# Interventions to reduce aggressive care at end of life among patients with cancer: a systematic review

*Nauzley C Abedini, Rachel K Hechtman, Achintya D Singh, Rafina Khateeb, Jason Mann, Whitney Townsend, Vineet Chopra*

**Little is known about effective interventions to reduce aggressive end-of-life care in patients with cancer. We did a systematic review to assess what interventions are associated with reductions in aggressive end-of-life cancer care. We searched MEDLINE, CINAHL, Embase, Scopus, and PsychINFO for randomised control trials (RCTs), quasi-experimental, and observational studies published before Jan 19, 2018, which aimed to improve measures of aggressive end-of-life care for patients with cancer. We developed a taxonomy of interventions using the Systems Engineering Initiative for Patient Safety (SEIPS) model to summarise existing interventions that addressed aggressive care for patients with cancer. Of the 6451 studies identified by our search, five RCTs and 31 observational studies met the final inclusion criteria. Using the SEIPS framework, 16 subcategories of interventions were identified. With the exception of documentation of end-of-life discussions in the electronic medical record, no single intervention type or SEIPS domain led to consistent improvements in aggressive end-of-life care measures. The ability to discern the interventions' effectiveness was limited by inconsistent use of validated measures of aggressive care. Seven (23%) of 31 observational studies and no RCTs were at low risk of bias according to Cochrane's Risk of Bias tool. Evidence for improving aggressive end-of-life cancer care is limited by the absence of standardised measurements and poor study design. Policies and studies to address the gaps present in end-of-life care for cancer are necessary.**

*Lancet Oncol* 2019; 20: e627–36

**Division of Hospital Medicine** (N C Abedini MD, R Khateeb MD, J Mann MSA, V Chopra MD), **Institute for Healthcare Policy and Innovation** (N C Abedini, V Chopra), **Department of Internal Medicine** (N C Abedini, R K Hechtman MD, R Khateeb, J Mann, V Chopra), **Division of Geriatric and Palliative Medicine** (R Khateeb), **and Taubman Health Sciences Library** (W Townsend MLIS), **University of Michigan, Ann Arbor, MI, USA; Department of Medicine, All India Institute of Medical Sciences, New Delhi, India** (A D Singh MBBS); **and Veterans Affairs Health System, Ann Arbor, MI, USA** (V Chopra)

Correspondence to:
Dr Nauzley C Abedini, Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, MI 48109-2800, USA
**nauzley@umich.edu**

## Introduction

Increasingly, patients with advanced cancer are exposed to aggressive end-of-life care[1–4] that can decrease quality of life and care satisfaction, prolong bereavement,[5–9] and increase health-care utilisation and costs.[10] Given these consequences, the National Quality Forum[11] and Centers for Medicare and Medicaid Services (CMS)[12] adopted several claims-based quality measures targeting aggressive end-of-life cancer care. These measures were informed by work by Earle and colleagues,[13] expert opinion, and recommendations from the American Society of Clinical Oncology (ASCO);[14] and included receipt of chemotherapy within 14 days before death, more than one emergency room visit or admission to hospital in the last 30 days of life, any intensive care unit (ICU) admission in the last 30 days of life, and late hospice referral (ie, <3 days before death).[11,12,14] More recently, claims-based measures have become important metrics in proposed alternative payment models to improve overall cancer care quality.[15–17]

Despite these efforts, important gaps in how aggressive care is measured and mitigated in patients with cancer remain. For example, a 2011 systematic review by Luta and colleagues[18] that included patients with cancer and those without cancer identified 28 different categories of aggressive end-of-life care measures with highly variable end-of-life timeframes, where the majority of these measures were unvalidated. More recently, a 2017 systematic review by Kamal and colleagues[19] identified 284 oncology quality measures within 13 palliative care domains. Although end-of-life care was included as a domain, this study did not explicitly focus on measures of aggressive end-of-life care and interventions related to end-of-life.[19] Hence, little is known about how end-of-life measures are used or what interventions might be successful in reducing aggressive end-of-life care among patients with cancer. Addressing these gaps is important to improve patients' and caregivers' quality of life, reduce inappropriate health-care utilisation, and ultimately inform payment and policy.

Since no previous systematic review has evaluated the nature, design, and effectiveness of interventions to reduce aggressive end-of-life cancer care, we aimed to search the literature to determine how measures of aggressive care are being used in patients with cancer, and what interventions are associated with reductions in aggressive end-of-life care. We hypothesised that care measures and interventions would be highly heterogeneous.

## Data collection

### Search strategy and selection criteria

Using relevant controlled vocabulary terms and keywords, a research librarian (WT) developed a comprehensive search strategy for each database using the following concepts: end-of-life care, aggressive or intense care, and cancer (appendix pp 14–16). Sequential, individualised searches in MEDLINE via Ovid, CINAHL, Embase, Scopus, and PsychINFO were done between Dec 1, 2017, and Jan 19, 2018. No filters for language, study design, or country of origin were used. We included all available articles published before Jan 19, 2018. Duplicates were removed in EndNote (version X9), and remaining articles were exported to the review management software Covidence for study selection. We followed PRISMA recommendations.[20] The study protocol was registered with PROSPERO (number CRD42018087528).

