am Osteopath Assoc* 2005;105:S9-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16368908>.

113. Hui D, Kim SH, Kwon JH, et al. Access to palliative care among patients treated at a comprehensive cancer center. *Oncologist* 2012;17:1574-1580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23220843>.



114. Jang RW, Krzyzanowska MK, Zimmermann C, et al. Intensity of Palliative Care and its Impact on the Aggressiveness of End-of-Life Care in Patients with Advanced Pancreatic Cancer [Abstract]. J Clin Oncol 2013;31(Suppl):Suppl; Abstract 9518. Available at: <http://meetinglibrary.asco.org/content/111841-132>.

115. Mulvey CL, Smith TJ, Gourin CG. Use of inpatient palliative care services in patients with metastatic incurable head and neck cancer. Head Neck 2016;38:355-363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25331744>.

116. Wentlandt K, Krzyzanowska MK, Swami N, et al. Referral practices of oncologists to specialized palliative care. J Clin Oncol 2012;30:4380-4386. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23109708>.

117. Reville B, Reifsnnyder J, McGuire DB, et al. Education and referral criteria: impact on oncology referrals to palliative care. J Palliat Med 2013;16:786-789. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23510168>.

118. Pelayo-Alvarez M, Perez-Hoyos S, Agra-Varela Y. Clinical effectiveness of online training in palliative care of primary care physicians. J Palliat Med 2013;16:1188-1196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23987657>.

119. Mougalian SS, Lessen DS, Levine RL, et al. Palliative care training and associations with burnout in oncology fellows. J Support Oncol 2013;11:95-102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23967496>.

120. Morita T, Miyashita M, Yamagishi A, et al. Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study. Lancet Oncol 2013;14:638-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23664708>.

121. Weeks JC, Catalano PJ, Cronin A, et al. Patients' expectations about effects of chemotherapy for advanced cancer. N Engl J Med 2012;367:1616-1625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23094723>.

122. Smith TJ, Longo DL. Talking with patients about dying. N Engl J Med 2012;367:1651-1652. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23094729>.

123. Mack JW, Walling A, Dy S, et al. Patient beliefs that chemotherapy may be curative and care received at the end of life among patients with metastatic lung and colorectal cancer. Cancer 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25677655>.

124. Chen AB, Cronin A, Weeks JC, et al. Expectations about the effectiveness of radiation therapy among patients with incurable lung cancer. J Clin Oncol 2013;31:2730-2735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23775958>.

125. Liu PH, Landrum MB, Weeks JC, et al. Physicians' propensity to discuss prognosis is associated with patients' awareness of prognosis for metastatic cancers. J Palliat Med 2014;17:673-682. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24742212>.

126. Mack JW, Smith TJ. Reasons why physicians do not have discussions about poor prognosis, why it matters, and what can be improved. J Clin Oncol 2012;30:2715-2717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22753911>.

127. Otani H, Morita T, Esaki T, et al. Burden on oncologists when communicating the discontinuation of anticancer treatment. Jpn J Clin Oncol 2011;41:999-1006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21764830>.

128. Lefkowitz C, Sukumvanich P, Claxton R, et al. Needs assessment of palliative care education in gynecologic oncology fellowship: we're not teaching what we think is most important. Gynecol Oncol 2014;135:255-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25135001>.

129. Barth J, Lannen P. Efficacy of communication skills training courses in oncology: a systematic review and meta-analysis. Ann Oncol 2011;22:1030-1040. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20974653>.

130. Kissane DW, Bylund CL, Banerjee SC, et al. Communication skills training for oncology professionals. *J Clin Oncol* 2012;30:1242-1247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412145>.

131. Moore PM, Rivera Mercado S, Grez Artigues M, Lawrie TA. Communication skills training for healthcare professionals working with people who have cancer. *Cochrane Database Syst Rev* 2013;3:CD003751. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23543521>.

132. Rao JK, Anderson LA, Inui TS, Frankel RM. Communication interventions make a difference in conversations between physicians and patients: a systematic review of the evidence. *Med Care* 2007;45:340-349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17496718>.

133. Epstein RM, Duberstein PR, Fenton JJ, et al. Effect of a Patient-Centered Communication Intervention on Oncologist-Patient Communication, Quality of Life, and Health Care Utilization in Advanced Cancer: The VOICE Randomized Clinical Trial. *JAMA Oncol* 2017;3:92-100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27612178>.

134. Krasner MS, Epstein RM, Beckman H, et al. Association of an educational program in mindful communication with burnout, empathy, and attitudes among primary care physicians. *JAMA* 2009;302:1284-1293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19773563>.

135. Goelz T, Wuensch A, Stubenrauch S, et al. Specific training program improves oncologists' palliative care communication skills in a randomized controlled trial. *J Clin Oncol* 2011;29:3402-3407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21825268>.

136. de Haes H, Teunissen S. Communication in palliative care: a review of recent literature. *Curr Opin Oncol* 2005;17:345-350. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15933465>.

137. Sinclair CT. Communicating a prognosis in advanced cancer. *J Support Oncol* 2006;4:201-204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16669464>.

138. van Vliet LM, van der Wall E, Plum NM, Bensing JM. Explicit prognostic information and reassurance about nonabandonment when entering palliative breast cancer care: findings from a scripted video-vignette study. *J Clin Oncol* 2013;31:3242-3249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23940230>.

139. Hinkle LJ, Bosslet GT, Torke AM. Factors associated with family satisfaction with end-of-life care in the ICU: a systematic review. *Chest* 2015;147:82-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25103451>.

140. Virdun C, Lockett T, Davidson PM, Phillips J. Dying in the hospital setting: A systematic review of quantitative studies identifying the elements of end-of-life care that patients and their families rank as being most important. *Palliat Med* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25921707>.

141. Furber L, Cox K, Murphy R, Steward W. Investigating communication in cancer consultations: what can be learned from doctor and patient accounts of their experience? *Eur J Cancer Care (Engl)* 2013;22:653-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23701317>.

142. Enzinger AC, Zhang B, Schrag D, Prigerson HG. Outcomes of prognostic disclosure: Associations with prognostic understanding, distress, and relationship with physician among patients with advanced cancer. *J Clin Oncol* 2015;33:3809-3816. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26438121>.

143. Ciechanowski PS, Katon WJ, Russo JE, Walker EA. The patient-provider relationship: attachment theory and adherence to treatment in diabetes. *Am J Psychiatry* 2001;158:29-35. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11136630>.

144. Stewart MA. Effective physician-patient communication and health outcomes: a review. *CMAJ* 1995;152:1423-1433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7728691>.

145. Grenklo TB, Kreicbergs UC, Valdimarsdottir UA, et al. Communication and trust in the care provided to a dying parent: a



nationwide study of cancer-bereaved youths. *J Clin Oncol* 2013;31:2886-2894. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23857973>.

146. Cleeland CS, Zhao F, Chang VT, et al. The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. *Cancer* 2013;119:4333-4340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24114037>.

147. LoPresti MA, Dement F, Gold HT. End-of-life care for people with cancer from ethnic minority groups: a systematic review. *Am J Hosp Palliat Care* 2016;33:291-305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25550406>.