Two reviewers (NCA, RKH) independently screened all titles and abstracts. Disagreements were resolved by a

See **Online** for appendix

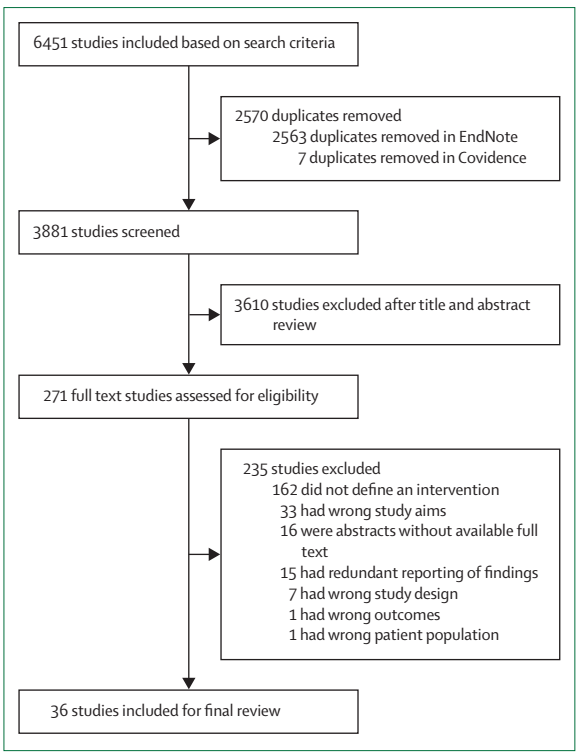


*Figure 1:* **Flowchart of selected studies**

third reviewer (VC). If a relevant abstract without a full-text article was identified, we emailed the corresponding author to obtain the full-text manuscript. All full-text manuscripts were independently appraised by three reviewers (NCA, RKH, ADS). We included studies of patients aged 18 years or more who were diagnosed with cancer and had used at least one quantifiable outcome measure of aggressive end-of-life care (defined as measures describing health-care utilisation such as admission to a hospital, ICU admissions, emergency room visits, and hospice enrolment; or life-sustaining interventions or life-prolonging measures, such as cardiopulmonary resuscitation, mechanical ventilation, dialysis, chemotherapy, radiation therapy, or surgery); defined the end-of-life timeframe for measures as 1 year or less, in accordance with a previous systematic review;[18] and defined an intervention aiming to reduce aggressive care at end of life. We excluded studies that reported exclusively on cost and those studies that did not define an intervention or comparator group. We also excluded editorials, perspective pieces, qualitative studies, non-human studies, and case reports.

### Data extraction and quality assessment

Three investigators (NCA, RKH, ADS) entered data from studies that met the inclusion criteria into an electronic abstraction template adapted from the Cochrane Collaboration.[21] The template included fields such as study population, intervention, study design, and outcomes. Examples of outcomes included the use of claims-based[11,12,14] or previously validated measures of aggressiveness,[13] or both; whether the intervention led to significant reductions in aggressive care (based on a reported $p \leq 0 \cdot 05$); and linkage of measures with patient-reported or caregiver-reported outcomes, such as quality of life or satisfaction scores. We also assessed the risk of study bias using the Cochrane Risk of Bias Tool for randomised control trials,[22] and the Newcastle-Ottawa Quality Assessment Scale for observational studies.[23]

### Conceptual framework

We determined whether studies used validated measures of aggressive end-of-life care based on the use of claims-based measures endorsed by ASCO, National Quality Forum, or CMS (ie, those reported for purposes of reimbursement from administrative or billing data);[11,12,14] other measures validated by Earle and colleagues[13] (eg, any hospice use; hospital death; more than 14 hospital days, any exposure to chemotherapy or targeted agent, or initiation of a new chemotherapy regimen in the last month of life; and a composite score for total aggressive end-of-life care); or novel measures that were internally validated by study investigators. For the purposes of our systematic review, all other measures were considered unvalidated. Given that claims-based measures of aggressive end-of-life care were not adopted until January, 2012, we identified studies that were published either before or after this date.

Using the Systems Engineering Initiative for Patient Safety (SEIPS) model as a framework, we developed a taxonomy system to summarise existing interventions that addressed aggressive care in patients with cancer.[24] The SEIPS framework uses the concept of a dynamic work system consisting of interactions between six elements: person (eg, patients, providers, or the collective health-care team), tasks (eg, major tasks of care delivery such as care coordination and communication), tools and technologies (eg, use of health information technologies such as the electronic health record), physical environment (eg, the physical layout of a care setting), organisation (eg, organisational culture and rules), and external environment (eg, social, ecological, or policy factors).[24] We also categorised studies as multimodal (ie, more than one intervention to reduce aggressive care) or unimodal (only one intervention to reduce aggressive care).

The use of SEIPS to examine studies was important for several reasons. First, SEIPS incorporates the structure–process–outcome model of health-care quality,[25] allowing analysis of issues related to care delivery and quality. Second, given the expected heterogeneity of interventions and measures related to aggressive end-of-life cancer care and quality, SEIPS categories provide a useful lens to evaluate interventions using a standardised comparator. Third, use of SEIPS permits identification of gaps in study design and outcome ascertainment, which might be useful to guide future study design.

### Statistical analysis

We calculated descriptive statistics (eg, proportions) using Stata SE (version 15.1). Given substantial heterogeneity in study design, interventions, and outcomes, formal meta-analyses were not attempted. To graphically display findings, we constructed a heatmap that included what measures were assessed in each study according to the SEIPS category and intervention type, and whether the intervention improved the measure of aggressive end-of-life care or not.

## Findings

The initial search yielded 6451 references of which 2570 were duplicates. Of the 3881 studies screened, 3610 were deemed not relevant based on title and abstract screening. 271 studies were eligible for full-text review, of which 36 studies[5,10,26–59] met the inclusion criteria and were included (figure 1). Inter-rater reliability for screening and data abstraction was excellent (κ 0·98). The appendix (pp 1–9) summarises the study characteristics, designs, and findings. The table shows the summative characteristics of the studies. The majority of studies (29 [81%] of 36)[10,26–28,31–34,36–43,45–51,53–55,57–59] were published after the 2012 adoption of aggressive end-of-life care claims-based measures by ASCO, the National Quality Form, and CMS. 22 (61%) of 36 studies were based in the USA,[5,26,28–30,32–36,38,41–43,47,50,53,55–58] and 16 (44%) were single-centre reports.[27,35,36,38,40,42,44,46–48,50,52,53,56,58,59] Only five (14%) of 36 studies were randomised controlled trials (RCTs).[28,34,36,45,56] Lung cancer was the most prevalent cancer type assessed (29 [81%] of 36 studies).[5,10,26–30,32–38,41,43,44,46,48,49,51–59] No studies reported exclusively on haematological malignancies (table).

With the exception of three studies,[24,50,56] all included studies evaluated aggressive care measures as primary outcomes of interest. All studies used at least one validated measure of aggressive end-of-life care, and one study[41] used internally validated measures of aggressive end-of-life care (ventilation or resuscitation attempts in the last week of life). However, 26 studies used additional unvalidated measures.[5,10,26–30,34–38,41,42,45,46,48,49,52–59] Notably, 20 of these studies were published after 2012,[10,26–28,34,36–38,41,42,45,46,48,49,53–55,57–59] of which 11 were published in the USA[26,28,34,36,38,41,42,53,55,57,58] (figure 2; table).

Overall, three studies used all five validated claims-based measures,[31,42,47] and six studies used four of five validated claims-based measures.[10,33,35,38–40] 17 studies used one or no validated claims-based measures,[5,26,28–30,32,36,37,41,44,45,48,49,51,55,57,58] 12 of which were after 2012[26,28,32,37,41,45,48,49,51,55,57,58] (figure 3).

Validated measures of aggressive care were also used inconsistently. For example, of the validated claims-based measures, only 19 (53%) of 36 studies assessed use of chemotherapy in the last 14 days of life,[10,28,31,33,36,38–40,42,43,45–47,50–52,56,58,59] 14 (39%) assessed whether someone had more than one emergency room visit[10,27,31,33–35,38–40,42,47,53,54,59] or more than one admission to hospital in the last 30 days of life,[10,27,31,33,35,38–40,42,43,47,54–56]

| | Number of studies (n=36) | References |
|---|---|---|
| **Year published** | | |
| Before 2012 | 7 (19%) | 5,29,30,35,44,52,56 |
| 2012 to 2018* | 29 (81%) | 10,26–28,31–34,36–43,45–51,53–55,57–59 |
| **Country** | | |
| USA | 22 (61%) | 5,26,28–30,32–36,38,41–43,47,50,53,55–58 |
| Japan | 4 (11%) | 27,46,51,52 |
| Italy | 3 (8%) | 44,45,49 |
| Korea | 2 (6%) | 40,59 |
| Canada | 2 (6%) | 10,39 |
| UK | 1 (3%) | 37 |
| Norway | 1 (3%) | 48 |
| Taiwan | 1 (3%) | 54 |
| **Sample source** | | |
| Single institution | 16 (44%) | 27,35,36,38,40,42,44,46–48,50,52,53,56,58,59 |
| Multiple institutions | 11 (31%) | 5,26,28–30,33,34,41,43,45,51 |
| Population-based | 9 (25%) | 10,31,32,37,39,49,54,55,57 |
| **Study design** | | |
| Randomised controlled trial | 5 (14%) | 28,34,36,45,56 |
| Prospective cohort | 6 (17%) | 5,29,30,41,43,50 |
| Retrospective cohort | 25 (69%) | 10,26,27,31–33,35,37–40,42,44,46–49, 51–55,57–59 |
| **Cancer type** | | |
| Lung | 29 (81%) | 5,10,26–30,32–38,41,43,44,46,48,49,51–59 |
| Colorectal | 23 (64%) | 5,10,26–30,32,34,35,37,38,40,41,43,44,49, 51–54,57,58 |
| Breast | 22 (61%) | 5,10,27–32,34,35,37,38,41,44,49–54,57,58 |
| Other solid tumours | 22 (61%) | 5,10,27–30,32,34,35,37,38,41,42,44,47,49, 51–54,57,58 |
| Pancreatic | 20 (56%) | 5,10,26–30,34,35,37–39,41,44,45,49,52–54,58 |
| Haematological malignancies | 14 (39%) | 5,10,27–30,35,37,38,41,44,49,52,54 |
| **Multi-modal *vs* single-modal intervention or exposure** | | |
| Multi-modal intervention | 13 (36%) | 26,28,35–38,42,43,45,48,50,56,58 |
| Unimodal interventions | 23 (64%) | 5,10,27,29–34,39–41,44,46,47,49,51–55,57,59 |
| **Use of measures** | | |
| Used validated measures† | 36 (100%) | 5,10,26–59 |
| Used unvalidated measures‡ | 26 (72%) | 5,10,26–30,34–38,41,42,45,46,48,49,52–59 |
| Before 2012 | 6/26 (23%) | 5,29,30,35,52,56 |
| Published in USA | 5/6 (83%) | 5,29,30,35,56 |
| 2012 to 2018 | 20/26 (77%) | 10,26–28,34,36–38,41,42,45,46,48,49, 53–55,57–59 |
| Published in USA | 11/20 (55%) | 26,28,34,36,38,41,42,53,55,57,58 |

Data are n (%) or n/N (%). *The National Quality Forum and Centers for Medicare and Medicaid Services adopted claims-based quality measures for aggressive end-of-life care in 2012. †Validated measures included claims-based measures, validated measures from seminal work by Earle and colleagues,[13] and other internally validated measures. ‡In addition to validated measures.

***Table:*** **Summative characteristics of the 36 studies included in this systematic review**

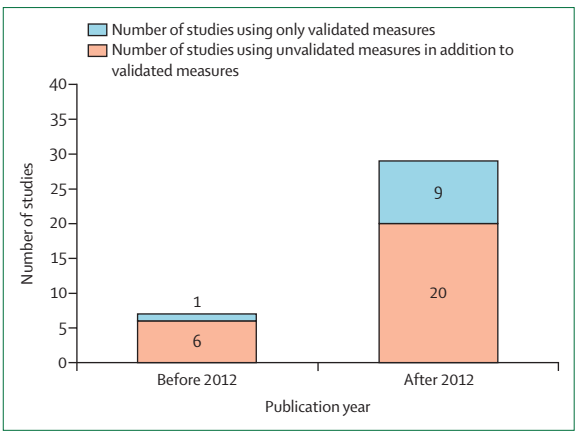


*Figure 2:* **Studies using unvalidated measures of aggressive end-of-life care before and after the 2012 adoption of claims-based American Society of Clinical Oncology measures by the National Quality Forum and Centers for Medicare and Medicaid Services**

18 (50%) assessed whether the patient had an ICU admission in the last 30 days of life,[10,27,31,33,35,38–40,42,43,46,47,50,52–55,59] and only 11 (31%) assessed late hospice enrolment (<3 days before death).[26,31,32,34,35,42,47,50,56,57] The remaining validated measures derived from Earle and colleagues[13] were also used inconsistently (figure 4).