148. Diver E, O'Connor O, Garrett L, et al. Modest benefit of total parenteral nutrition and chemotherapy after venting gastrostomy tube placement. *Gynecol Oncol* 2013;129:332-335. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23402902>.

149. Richards DM, Tanikella R, Arora G, et al. Percutaneous endoscopic gastrostomy in cancer patients: predictors of 30-day complications, 30-day mortality, and overall mortality. *Dig Dis Sci* 2013;58:768-776. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23007733>.

150. Salpeter SR, Malter DS, Luo EJ, et al. Systematic review of cancer presentations with a median survival of six months or less. *J Palliat Med* 2012;15:175-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22023378>.

151. El-Jawahri A, Traeger L, Park ER, et al. Associations among prognostic understanding, quality of life, and mood in patients with advanced cancer. *Cancer* 2014;120:278-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24122784>

152. Gwilliam B, Keeley V, Todd C, et al. Prognosticating in patients with advanced cancer--observational study comparing the accuracy of clinicians' and patients' estimates of survival. *Ann Oncol* 2013;24:482-488. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23028038>.

153. Hagerty RG, Butow PN, Ellis PA, et al. Cancer patient preferences for communication of prognosis in the metastatic setting. *J Clin Oncol* 2004;22:1721-1730. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15117995>.

154. Hagerty RG, Butow PN, Ellis PM, et al. Communicating with realism and hope: incurable cancer patients' views on the disclosure of prognosis. *J Clin Oncol* 2005;23:1278-1288. Available at: <http://www.jco.org/cgi/content/abstract/23/6/1278>.

155. Weeks JC, Cook EF, O'Day SJ, et al. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA* 1998;279:1709-1714. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9624023>.

156. Lo B, Ruston D, Kates LW, et al. Discussing religious and spiritual issues at the end of life: a practical guide for physicians. *JAMA* 2002;287:749-754. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11851542>.

157. Communicating with Patients on Health Care Evidence. Institute of Medicine; 2012. Available at: <http://www.iom.edu/Global/Perspectives/2012/Evidence.aspx>. Accessed May 17, 2013.

158. Novelli WD, Halvorson GC, Santa J. Recognizing an Opinion: Findings From the IOM Evidence Communication Innovation Collaborative. *JAMA* 2012;308:1531-1532. Available at: <http://jama.jamanetwork.com/article.aspx?articleid=1363268>.

159. Freelove R, Walling AD. Pancreatic cancer: diagnosis and management. *Am Fam Physician* 2006;73:485-492. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16477897>.

160. Guarneri V, Conte PF. The curability of breast cancer and the treatment of advanced disease. *Eur J Nucl Med Mol Imaging* 2004;31 Suppl 1:S149-161. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15107948>.

161. Pienta KJ, Smith DC. Advances in prostate cancer chemotherapy: a new era begins. *CA Cancer J Clin* 2005;55:300-318; quiz 323-305. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16166075>.

162. Prommer E. Guidelines for the Use of Palliative Chemotherapy. *AAHPM Bulletin* 2004;5:2-13. Available at: <http://www.aahpm.org/pdf/04spring.pdf>.

163. Ajani JA. Evolving chemotherapy for advanced gastric cancer. *Oncologist* 2005;10 Suppl 3:49-58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16368871>.

164. Brown J, Thorpe H, Napp V, et al. Assessment of quality of life in the supportive care setting of the big lung trial in non-small-cell lung cancer. *J Clin Oncol* 2005;23:7417-7427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16157935>.

165. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. *J Clin Oncol* 2014;32:2913-2919. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25113773>.

166. Silvestri GA, Rivera MP. Targeted therapy for the treatment of advanced non-small cell lung cancer: a review of the epidermal growth factor receptor antagonists. *Chest* 2005;128:3975-3984. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16354869>.

167. Clarke G, Johnston S, Corrie P, et al. Withdrawal of anticancer therapy in advanced disease: a systematic literature review. *BMC Cancer* 2015;15:892. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26559912>.

168. Prigerson HG, Bao Y, Shah MA, et al. Chemotherapy use, performance status, and quality of life at the end of life. *JAMA Oncol* 2015;1:778-784. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26203912>.

169. Chen AB, Cronin A, Weeks JC, et al. Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)

Study. *J Clin Oncol* 2013;31:558-564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23295799>.

170. Zafar SY, Malin JL, Grambow SC, et al. Chemotherapy use and patient treatment preferences in advanced colorectal cancer: a prospective cohort study. *Cancer* 2013;119:854-862. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22972673>.

171. LeBlanc TW, McNeil MJ, Kamal AH, et al. Polypharmacy in patients with advanced cancer and the role of medication discontinuation. *Lancet Oncol* 2015;16:e333-341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26149885>.

172. Higginson IJ, Finlay IG, Goodwin DM, et al. Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? *J Pain Symptom Manage* 2003;25:150-168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12590031>.

173. Kinzbrunner BM. Hospice: what to do when anti-cancer therapy is no longer appropriate, effective, or desired. *Semin Oncol* 1994;21:792-798. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7527597>.

174. Trajkovic-Vidakovic M, de Graeff A, Voest EE, Teunissen SC. Symptoms tell it all: a systematic review of the value of symptom assessment to predict survival in advanced cancer patients. *Crit Rev Oncol Hematol* 2012;84:130-148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22465016>.

175. Yennurajalingam S, Kwon JH, Urbauer DL, et al. Consistency of symptom clusters among advanced cancer patients seen at an outpatient supportive care clinic in a tertiary cancer center. *Palliat Support Care* 2013;11:473-480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23388652>.

176. Van Lancker A, Velghe A, Van Hecke A, et al. Prevalence of symptoms in older cancer patients receiving palliative care: a systematic review and meta-analysis. *J Pain Symptom Manage* 2014;47:90-104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23764109>.

177. Ferrell B, Levy MH, Paice J. Managing pain from advanced cancer in the palliative care setting. *Clin J Oncol Nurs* 2008;12:575-581. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18676325>.
178. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO Evidence-Based Guideline. *Pract Radiat Oncol* 2017;7:4-12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27663933>.
179. Westhoff PG, de Graeff A, Monninkhof EM, et al. Quality of life in relation to pain response to radiation therapy for painful bone metastases. *Int J Radiat Oncol Biol Phys* 2015;93:694-701. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26281825>.
180. Temel JS, Pirl WF, Lynch TJ. Comprehensive symptom management in patients with advanced-stage non-small-cell lung cancer. *Clin Lung Cancer* 2006;7:241-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16512977>.
181. Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. *Am J Respir Crit Care Med* 1999;159:321-340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9872857>.
182. DeCamp MM, Jr., Mentzer SJ, Swanson SJ, Sugarbaker DJ. Malignant effusive disease of the pleura and pericardium. *Chest* 1997;112:291S-295S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9337306>.
183. Dy SM, Lorenz KA, Naeim A, et al. Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. *J Clin Oncol* 2008;26:3886-3895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18688057>.
184. Swanson N, Mirza I, Wijesinghe N, Devlin G. Primary percutaneous balloon pericardiectomy for malignant pericardial effusion. *Catheter Cardiovasc Interv* 2008;71:504-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18307242>.
185. Simon ST, Higginson IJ, Booth S, et al. Benzodiazepines for the relief of breathlessness in advanced malignant and non-malignant diseases in adults. *Cochrane Database Syst Rev* 2016;10:CD007354. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27764523>.
186. Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. *Cochrane Database Syst Rev* 2016;3:CD011008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27030166>.
187. Dy SM, Apostol CC. Evidence-based approaches to other symptoms in advanced cancer. *Cancer J* 2010;16:507-513. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20890148>.
188. Ben-Aharon I, Gafer-Gvili A, Paul M, et al. Interventions for alleviating cancer-related dyspnea: a systematic review. *J Clin Oncol* 2008;26:2396-2404. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18467732>.
189. Ben-Aharon I, Gafer-Gvili A, Leibovici L, Stemmer SM. Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. *Acta Oncol* 2012;51:996-1008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22934558>.
190. Clemens KE, Quednau I, Klaschik E. Is there a higher risk of respiratory depression in opioid-naïve palliative care patients during symptomatic therapy of dyspnea with strong opioids? *J Palliat Med* 2008;11:204-216. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18333735>.
191. Gomutbutra P, O'Riordan DL, Pantilat SZ. Management of moderate-to-severe dyspnea in hospitalized patients receiving palliative care. *J Pain Symptom Manage* 2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22940561>.
192. Coyne PJ, Viswanathan R, Smith TJ. Nebulized fentanyl citrate improves patients' perception of breathing, respiratory rate, and oxygen saturation in dyspnea. *J Pain Symptom Manage* 2002;23:157-160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11844637>.