13 (31%) of 36 studies examined multimodal interventions to reduce aggressive end-of-life care and improve end-of-life quality of care in cancer.[26,28,35–38,42,43,45,48,50,56,58] Overall, 50 interventions were assessed in 36 studies. Interventions were organised into 16 sub-categories within the six SEIPS domains. Interventions targeting task-related factors were most common (29 [58%] of 50 interventions)[5,10,26–28,31,33–39,42,43,45,47–51,53,55–59] and included early versus late subspecialty palliative care referral (11 [22%]),[27,28,35,36,38,45,47,48,50,53,56] any palliative care referral (in which timing was not specified) versus none (eight [16%]),[10,35,39,48,51,57–59] quality of communication and end-of-life discussions (five [10%]),[5,26,34,42,43] exposure to primary care visits (two [4%]),[37,55] home care visits (one [2%]),[49] enrolment in hospice (one [2%]),[33] and early exposure to medications to manage common symptoms associated with breast cancer (one [2%])[31] (appendix p 10). Interventions targeting organisational factors (six [12%] of 50)[28,36,44,45,50,56] physical environment (six [12%]),[37,38,40,46,52,58] and technology and tools (six [12%])[26,28,32,41–43] were also prevalent. Organisational interventions focused on introducing subspecialty palliative care soon after diagnosis of advanced cancer and in conjunction with other oncological therapies (often called integrated palliative care;[15,60] six [12%]).[28,36,44,45,50,56] Physical environment factors included location of palliative care delivery, such as outpatient versus inpatient palliative care (four [8%]),[37,38,40,58] or designated palliative care units versus general wards (two [4%]).[46,52] Technology and tool-based interventions included documentation of advance care planning in the electronic medical record (three [6%]),[26,42,43] telehealth for palliative care delivery (one [2%]),[28] use of advanced imaging (one [2%]),[32] and exposure to radiotherapy (one [2%]).[41] Person-level interventions (two [4%]), such as spiritual care and the influence of personal spiritual coping,[29,30] and external factors (one [2%]), such as policy introducing universal hospice coverage,[54] were least prevalent (appendix p 10).

We explored the effectiveness of interventions by SEIPS category to understand what factors might have had the greatest effect on reducing aggressive end-of-life care (figure 3). Within the SEIPS domain of technology and tool-based interventions, two of the three studies[42,43] pertaining to documentation of end-of-life discussions in the electronic medical record showed improvements in multiple aggressive care measures. Aside from this subgroup of interventions, no single intervention subcategory or SEIPS domain appeared to be associated with consistent reductions in multiple validated measures of aggressive end-of-life care.

Four studies did not do tests of statistical significance to assess the effect of their interventions, although comparison of proportions before and after the intervention did show improvements in most measures of aggressive care targeted.[10,47,52,56] Of the 23 studies that did tests for statistical significance and used more than one validated measure,[27,28,31–36,38–40,42,43,45,46,48-50,53–55,57,59] only five included interventions that were associated with significant improvements in all measures that were assessed.[33,39,43,53,57] These five studies were all observational and highly variable with regard to design and population. Interventions in these studies included hospice enrolment,[33] any subspecialty palliative care before death,[39,57] self-reported and documented end-of-life discussions in the electronic medical record,[43] and early palliative care.[53]

Two interventions were associated with significant worsening of aggressive end-of-life care, including exposure to frequent primary care visits before diagnosis of advanced cancer[55] and exposure to advanced imaging such as CT or MRI after diagnosis.[32] Interventions from seven studies did not show any change in measures of aggressive end-of-life care assessed.[5,26,28,31,34,36,58] Three of these studies were RCTs.[28,34,36] Two assessed early, integrated subspecialty palliative care[28,36] and one assessed an intervention to enhance end-of-life communication.[34] Of the remaining two RCTs, one study assessed early, integrated subspecialty palliative care but was not powered to show significant reductions in aggressive end-of-life care.[56] The other RCT assessing early, integrated palliative care models showed no difference in three of four measures assessed.[45] Only eight studies reported patient-reported or caregiver-reported outcomes, or both.[5,28–30,34,41,50,56] Three of these eight studies showed a significant improvement in patient-reported or caregiver-reported outcomes, or both (appendix p 10).[29,41,56]

Risk of bias was assessed using the Cochrane Risk of Bias tool[22] for five RCTs and the Newcastle-Ottawa Quality Assessment Scale[23] for 31 observational studies. Of the

five RCTs, three were rated with uncertain risk of bias[28,34,36] and two with high risk of bias[45,56] (appendix p 11). The quality assessment for observational studies is included in the appendix (pp 12,13); seven observational studies scored the maximum score of 9 (range 4–9).[5,31,41,43,46,54,57]

## Discussion

This systematic review identified five RCTs and 31 observational studies that aimed to reduce aggressive end-of-life care for patients with cancer. Using the SEIPS framework, aggressive end-of-life care was

| | Measures of agressive care | | | | | | | | | | | Patient-reported or caregiver-reported outcomes* | Risk of bias† |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Claims-based measures of aggressive care | | | | | Other commonly used validated measures from Earle and colleagues[13] | | | | | | | |
| | Chemotherapy in last 14 days of life | >1 ER visit in last 30 days of life | ICU stay in last 30 days of life | >1 hospital admission in last 30 days of life | Hospice <3 days before death | Any hospice | Hospital death | Any use of chemotherapy or targeted agent in last 30 days of life | New CR in last 30 days of life | New CR in last 30 days of life | Composite measure of aggressiveness | | |
| **Tasks (n=29)** | | | | | | | | | | | | | |
| Early subspecialty palliative care referral (n=11) | | | | | | | | | | | | | |
| Temel et al (2010)[56]‡ | | | | | | | | | | | | | High |
| Gonsalves et al (2011)[35] | | | | | | | | | | | | | 8 |
| Greer et al (2012)[36]‡ | | | | | | | | | | | | | Uncertain |
| Hui et al (2014)[38] | | | | | | | | | | | | | 7 |
| Nevadunsky et al (2014)[47] | | | | | | | | | | | | | 8 |
| Amano et al (2015)[27] | | | | | | | | | | | | | 7 |
| Bakitas et al (2015)[28]‡ | | | | | | | | | | | | | Uncertain |
| Maltoni et al (2016)[45]‡ | | | | | | | | | | | | | High |
| Nieder et al (2016)[48] | | | | | | | | | | | | | 8 |
| Scibetta et al (2016) | | | | | | | | | | | | | 8 |
| Rabow et al (2018)[50] | | | | | | | | | | | | | 7 |
| Any subspecialty palliative care referral independent of timing (n=8) | | | | | | | | | | | | | |
| Gonsalves et al (2011)[35] | | | | | | | | | | | | | 8 |
| Cheung et al (2015)[10] | | | | | | | | | | | | | 7 |
| Jang et al (2015)[39] | | | | | | | | | | | | | 8 |
| Nieder et al (2016)[48] | | | | | | | | | | | | | 8 |
| Sano et al (2017)[51] | | | | | | | | | | | | | 8 |
| Triplett et al (2017)[57] | | | | | | | | | | | | | 9 |
| Wiesenthal et al (2017)[58] | | | | | | | | | | | | | 7 |
| Yoo et al (2017)[59] | | | | | | | | | | | | | 7 |
| Communication and EOL discussions (n=5) | | | | | | | | | | | | | |
| Wright et al (2008)[5] | | | | | | | | | | | | | 9 |
| Mack et al (2012)[43] | | | | | | | | | | | | | 9 |
| Lopez-Acevedo et al (2013)[42] | | | | | | | | | | | | | 7 |
| Ahluwalia et al (2015)[26] | | | | | | | | | | | | | 8 |
| Epstein et al (2017)[34]‡ | | | | | | | | | | | | | Uncertain |
| Primary care visits (n=2) | | | | | | | | | | | | | |
| Sharma et al (2013)[55] | | | | | | | | | | | | | 7 |
| Henson et al (2016)[37] | | | | | | | | | | | | | 4 |
| Home palliative care visits (n=1) | | | | | | | | | | | | | |
| Pellizzari et al (2018)[49] | | | | | | | | | | | | | 8 |
| Enrollment in hospice (n=1) | | | | | | | | | | | | | |
| Duggan et al (2017)[33] | | | | | | | | | | | | | 8 |
| Medications to control symptoms (n=1) | | | | | | | | | | | | | |
| Check et al (2016)[31] | | | | | | | | | | | | | 9 |

Significant improvement in aggressive care measure
Improvement in aggressive care measure (significance not reported)
No significant improvement in aggressive care measure
No improvement in aggressive care measure (significance not reported)
Significant worsening in aggressive care measure
Worsening in aggressive care measure (significance not reported)
No data available for comparator group
Not applicable

(Figure 3 continues on next page)