193. Smith TJ, Coyne P, French W, et al. Failure to accrue to a study of nebulized fentanyl for dyspnea: lessons learned. *J Palliat Med* 2009;12:771-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19719370>.
194. Simon ST, Koskeroglu P, Gaertner J, Voltz R. Fentanyl for the relief of refractory breathlessness: a systematic review. *J Pain Symptom Manage* 2013;46:874-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23742735>.
195. Hui D, Xu A, Frisbee-Hume S, et al. Effects of prophylactic subcutaneous fentanyl on exercise-induced breakthrough dyspnea in cancer patients: a preliminary double-blind, randomized, controlled trial. *J Pain Symptom Manage* 2014;47:209-217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23830530>.
196. Jensen D, Alshail A, Viola R, et al. Inhaled fentanyl citrate improves exercise endurance during high-intensity constant work rate cycle exercise in chronic obstructive pulmonary disease. *J Pain Symptom Manage* 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22168961>.
197. Kawabata M, Kaneishi K. Continuous subcutaneous infusion of compound oxycodone for the relief of dyspnea in patients with terminally ill cancer: a retrospective study. *Am J Hosp Palliat Care* 2013;30:305-311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22669937>.
198. Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. *Palliat Med* 2001;15:329-336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12054150>.
199. Davis MP, Furste A. Glycopyrrolate: a useful drug in the palliation of mechanical bowel obstruction. *J Pain Symptom Manage* 1999;18:153-154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10517034>.
200. Hughes A, Wilcock A, Corcoran R, et al. Audit of three antimuscarinic drugs for managing retained secretions. *Palliat Med* 2000;14:221-222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10858832>.
201. Wildiers H, Menten J. Death rattle: prevalence, prevention and treatment. *J Pain Symptom Manage* 2002;23:310-317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11997200>.
202. Wildiers H, Dhaenekint C, Demeulenaere P, et al. Atropine, hyoscine butylbromide, or scopolamine are equally effective for the treatment of death rattle in terminal care. *J Pain Symptom Manage* 2009;38:124-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19361952>.
203. Grum DF, Osborne LR. Central anticholinergic syndrome following glycopyrrolate. *Anesthesiology* 1991;74:191-193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1986648>.
204. Wingard DW. Glycopyrrolate and the central anticholinergic syndrome. *Anesthesiology* 1991;75:1125-1126. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1741510>.
205. Mirakhor RK, Dundee JW. Glycopyrrolate: pharmacology and clinical use. *Anaesthesia* 1983;38:1195-1204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6660460>.
206. #109 Death Rattle and Oral Secretions, 2nd ed. End of Life / Palliative Education Resource Center (EPERC); Available at: [http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff\\_109.htm](http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_109.htm). Accessed May 20, 2013.
207. Straka C, Ying J, Kong FM, et al. Review of evolving etiologies, implications and treatment strategies for the superior vena cava syndrome. *Springerplus* 2016;5:229. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27026923>.
208. Galbraith S, Fagan P, Perkins P, et al. Does the use of a handheld fan improve chronic dyspnea? A randomized, controlled, crossover trial. *J Pain Symptom Manage* 2010;39:831-838. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20471544>.
209. Abernethy AP, McDonald CF, Frith PA, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet*

2010;376:784-793. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20816546>.

210. Nava S, Ferrer M, Esquinas A, et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol* 2013;14:219-227. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23406914>.

211. Hui D, Morgado M, Chisholm G, et al. High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage* 2013;46:463-473. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23739633>.

212. Kumar NB, Kazi A, Smith T, et al. Cancer cachexia: traditional therapies and novel molecular mechanism-based approaches to treatment. *Curr Treat Options Oncol* 2010;11:107-117. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21128029>.

213. Laviano A, Meguid MM, Inui A, et al. Therapy insight: Cancer anorexia-cachexia syndrome--when all you can eat is yourself. *Nat Clin Pract Oncol* 2005;2:158-165. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16264909>.

214. Oberholzer R, Hopkinson JB, Baumann K, et al. Psychosocial Effects of Cancer Cachexia: A Systematic Literature Search and Qualitative Analysis. *J Pain Symptom Manage* 2012. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23159682>.

215. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013;31:1539-1547. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23530101>.

216. Mercadante S, Aielli F, Adile C, et al. Prevalence of oral mucositis, dry mouth, and dysphagia in advanced cancer patients. *Support Care Cancer* 2015;23:3249-3255. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/25832897>.

217. Pascual Lopez A, Roque i Figuls M, Urrutia Cuchi G, et al. Systematic review of megestrol acetate in the treatment of anorexia-cachexia syndrome. *J Pain Symptom Manage* 2004;27:360-369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15050664>.

218. Ruiz Garcia V, Lopez-Briz E, Carbonell Sanchis R, et al. Megestrol acetate for treatment of anorexia-cachexia syndrome. *Cochrane Database Syst Rev* 2013;3:CD004310. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23543530>.

219. Yavuzsen T, Davis MP, Walsh D, et al. Systematic review of the treatment of cancer-associated anorexia and weight loss. *J Clin Oncol* 2005;23:8500-8511. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16293879>.

220. Miller S, McNutt L, McCann MA, McCorry N. Use of corticosteroids for anorexia in palliative medicine: a systematic review. *J Palliat Med* 2014;17:482-485. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24702642>.

221. Navari RM, Brenner MC. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. *Support Care Cancer* 2010;18:951-956. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19756773>.

222. Mantovani G, Maccio A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist* 2010;15:200-211. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20156909>.

223. Maccio A, Madeddu C, Gramignano G, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. *Gynecol Oncol* 2012;124:417-425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22198049>.

224. Walsh D, Nelson KA, Mahmoud FA. Established and potential therapeutic applications of cannabinoids in oncology. *Support Care*



Cancer 2003;11:137-143. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12618922>.

225. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. *J Clin Oncol* 2006;24:3394-3400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16849753>.

226. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20:567-573. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11786587>.

227. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer* 2004;91:447-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15226773>.

228. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. *J Clin Oncol* 2005;23:1431-1438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15684319>.

229. Trentham K. Palliative Care. In: Marian M, Roberts S, eds. *Clinical Nutrition for Oncology Patients*. Sudbury, MA: Jones and Bartlett Publishers LLC; 2010.

230. Baldwin C, Spiro A, McGough C, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. *J Hum Nutr Diet* 2011;24:431-440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21733143>.

231. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012;104:371-385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22345712>.

232. August DA, Huhmann MB. A.S.P.E.N. clinical guidelines: nutrition support therapy during adult anticancer treatment and in hematopoietic cell transplantation. *JPEN J Parenter Enteral Nutr* 2009;33:472-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19713551>.

233. McCann RM, Hall WJ, Groth-Juncker A. Comfort care for terminally ill patients. The appropriate use of nutrition and hydration. *JAMA* 1994;272:1263-1266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7523740>.

234. Weiner RS, Kramer BS, Clamon GH, et al. Effects of intravenous hyperalimentation during treatment in patients with small-cell lung cancer. *J Clin Oncol* 1985;3:949-957. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2991475>.

235. Winter SM. Terminal nutrition: framing the debate for the withdrawal of nutritional support in terminally ill patients. *Am J Med* 2000;109:723-726. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11137488>.

236. Bruera E, Hui D, Dalal S, et al. Parenteral hydration in patients with advanced cancer: a multicenter, double-blind, placebo-controlled randomized trial. *J Clin Oncol* 2013;31:111-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23169523>.

237. Schwartzberg L. Chemotherapy-induced nausea and vomiting: state of the art in 2006. *J Support Oncol* 2006;4:3-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16499138>.

238. Shoemaker LK, Estfan B, Induru R, Walsh TD. Symptom management: an important part of cancer care. *Cleve Clin J Med* 2011;78:25-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21199904>.

239. Yamanaka R, Koga H, Yamamoto Y, et al. Characteristics of patients with brain metastases from lung cancer in a palliative care center. *Support Care Cancer* 2011;19:467-473. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20217148>.
240. Gofton TE, Graber J, Carver A. Identifying the palliative care needs of patients living with cerebral tumors and metastases: a retrospective analysis. *J Neurooncol* 2012;108:527-534. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22467138>.
241. Holt DW, Volans GN. Gastrointestinal symptoms of digoxin toxicity. *Br Med J* 1977;2:704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/268993>.
242. Hwang WJ, Tsai JJ. Acute phenytoin intoxication: causes, symptoms, misdiagnoses, and outcomes. *Kaohsiung J Med Sci* 2004;20:580-585. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15696787>.
243. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients. *Cochrane Database Syst Rev* 2015:CD006271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26524474>.
244. Davis MP, Hallerberg G. A systematic review of the treatment of nausea and/or vomiting in cancer unrelated to chemotherapy or radiation. *J Pain Symptom Manage* 2010;39:756-767. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20413062>.
245. Hardy JR, O'Shea A, White C, et al. The efficacy of haloperidol in the management of nausea and vomiting in patients with cancer. *J Pain Symptom Manage* 2010;40:111-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20619214>.
246. Gralla RJ, Itri LM, Pisko SE, et al. Antiemetic efficacy of high-dose metoclopramide: randomized trials with placebo and prochlorperazine in patients with chemotherapy-induced nausea and vomiting. *N Engl J Med* 1981;305:905-909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7024807>.
247. Buzdar AU, Esparza L, Natale R, et al. Lorazepam-enhancement of the antiemetic efficacy of dexamethasone and promethazine. A placebo-controlled study. *Am J Clin Oncol* 1994;17:417-421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8092114>.
248. Tan L, Liu J, Liu X, et al. Clinical research of olanzapine for prevention of chemotherapy-induced nausea and vomiting. *J Exp Clin Cancer Res* 2009;28:131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19775450>.
249. Navari RM, Gray SE, Kerr AC. Olanzapine versus aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a randomized phase III trial. *J Support Oncol* 2011;9:188-195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22024310>.
250. Aapro MS, Plezia PM, Alberts DS, et al. Double-blind crossover study of the antiemetic efficacy of high-dose dexamethasone versus high-dose metoclopramide. *J Clin Oncol* 1984;2:466-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6539363>.
251. Kris MG, Gralla RJ, Clark RA, et al. Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone. A double-blind, randomized trial. *Cancer* 1987;60:2816-2822. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3315176>.
252. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT<sub>3</sub> antagonists with good antinausea effects. *Eur J Cancer Care (Engl)* 2007;16:351-354. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17587360>.
253. Grunberg SM, Stevenson LL, Russell CA, McDermed JE. Dose ranging phase I study of the serotonin antagonist GR38032F for prevention of cisplatin-induced nausea and vomiting. *J Clin Oncol* 1989;7:1137-1141. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2526864>.
254. Marty M, Pouillart P, Scholl S, et al. Comparison of the 5-hydroxytryptamine<sub>3</sub> (serotonin) antagonist ondansetron (GR 38032F) with

high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 1990;322:816-821. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2137902>.

255. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med* 1979;300:1295-1297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/375088>.

256. Slatkin NE. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting: beyond prevention of acute emesis. *J Support Oncol* 2007;5:1-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17566383>.

257. Mamtani R, Cimino A. A primer of complementary and alternative medicine and its relevance in the treatment of mental health problems. *Psychiatr Q* 2002;73:367-381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12418362>.

258. Mansky PJ, Wallerstedt DB. Complementary medicine in palliative care and cancer symptom management. *Cancer J* 2006;12:425-431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17034678>.

259. Marchioro G, Azzarello G, Viviani F, et al. Hypnosis in the treatment of anticipatory nausea and vomiting in patients receiving cancer chemotherapy. *Oncology* 2000;59:100-104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10971166>.

260. Morita T, Takigawa C, Onishi H, et al. Opioid rotation from morphine to fentanyl in delirious cancer patients: an open-label trial. *J Pain Symptom Manage* 2005;30:96-103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16043013>.

261. Becker G, Galandi D, Blum HE. Peripherally acting opioid antagonists in the treatment of opiate-related constipation: a systematic review. *J Pain Symptom Manage* 2007;34:547-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17900855>.

262. Mancini I, Bruera E. Constipation in advanced cancer patients. *Support Care Cancer* 1998;6:356-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9695203>.

263. Dhingra L, Shuk E, Grossman B, et al. A qualitative study to explore psychological distress and illness burden associated with opioid-induced constipation in cancer patients with advanced disease. *Palliat Med* 2013;27:447-456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22707180>.

264. American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain (ed 5th). Glenview, IL: American Pain Society; 2003.

265. Candy B, Jones L, Larkin PJ, et al. Laxatives for the management of constipation in people receiving palliative care. *Cochrane Database Syst Rev* 2015;5:CD003448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25967924>.

266. Hawley PH, Byeon JJ. A comparison of sennosides-based bowel protocols with and without docusate in hospitalized patients with cancer. *J Palliat Med* 2008;11:575-581. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18454610>.

267. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. *J Pain Symptom Manage* 2008;35:458-468. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18440447>.

268. Thomas J, Karver S, Cooney GA, et al. Methylnaltrexone for opioid-induced constipation in advanced illness. *N Engl J Med* 2008;358:2332-2343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18509120>.

269. Webster L, Chey WD, Tack J, et al. Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation. *Aliment Pharmacol Ther* 2014;40:771-779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25112584>.





270. Chey WD, Webster L, Sostek M, et al. Naloxegol for opioid-induced constipation in patients with noncancer pain. *N Engl J Med* 2014;370:2387-2396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24896818>.

271. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. *Am J Gastroenterol* 2015;110:725-732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25916220>.

272. Lacy BE, Levy LC. Lubiprostone: a novel treatment for chronic constipation. *Clin Interv Aging* 2008;3:357-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18686757>.

273. Chey WD, Lembo AJ, Lavins BJ, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. *Am J Gastroenterol* 2012;107:1702-1712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22986437>.

274. Chang L, Lembo AJ, Lavins BJ, et al. The impact of abdominal pain on global measures in patients with chronic idiopathic constipation, before and after treatment with linaclotide: a pooled analysis of two randomised, double-blind, placebo-controlled, phase 3 trials. *Aliment Pharmacol Ther* 2014;40:1302-1312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25312449>.

275. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. *Gastroenterology* 2014;147:1146-1148. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25224526>.

276. PDQ® Gastrointestinal Complications. Bethesda, MD: National Cancer Institute; Available at: <http://cancer.gov/cancertopics/pdq/supportivecare/gastrointestinalcomplications/HealthProfessional>. Accessed March 17, 2015.

277. Pessi MA, Zilembo N, Haspinger ER, et al. Targeted therapy-induced diarrhea: A review of the literature. *Crit Rev Oncol Hematol* 2014;90:165-179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24373918>.

278. Cherny NI. Evaluation and management of treatment-related diarrhea in patients with advanced cancer: a review. *J Pain Symptom Manage* 2008;36:413-423. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18411014>.

279. Benson AB, 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. *J Clin Oncol* 2004;22:2918-2926. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15254061>.

280. Andreyev J, Ross P, Donnellan C, et al. Guidance on the management of diarrhoea during cancer chemotherapy. *Lancet Oncol* 2014;15:e447-460. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25186048>.

281. Cousins SE, Tempest E, Feuer DJ. Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2016:CD002764. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26727399>.

282. Francescutti V, Miller A, Satchidanand Y, et al. Management of bowel obstruction in patients with stage IV cancer: predictors of outcome after surgery. *Ann Surg Oncol* 2013;20:707-714. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22990648>.

283. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2000:CD001219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10796761>.

284. Kaneishi K, Kawabata M, Morita T. Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction. *J Pain Symptom Manage* 2012;44:604-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22771132>.

285. Porzio G, Aielli F, Verna L, et al. Can malignant bowel obstruction in advanced cancer patients be treated at home? *Support Care Cancer* 2011;19:431-433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20872024>.
286. Mercadante S, Ferrera P, Villari P, Marrazzo A. Aggressive pharmacological treatment for reversing malignant bowel obstruction. *J Pain Symptom Manage* 2004;28:412-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15471659>.
287. Zelek L, Laval G, Asselain B. Somatostatin analogs for malignant bowel obstruction resulting from peritoneal carcinomatosis. *J Clin Oncol* 2013;31:2519-2520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23733778>.
288. Berger J, Lester P, Rodrigues L. Medical therapy of malignant bowel obstruction with octreotide, dexamethasone, and metoclopramide. *Am J Hosp Palliat Care* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25646530>.
289. Mercadante S, Casuccio A, Mangione S. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. *J Pain Symptom Manage* 2007;33:217-223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17280927>.
290. Mercadante S, Porzio G. Octreotide for malignant bowel obstruction: twenty years after. *Crit Rev Oncol Hematol* 2012;83:388-392. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22277783>.
291. Currow DC, Clark K, Cartmill J, et al. A multi-site, fixed dose, parallel arm, double-blind, placebo controlled, block randomised trial of the addition of infusional octreotide or placebo to regular ranitidine and dexamethasone for the evaluation of vomiting associated with bowel obstruction at the end of life. [Abstract]. 2012 ASCO Annual Meeting: American Society for Clinical Oncology; 2012:TPS9153. Available at: <http://meetinglibrary.asco.org/content/101301-114>.
292. Baron TH. Interventional palliative strategies for malignant bowel obstruction. *Curr Oncol Rep* 2009;11:293-297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19508834>.
293. Brooksbank MA, Game PA, Ashby MA. Palliative venting gastrostomy in malignant intestinal obstruction. *Palliat Med* 2002;16:520-526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12465700>.
294. Mucke M, Mochamat, Cuhls H, et al. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev* 2015;5:CD006788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26026155>.
295. Escalante CP, Meyers C, Reuben JM, et al. A randomized, double-blind, 2-period, placebo-controlled crossover trial of a sustained-release methylphenidate in the treatment of fatigue in cancer patients. *Cancer J* 2014;20:8-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24445757>.
296. Gong S, Sheng P, Jin H, et al. Effect of methylphenidate in patients with cancer-related fatigue: a systematic review and meta-analysis. *PLoS One* 2014;9:e84391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24416225>.
297. Moraska AR, Sood A, Dakhil SR, et al. Phase III, randomized, double-blind, placebo-controlled study of long-acting methylphenidate for cancer-related fatigue: North Central Cancer Treatment Group NCCTG-N05C7 trial. *J Clin Oncol* 2010;28:3673-3679. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20625123>.
298. Hovey E, de Souza P, Marx G, et al. Phase III, randomized, double-blind, placebo-controlled study of modafinil for fatigue in patients treated with docetaxel-based chemotherapy. *Support Care Cancer* 2014;22:1233-1242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24337761>.
299. Jean-Pierre P, Morrow GR, Roscoe JA, et al. A phase 3 randomized, placebo-controlled, double-blind, clinical trial of the effect of modafinil on cancer-related fatigue among 631 patients receiving chemotherapy: a University of Rochester Cancer Center Community Clinical Oncology



Program Research base study. Cancer 2010;116:3513-3520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20564068>.

300. Palesh OG, Roscoe JA, Mustian KM, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. J Clin Oncol 2010;28:292-298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19933917>.

301. Savard J, Ivers H, Villa J, et al. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. J Clin Oncol 2011;29:3580-3586. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21825267>.

302. Palesh O, Aldridge-Gerry A, Ulusakarya A, et al. Sleep disruption in breast cancer patients and survivors. J Natl Compr Canc Netw 2013;11:1523-1530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24335687>.

303. Yennurajalingam S, Chisholm G, Palla SL, et al. Self-reported sleep disturbance in patients with advanced cancer: Frequency, intensity, and factors associated with response to outpatient supportive care consultation - A preliminary report. Palliat Support Care 2013;1-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24182896>.

304. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1798888>.

305. Payne RJ, Hier MP, Kost KM, et al. High prevalence of obstructive sleep apnea among patients with head and neck cancer. J Otolaryngol 2005;34:304-311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16181591>.

306. Stern TP, Auckley D. Obstructive sleep apnea following treatment of head and neck cancer. Ear Nose Throat J 2007;86:101-103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17385619>.