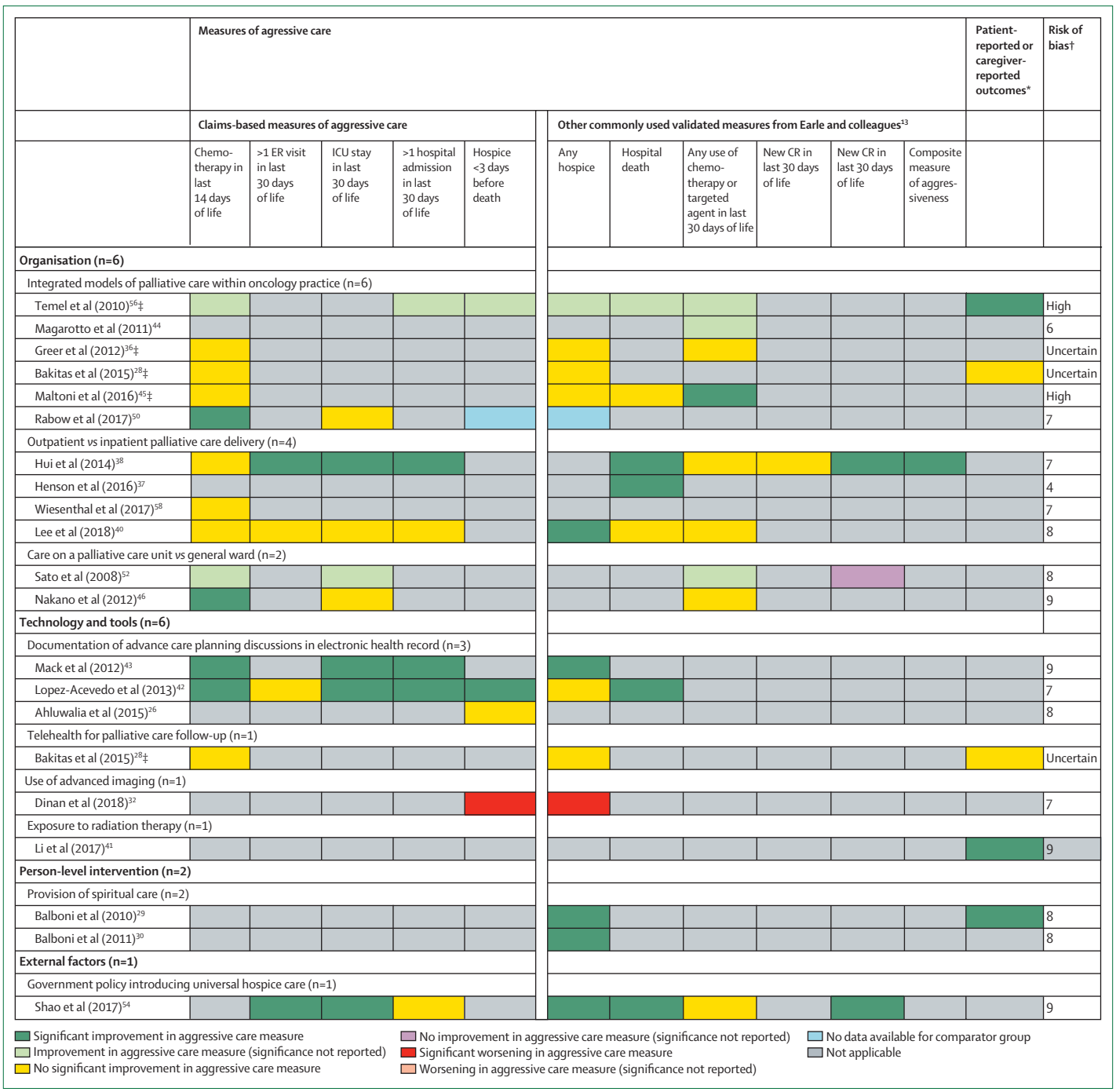


***Figure 3*: Heatmap of study interventions and outcomes related to individual measures of aggressive care by SEIPS category**

*Includes quality of life. ICU=intensive care unit. ER=emergency room. CR=chemotherapy regimen. SEIPS=Systems Engineering Initiative for Patient Safety. †Risk of bias assessed using the Cochrane Risk of Bias Tool[22] for randomised control trials and the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (maximum score of 9).[23] More detailed reports can be found in the appendix (pp 11–13). ‡This study is a randomised controlled trial.

measured variably across categories, making comparisons between studies difficult. Consequently, effective interventions to mitigate aggressive end-of-life cancer care and downstream consequences for patients and caregivers remain unclear. Given the continued increase of aggressive end-of-life cancer care,[4] our findings have important clinical and policy ramifications. CMS and ASCO recently proposed alternative payment models for oncology that include claims-based measures of aggressive end-of-life care.[16,17]

However, without consistent measurement to assess efficacy of interventions, whether these policies will have their intended effect or improve end-of-life cancer care is debatable.

Unfortunately, the high degree of heterogeneity in measures of aggressive end-of-life care is not surprising. Two previous systematic reviews have shown substantial variation in measures pertaining to aggressive end-of-life care and oncology quality.[18,19] However, what is surprising is the infrequent and inconsistent use of validated and claims-based outcomes even in studies done in the USA where such measures originated and have not only been adopted,[12] but also incorporated into alternative payment models.[16,17] By contrast, most studies in our Review used unvalidated measures. Although some outcomes such as cardiopulmonary resuscitation, mechanical ventilation, dialysis, and artificial feeding can provide essential context to the end-of-life experience of patients with cancer, consistent use of validated outcome measures (particularly claims-based measures) is necessary to allow for comparisons in intervention studies. Understanding why investigators are choosing to omit certain measures or using alternative measures with qualitative or survey-based studies is therefore important to investigate.

Despite inconsistencies in measurement, use of the SEIPS categorisation allowed identification of an intervention subgroup that might hold promise in improving aggressive end-of-life care. For example, two of the three studies targeting electronic documentation of end-of-life discussions led to reductions in multiple measures of aggressive care.[42,43] On the basis of study design, it is difficult to explain whether these effects were solely due to documentation alone or whether there was some contribution from enhanced communication occurring upstream of documentation. Regardless, it is possible that documentation in the electronic medical record might contribute to reductions in aggressive care because aggressive care often occurs in care areas (eg, hospitals and ICUs) where the patients' primary oncologist or providers most familiar with the patients' wishes might not be available. Electronic documentation might facilitate communication between providers across care settings, informing decisions about aggressiveness of care in emergent situations. How to leverage technology to reduce aggressive end-of-life care for patients with cancer is an important area for future studies.

Six studies[28,36,44,45,50,56] in our Review evaluated the effect of integrated palliative care models on aggressive end-of-life cancer care—a commonly heralded approach to improving end-of-life cancer care.[15,60,61] However, five studies[28,36,44,45,50] did not show consistent reductions in these measures, perhaps because of the low study quality. Four RCTs had uncertain or high risk of bias,[28,36,45,56] owing in part to inadequate or no masking of participants and researchers among other sources of bias (appendix p 11). Although masking might be less likely to bias aggressive care outcome measures because of their quantitative nature, it might have important implications for patient-reported or caregiver-reported outcomes, which were included in several of the RCTs. Two observational studies evaluating integrated palliative care models achieved lower quality scores because of concerns regarding the comparability of cohorts, among other reasons (appendix p 12).[44,50] Additionally, sparse use of validated measures of aggressive end-of-life care and lack of statistical power[56] made it difficult to draw conclusions about the effectiveness of integrated palliative care in reducing aggressive end-of-life care.