307. Antonescu-Turcu A, Parthasarathy S. CPAP and bi-level PAP therapy: new and established roles. Respir Care 2010;55:1216-1229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20800002>.

308. Allen RP, Chen C, Garcia-Borreguero D, et al. Comparison of pregabalin with pramipexole for restless legs syndrome. N Engl J Med 2014;370:621-631. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24521108>.

309. Bassetti CL, Bornatico F, Fuhr P, et al. Pramipexole versus dual release levodopa in restless legs syndrome: a double blind, randomised, cross-over trial. Swiss Med Wkly 2011;141:w13274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22101745>.

310. Ferini-Strambi L, Aarskog D, Partinen M, et al. Effect of pramipexole on RLS symptoms and sleep: a randomized, double-blind, placebo-controlled trial. Sleep Med 2008;9:874-881. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18952497>.

311. Kaplan PW, Allen RP, Buchholz DW, Walters JK. A double-blind, placebo-controlled study of the treatment of periodic limb movements in sleep using carbidopa/levodopa and propoxyphene. Sleep 1993;16:717-723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8165385>.

312. Manconi M, Ferri R, Zucconi M, et al. Pramipexole versus ropinirole: polysomnographic acute effects in restless legs syndrome. Mov Disord 2011;26:892-895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21370262>.

313. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. Neurology 1999;52:938-943. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10102409>.

314. Oertel WH, Stiasny-Kolster K, Bergtholdt B, et al. Efficacy of pramipexole in restless legs syndrome: a six-week, multicenter, randomized, double-blind study (effect-RLS study). Mov Disord 2007;22:213-219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17133582>.

315. Trenkwalder C, Garcia-Borreguero D, Montagna P, et al. Ropinirole in the treatment of restless legs syndrome: results from the TREAT RLS 1 study, a 12 week, randomised, placebo controlled study in 10 European countries. *J Neurol Neurosurg Psychiatry* 2004;75:92-97. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14707315>.

316. Walters AS, Ondo WG, Dreykluft T, et al. Ropinirole is effective in the treatment of restless legs syndrome. TREAT RLS 2: a 12-week, double-blind, randomized, parallel-group, placebo-controlled study. *Mov Disord* 2004;19:1414-1423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15390050>.

317. Berger AM. Update on the state of the science: sleep-wake disturbances in adult patients with cancer. *Oncol Nurs Forum* 2009;36:E165-177. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19581220>.

318. Harsora P, Kessmann J. Nonpharmacologic management of chronic insomnia. *Am Fam Physician* 2009;79:125-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19178064>.

319. Jungquist CR, O'Brien C, Matteson-Rusby S, et al. The efficacy of cognitive-behavioral therapy for insomnia in patients with chronic pain. *Sleep Med* 2010;11:302-309. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20133188>.

320. Howell D, Oliver TK, Keller-Olaman S, et al. Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice. *Ann Oncol* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24287882>.

321. Garland SN, Carlson LE, Stephens AJ, et al. Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. *J Clin Oncol* 2014;32:449-457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24395850>.

322. Kim SW, Shin IS, Kim JM, et al. Effectiveness of mirtazapine for nausea and insomnia in cancer patients with depression. *Psychiatry Clin*

*Neurosci* 2008;62:75-83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18289144>.

323. Stewart SA. The effects of benzodiazepines on cognition. *J Clin Psychiatry* 2005;66 Suppl 2:9-13. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15762814>.

324. U.S. Food and Drug Administration. Zolpidem Containing Products: Drug Safety Communication - FDA Requires Lower Recommended Doses. 2013. Available at: <http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm334738.htm>. Accessed March 3, 2014.

325. Bruera E, Fainsinger R, MacEachern T, Hanson J. The use of methylphenidate in patients with incident cancer pain receiving regular opiates. A preliminary report. *Pain* 1992;50:75-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1381072>.

326. 2011 Physicians' Desk Reference (ed 65). Montvale, NJ: PDR Network, LLC; 2010.

327. Diagnostic and statistical manual of mental disorders (ed 4th). Washington, DC: American Psychiatric Association; 1994.

328. Bush SH, Kanji S, Pereira JL, et al. Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. *J Pain Symptom Manage* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24480529>.

329. Irwin SA, Pirrello RD, Hirst JM, et al. Clarifying delirium management: practical, evidenced-based, expert recommendations for clinical practice. *J Palliat Med* 2013;16:423-435. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23480299>.

330. Hosie A, Davidson PM, Agar M, et al. Delirium prevalence, incidence, and implications for screening in specialist palliative care inpatient settings: a systematic review. *Palliat Med* 2013;27:486-498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22988044>.

331. de la Cruz M, Fan J, Yennu S, et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Support Care Cancer* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25617070>.
332. Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. *J Clin Oncol* 2012;30:1206-1214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412123>.
333. Zimmerman KM, Salow M, Skarf LM, et al. Increasing anticholinergic burden and delirium in palliative care inpatients. *Palliat Med* 2014;28:335-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24534725>.
334. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med* 2010;38:419-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19915454>.
335. Grover S, Mattoo SK, Gupta N. Usefulness of atypical antipsychotics and choline esterase inhibitors in delirium: A review. *Pharmacopsychiatry* 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21394715>.
336. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA* 2011;306:1359-1369. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21954480>.
337. Lacasse H, Perreault MM, Williamson DR. Systematic review of antipsychotics for the treatment of hospital-associated delirium in medically or surgically ill patients. *Ann Pharmacother* 2006;40:1966-1973. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17047137>.
338. Jacobson SA. Delirium in the elderly. *Psychiatr Clin North Am* 1997;20:91-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9139298>.
339. Mercadante S, Valle A, Porzio G, et al. Prognostic factors of survival in patients with advanced cancer admitted to home care. *J Pain Symptom Manage* 2013;45:56-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23017625>.
340. Hui D. Prognostication of Survival in Patients With Advanced Cancer: Predicting the Unpredictable? *Cancer Control* 2015;22:489-497. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26678976>.
341. Cui J, Zhou L, Wee B, et al. Predicting survival time in noncurative patients with advanced cancer: a prospective study in China. *J Palliat Med* 2014;17:545-552. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24708258>.
342. Caraceni A, Nanni O, Maltoni M, et al. Impact of delirium on the short term prognosis of advanced cancer patients. Italian Multicenter Study Group on Palliative Care. *Cancer* 2000;89:1145-1149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10964345>.
343. Kehl KA. Treatment of terminal restlessness: a review of the evidence. *J Pain Palliat Care Pharmacother* 2004;18:5-30. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15148006>.
344. Jacobsen PB, Wagner LI. A new quality standard: the integration of psychosocial care into routine cancer care. *J Clin Oncol* 2012;30:1154-1159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412134>.
345. Moreno PI, Stanton AL. Personal growth during the experience of advanced cancer: A systematic review. *Cancer J* 2013;19:421-430. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24051616>.
346. Northouse L, Williams AL, Given B, McCorkle R. Psychosocial care for family caregivers of patients with cancer. *J Clin Oncol* 2012;30:1227-1234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412124>.
347. Hudson P, Trauer T, Kelly B, et al. Reducing the psychological distress of family caregivers of home based palliative care patients: longer term effects from a randomised controlled trial. *Psychooncology* 2015;24:19-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25044819>.



348. Applebaum AJ, Kulikowski JR, Breitbart W. Meaning-Centered Psychotherapy for Cancer Caregivers (MCP-C): Rationale and Overview. Palliat Support Care 2015;1-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26000705>.

349. Keall RM, Clayton JM, Butow PN. Therapeutic life review in palliative care: a systematic review of quantitative evaluations. J Pain Symptom Manage 2015;49:747-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25261637>.

350. Khatcheressian J, Cassel JB, Lyckholm L, et al. Improving palliative and supportive care in cancer patients. Oncology (Williston Park) 2005;19:1365-1376; discussion 1377-1368, 1381-1362, 1384 passim. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16285228>.

351. Morrison RS, Meier DE. Clinical practice. Palliative care. N Engl J Med 2004;350:2582-2590. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15201415>.

352. Singer PA, Martin DK, Kelner M. Quality end-of-life care: patients' perspectives. JAMA 1999;281:163-168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9917120>.

353. Byock I, ed Dying Well: The Prospect for Growth at the End of Life. New York: Riverhead Books; 1997.

354. Mack JW, Cronin A, Taback N, et al. End-of-life care discussions among patients with advanced cancer: A cohort study. Ann Intern Med 2012;156:204-210. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22312140>.

355. Almack K, Cox K, Moghaddam N, et al. After you: conversations between patients and healthcare professionals in planning for end of life care. BMC Palliat Care 2012;11:15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22985010>.

356. Kao CY, Wang HM, Tang SC, et al. Predictive factors for do-not-resuscitate designation among terminally ill cancer patients receiving care from a palliative care consultation service. J Pain Symptom Manage

2014;47:271-282. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23856097>.

357. Mack JW, Cronin A, Keating NL, et al. Associations between end-of-life discussion characteristics and care received near death: a prospective cohort study. J Clin Oncol 2012;30:4387-4395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23150700>.

358. Doll KM, Stine JE, Van Le L, et al. Outpatient end of life discussions shorten hospital admissions in gynecologic oncology patients. Gynecol Oncol 2013;130:152-155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23542684>

359. Zhang B, Nilsson ME, Prigerson HG. Factors important to patients' quality of life at the end of life. Arch Intern Med 2012;172:1133-1142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22777380>.

360. Gomes B, Higginson IJ, Calanzani N, et al. Preferences for place of death if faced with advanced cancer: a population survey in England, Flanders, Germany, Italy, the Netherlands, Portugal and Spain. Ann Oncol 2012;23:2006-2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22345118>.

361. Jeurkar N, Farrington S, Craig TR, et al. Which hospice patients with cancer are able to die in the setting of their choice? Results of a retrospective cohort study. J Clin Oncol 2012;30:2783-2787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22734023>.

362. Volandes AE, Paasche-Orlow MK, Mitchell SL, et al. Randomized controlled trial of a video decision support tool for cardiopulmonary resuscitation decision making in advanced cancer. J Clin Oncol 2013;31:380-386. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23233708>.

363. Stein RA, Sharpe L, Bell ML, et al. Randomized controlled trial of a structured intervention to facilitate end-of-life decision making in patients with advanced cancer. J Clin Oncol 2013;31:3403-3410. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23897967>.



364. Temel JS, Greer JA, Gallagher ER, et al. Electronic prompt to improve outpatient code status documentation for patients with advanced lung cancer. *J Clin Oncol* 2013;31:710-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23284038>.
365. Austin CA, Mohottige D, Sudore RL, et al. Tools to Promote Shared Decision Making in Serious Illness: A Systematic Review. *JAMA Intern Med* 2015;175:1213-1221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25985438>.
366. Hickman SE, Keevern E, Hammes BJ. Use of the physician orders for life-sustaining treatment program in the clinical setting: a systematic review of the literature. *J Am Geriatr Soc* 2015;63:341-350. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25644280>.
367. Elsayem A, Smith ML, Parmley L, et al. Impact of a palliative care service on in-hospital mortality in a comprehensive cancer center. *J Palliat Med* 2006;9:894-902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16910804>.
368. Wright AA, Keating NL, Balboni TA, et al. Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health. *J Clin Oncol* 2010;28:4457-4464. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20837950>.
369. Poulouse JV, Do YK, Neo PS. Association between referral-to-death interval and location of death of patients referred to a hospital-based specialist palliative care service. *J Pain Symptom Manage* 2013;46:173-181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23177723>.
370. Loggers ET, Starks H, Shannon-Dudley M, et al. Implementing a Death with Dignity program at a comprehensive cancer center. *N Engl J Med* 2013;368:1417-1424. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23574120>.
371. Vermont Department of Health, Agency of Human Services. Patient Choice and Control at End of Life. 2013. Available at: [http://healthvermont.gov/family/end\\_of\\_life\\_care/patient\\_choice.aspx](http://healthvermont.gov/family/end_of_life_care/patient_choice.aspx). Accessed
372. Oregon Public Health Division. Oregon's Death with Dignity Act-2012. 2012. Available at: <http://public.health.oregon.gov/ProviderPartnerResources/EvaluationResearch/DeathwithDignityAct/Documents/year15.pdf>
373. Washington State Department of Health. Washington State Department of Health 2012 Death with Dignity Act Report. 2012. Available at: <http://www.doh.wa.gov/portals/1/Documents/Pubs/422-109-DeathWithDignityAct2012.pdf>.
374. End of Life Option Act. California Department of Public Health; Available at: <https://www.cdph.ca.gov/Programs/CHSI/Pages/End-of-Life-Option-Act-.aspx>.
375. Hui D, dos Santos R, Chisholm G, et al. Clinical signs of impending death in cancer patients. *Oncologist* 2014;19:681-687. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24760709>.
376. Lindqvist O, Tishelman C, Hagelin CL, et al. Complexity in non-pharmacological caregiving activities at the end of life: an international qualitative study. *PLoS Med* 2012;9:e1001173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22347815>.
377. Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A. Prevalence, impact, and treatment of death rattle: a systematic review. *J Pain Symptom Manage* 2014;47:105-122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23790419>.
378. Lampert R, Hayes DL, Annas GJ, et al. HRS Expert Consensus Statement on the Management of Cardiovascular Implantable Electronic Devices (CIEDs) in patients nearing end of life or requesting withdrawal of therapy. *Heart Rhythm* 2010;7:1008-1026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20471915>.
379. Braun TC, Hagen NA, Clark T. Development of a clinical practice guideline for palliative sedation. *J Palliat Med* 2003;6:345-350. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14509479>.

380. Cherny NI, Portenoy RK. Sedation in the management of refractory symptoms: guidelines for evaluation and treatment. *J Palliat Care* 1994;10:31-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8089815>.

381. Cowan JD, Palmer TW. Practical guide to palliative sedation. *Curr Oncol Rep* 2002;4:242-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11937015>.

382. Levy MH, Cohen SD. Sedation for the relief of refractory symptoms in the imminently dying: a fine intentional line. *Semin Oncol* 2005;32:237-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15815971>.

383. Sykes N, Thorns A. The use of opioids and sedatives at the end of life. *Lancet Oncol* 2003;4:312-318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12732169>.

384. Wein S. Sedation in the imminently dying patient. *Oncology (Williston Park)* 2000;14:585-592; discussion 592, 597-588, 601. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10826317>.