Although absence of evidence is relevant, this effect should not be construed as lack of efficacy of integrated palliative care models. To the contrary, multiple RCTs have shown that integration of palliative care with standard oncological care soon after diagnosis with advanced cancer has a number of benefits to patients and caregivers at end of life, including improvements in quality of life and satisfaction, reductions in anxiety and depression, and higher ratings of overall care quality.[56,62–64] Similarly, a Cochrane database systematic review of seven RCTs showed that early exposure to palliative care led to several important improvements in end-of-life experience, including symptoms and health-related quality of life.[65] However, many recent RCTs did not assess measures of aggressive end-of-life care.[62–64] Ultimately, whether

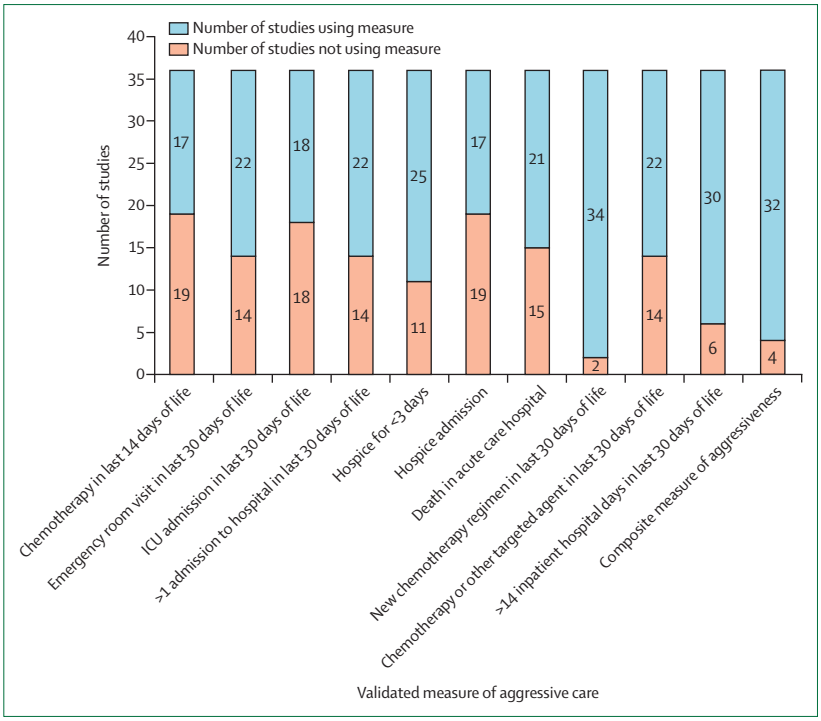


***Figure 4:*** **Proportion of studies using the most common validated measures of aggressive end-of-life care***
ICU=intensive care unit. *Includes claims-based measures from the American Society of Clinical Oncology, the National Quality Forum, and Centers for Medicare and Medicaid Services (chemotherapy in last 14 days of life, >1 emergency room or >1 admission to hospital in the last 30 days of life, ICU admission in the last 30 days of life, or hospice for <3 days); all other measures included are validated measures from Earle and colleagues' study.[13]

the patient-reported and caregiver-reported benefits of integrated palliative care models are mediated by reductions in aggressive end-of-life care remains unclear. High quality RCTs that use standardised measures of aggressive end-of-life care linked with patient-reported and caregiver-reported outcomes are needed to improve the evidence base in this area.

Given the challenges and nuance associated with evaluating care quality at end of life, organisations such as CMS should consider including patient-reported and caregiver-reported outcomes in addition to claims-based measures of aggressive end-of-life care. This approach is especially relevant for new alternative payment models that will tie reimbursement to measures related to end-of-life care quality. This approach is not novel; for example, in addition to measures of aggressive end-of-life care, the UK's National Health Service Quality Standard for End of Life Care for Adults[66] integrates patient-reported and caregiver-reported outcomes derived from expert opinion and consensus. Of note, of the eight studies evaluating patient-reported and caregiver-reported outcomes in our systematic review, seven showed concordance between both aggressive care outcomes and patient-reported and caregiver-reported experience (eg, studies reporting reductions in measures of aggressive care often showed improvements in patient-reported and caregiver-reported outcomes, and vice-versa). Collectively, a comprehensive approach that combines multiple measures of end-of-life care might be more appropriate to evaluate care quality at end of life in patients with cancer.

Our study has limitations. First, owing to the heterogeneity of aggressive end-of-life care measures and interventions, a meta-analysis could not be done. Second, a large number of observational studies were included, meaning that a risk of confounding even with application of a validated risk of bias tool remains. Third, we qualitatively assessed gaps in SEIPS categories; however, whether targeting these areas will lead to significant reductions in aggressive end-of-life care is unknown. Fourth, we used statistical significance to assess effectiveness of the interventions included, which can limit our understanding of non-quantitative benefits and is dependent on study power. Finally, we focused on measures that were validated by CMS and the National Quality Forum rather than measures proposed by individual study authors. Although this approach helped align current practice with policies, measures with contextual relevance might have been missed.

Despite these limitations, our systematic review also has a number of strengths. First, to our knowledge, this is the first systematic review to exclusively examine the breadth and use of aggressive end-of-life care measures in patients with cancer. Second, this study is also the first systematic review to exclusively evaluate the effectiveness of interventions to reduce aggressive end-of-life cancer care. Our findings highlight opportunities to improve how we measure aggressiveness and design studies to improve quality of end-of-life care in patients with cancer. Third, incorporation of studies into a conceptual SEIPS framework identifies gaps and opportunities in the design and implementation of interventions to reduce aggressive care.

## Conclusion

Standardisation of measurement is needed to ensure comparability and generalisability of studies aiming to reduce aggressive end-of-life care in patients with cancer. In a value-based repayment era, high-quality RCTs that include patient-reported and caregiver-reported outcomes are necessary to assess the efficacy of interventions to reduce aggressive end-of-life cancer care.

### Contributors

NCA proposed the hypothesis and idea for the systematic review, with RKH, JM, WT, and VC contributing to its development and analysis plan. NCA, RKH, and WT developed and did the initial literature search. NCA, RKH, ADS, and VC reviewed studies for inclusion. NCA, RKH, ADS, and RK did the data extraction and data checking. NCA did all analyses and developed the first draft of the manuscript. All authors reviewed and interpreted the results and edited the manuscript.

### Declaration of interests

We declare no competing interests.