385. Maltoni M, Scarpi E, Rosati M, et al. Palliative sedation in end-of-life care and survival: a systematic review. *J Clin Oncol* 2012;30:1378-1383. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412129>.

386. Beller EM, van Driel ML, McGregor L, et al. Palliative pharmacological sedation for terminally ill adults. *Cochrane Database Syst Rev* 2015;1:CD010206. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25553674>.

387. Maeda I, Morita T, Yamaguchi T, et al. Effect of continuous deep sedation on survival in patients with advanced cancer (J-Proval): a propensity score-weighted analysis of a prospective cohort study. *Lancet Oncol* 2016;17:115-122. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26610854>.

388. Gurschick L, Mayer DK, Hanson LC. Palliative Sedation: An Analysis of International Guidelines and Position Statements. *Am J Hosp Palliat*

Care 2015;32:660-671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24807825>.

389. Mercadante S, Porzio G, Valle A, et al. Palliative sedation in advanced cancer patients followed at home: a retrospective analysis. *J Pain Symptom Manage* 2012;43:1126-1130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22651952>.

390. Mercadante S, Porzio G, Valle A, et al. Palliative sedation in patients with advanced cancer followed at home: a prospective study. *J Pain Symptom Manage* 2014;47:860-866. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24099896>.

391. Hughes T, Schumacher M, Jacobs-Lawson JM, Arnold S. Confronting death: perceptions of a good death in adults with lung cancer. *Am J Hosp Palliat Care* 2008;25:39-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18160544>.

392. Kehl KA. Moving toward peace: an analysis of the concept of a good death. *Am J Hosp Palliat Care* 2006;23:277-286. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17060291>.

393. Mak JM, Clinton M. Promoting a good death: an agenda for outcomes research--a review of the literature. *Nurs Ethics* 1999;6:97-106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10358525>.

394. Steinhauser KE, Christakis NA, Clipp EC, et al. Factors considered important at the end of life by patients, family, physicians, and other care providers. *JAMA* 2000;284:2476-2482. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11074777>.

395. Field M, Cassel Ce, eds. *Approaching Death: Improving Care at the End of Life*. Washington, D.C: National Academy Press; 1997.

396. Guldin MB, Vedsted P, Zachariae R, et al. Complicated grief and need for professional support in family caregivers of cancer patients in palliative care: a longitudinal cohort study. *Support Care Cancer* 2011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21892795>.

397. Kacel E, Gao X, Prigerson HG. Understanding bereavement: what every oncology practitioner should know. *J Support Oncol* 2011;9:172-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22024306>.
398. Zhang B, El-Jawahri A, Prigerson HG. Update on bereavement research: evidence-based guidelines for the diagnosis and treatment of complicated bereavement. *J Palliat Med* 2006;9:1188-1203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17040157>.
399. Thomas K, Hudson P, Trauer T, et al. Risk factors for developing prolonged grief during bereavement in family carers of cancer patients in palliative care: A longitudinal study. *J Pain Symptom Manage* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23969327>
400. Steel JL, Geller DA, Kim KH, et al. Web-based collaborative care intervention to manage cancer-related symptoms in the palliative care setting. *Cancer* 2016;122:1270-1282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26970434>.
401. Hartmann LC. Unrealistic expectations. *J Clin Oncol* 2005;23:4231-4232; discussion 4233-4234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15961772>.
402. Kalemkerian GP. Commentary on "Unrealistic Expectations". *J Clin Oncol* 2005;23:4233-4234. Available at: <http://jco.ascopubs.org/content/23/18/4233.short>.
403. Najjar N, Davis LW, Beck-Coon K, Carney Doebbeling C. Compassion fatigue: a review of the research to date and relevance to cancer-care providers. *J Health Psychol* 2009;14:267-277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19237494>.
404. Cohen JS, Erickson JM. Ethical dilemmas and moral distress in oncology nursing practice. *Clin J Oncol Nurs* 2006;10:775-780. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17193943>.
405. Gaeta S, Price KJ. End-of-life issues in critically ill cancer patients. *Crit Care Clin* 2010;26:219-227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19944283>.
406. Irvin S. The experiences of the registered nurse caring for the person dying of cancer in a nursing home. *Collegian* 2000;7:30-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11858309>.
407. Shanafelt T, Dyrbye L. Oncologist burnout: causes, consequences, and responses. *J Clin Oncol* 2012;30:1235-1241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412138>.
408. Sherman AC, Edwards D, Simonton S, Mehta P. Caregiver stress and burnout in an oncology unit. *Palliat Support Care* 2006;4:65-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16889325>.
409. Slocum-Gori S, Hemsworth D, Chan WW, et al. Understanding Compassion Satisfaction, Compassion Fatigue and Burnout: a survey of the hospice palliative care workforce. *Palliat Med* 2013;27:172-178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22179596>.
410. Potter P, Deshields T, Berger JA, et al. Evaluation of a compassion fatigue resiliency program for oncology nurses. *Oncol Nurs Forum* 2013;40:180-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23448743>.
411. Back AL, Deignan PF, Potter PA. Compassion, compassion fatigue, and burnout: key insights for oncology professionals. *Am Soc Clin Oncol Educ Book* 2014:e454-459. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24857139>.
412. Sood A, Sharma V, Schroeder DR, Gorman B. Stress Management and Resiliency Training (SMART) program among Department of Radiology faculty: a pilot randomized clinical trial. *Explore (NY)* 2014;10:358-363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25443423>.
413. Sharma V, Sood A, Prasad K, et al. Bibliotherapy to decrease stress and anxiety and increase resilience and mindfulness: a pilot trial. *Explore (NY)* 2014;10:248-252. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25037668>.





414. Sood A, Prasad K, Schroeder D, Varkey P. Stress management and resilience training among Department of Medicine faculty: a pilot randomized clinical trial. *J Gen Intern Med* 2011;26:858-861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21279454>.

415. Dharmawardene M, Givens J, Wachholtz A, et al. A systematic review and meta-analysis of meditative interventions for informal caregivers and health professionals. *BMJ Support Palliat Care* 2016;6:160-169. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25812579>.

416. Aycock N, Boyle D. Interventions to manage compassion fatigue in oncology nursing. *Clin J Oncol Nurs* 2009;13:183-191. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19349265>.

417. Zambrano SC, Chur-Hansen A, Crawford GB. The experiences, coping mechanisms and impact of death and dying on palliative medicine specialists. *Palliat Support Care* 2013;1-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23750857>.

418. Sanchez-Reilly S, Morrison LJ, Carey E, et al. Caring for oneself to care for others: physicians and their self-care. *J Support Oncol* 2013;11:75-81. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23967495>.

419. Smith TJ, Dow LA, Virago EA, et al. A pilot trial of decision aids to give truthful prognostic and treatment information to chemotherapy patients with advanced cancer. *J Support Oncol* 2011;9:79-86. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21542415>.

420. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665-1673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18840840>.

421. Smith TJ, Swisher K. Telling the truth about terminal cancer. *JAMA* 1998;279:1746-1748. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9624031>.

422. Mack JW, Wolfe J, Cook EF, et al. Hope and prognostic disclosure. *J Clin Oncol* 2007;25:5636-5642. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18065734>.

Discussion  
update in  
progress