### Acknowledgments

NCA is supported by the National Clinician Scholars Program at the Institute for Healthcare Policy and Innovation, University of Michigan (Ann Arbor, MI, USA). VC is supported by grants from the Agency for Healthcare Research and Quality (1-R18-HS-025891-01), the Department of Veterans Affairs, Health Services Research and Development Service (I01 HX001101-01), and the Blue Cross/Blue Shield of Michigan.

### References

1 Barbera L, Taylor C, Dudgeon D. Why do patients with cancer visit the emergency department near the end of life? *CMAJ* 2010; **182:** 563–68.

2 Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol* 2008; **26:** 3860–66.

3 Earle CC, Neville BA, Landrum MB, Ayanian JZ, Block SD, Weeks JC. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 2004; **22:** 315–21.

4 Teno JM, Gozalo PL, Bynum JP, et al. Change in end-of-life care for Medicare beneficiaries: site of death, place of care, and health care transitions in 2000, 2005, and 2009. *JAMA* 2013; **309:** 470–77.

5 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:** 1665–73.

6 Wright AA, Zhang B, Keating NL, Weeks JC, Prigerson HG. Associations between palliative chemotherapy and adult cancer patients' end of life care and place of death: prospective cohort study. *BMJ* 2014; **348:** g1219.

7 Wright AA, Keating NL, Ayanian JZ, et al. Family perspectives on aggressive cancer care near the end of life. *JAMA* 2016; **315:** 284–92.

8 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:** 778–84.

9 Ersek M, Miller SC, Wagner TH, et al. Association between aggressive care and bereaved families' evaluation of end-of-life care for veterans with non-small cell lung cancer who died in Veterans Affairs facilities. *Cancer* 2017; **123:** 3186–94.

10 Cheung MC, Earle CC, Rangrej J, et al. Impact of aggressive management and palliative care on cancer costs in the final month of life. *Cancer* 2015; **121:** 3307–15.

11 National Quality Forum. NQF endorses cancer measures. 2012. https://www.qualityforum.org/News_And_Resources/Press_Releases/2012/NQF_Endorses_Cancer_Measures.aspx (accessed Sept 15, 2017).

12 Centers for Medicare and Medicaid Services. Consensus core set: medical oncology measures. 2015. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/QualityMeasures/Downloads/Medical-Oncology-Measures.pdf (accessed Sept 15, 2017).

13 Earle CC, Park ER, Lai B, Weeks JC, Ayanian JZ, Block S. Identifying potential indicators of the quality of end-of-life cancer care from administrative data. *J Clin Oncol* 2003; **21:** 1133–38.

14 American Society of Clinical Oncology. Quality Oncology Practice Initiative (QOPI)-related measures. 2018. https://practice.asco.org/sites/default/files/drupalfiles/QOPI-2018-Reporting-Tracks-Public-Posting.pdf (accessed Feb 12, 2018).

15 Kaufmann TL, Kamal AH. Oncology and palliative care integration: cocreating quality and value in the era of health care reform. *J Oncol Pract* 2017; **13:** 580–88.

16 American Society of Clinical Oncology. Patient-centered oncology payment model: payment reform to support higher quality, more affordable cancer care. 2015. https://practice.asco.org/sites/default/files/drupalfiles/asco-patient-centered-oncology-payment.pdf (accessed Feb 12, 2018).

17 Centers for Medicare and Medicaid. Evaluation of the oncology care model: performance period one. 2018. https://innovation.cms.gov/Files/reports/ocm-secondannualeval-pp1.pdf (accessed Feb 12, 2018).

18 Luta X, Maessen M, Egger M, Stuck AE, Goodman D, Clough-Gorr KM. Measuring intensity of end of life care: a systematic review. *PLoS One* 2015; **10:** e0123764.

19 Kamal AH, Gradison M, Maguire JM, Taylor D, Abernethy AP. Quality measures for palliative care in patients with cancer: a systematic review. *J Oncol Pract* 2014; **10:** 281–87.

20 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; **62:** 1006–12.

21 Higgins J, Green R. Cochrane handbook for systematic reviews of interventions: version 5.1. 2011. http://handbook-5-1.cochrane.org/ (accessed Sept 17, 2017).

22 Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; **343:** d5928.

23 Wells GA, Shea B, O'Connel D, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed Jan 12, 2018).

24 Carayon P, Wetterneck TB, Rivera-Rodriguez AJ, et al. Human factors systems approach to healthcare quality and patient safety. *Appl Ergon* 2014; **45:** 14–25.

25 Donabedian A. Quality assurance. Structure, process and outcome. *Nurs Stand* 1992; **7** (suppl 11)**:** 4–5.

26 Ahluwalia SC, Tisnado DM, Walling AM, et al. Association of early patient-physician care planning discussions and end-of-life care intensity in advanced cancer. *J Palliat Med* 2015; **18:** 834–41.

27 Amano K, Morita T, Tatara R, Katayama H, Uno T, Takagi I. Association between early palliative care referrals, inpatient hospice utilization, and aggressiveness of care at the end of life. *J Palliat Med* 2015; **18:** 270–73.

28 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; **33:** 1438–45.

29 Balboni TA, Paulk ME, Balboni MJ, et al. Provision of spiritual care to patients with advanced cancer: associations with medical care and quality of life near death. *J Clin Oncol* 2010; **28:** 445–52.

30 Balboni T, Balboni M, Paulk ME, et al. Support of cancer patients' spiritual needs and associations with medical care costs at the end of life. *Cancer* 2011; **117:** 5383–91.

31 Check DK, Rosenstein DL, Dusetzina SB. Early supportive medication use and end-of-life care among Medicare beneficiaries with advanced breast cancer. *Support Care Cancer* 2016; **24:** 3463–72.

32 Dinan MA, Curtis LH, Setoguchi S, Cheung WY. Advanced imaging and hospice use in end-of-life cancer care. *Support Care Cancer* 2018; **26:** 3619–25.

33 Duggan KT, Hildebrand Duffus S, D'Agostino RB, Petty WJ, Streer NP, Stephenson RC. The Impact of hospice services in the care of patients with advanced stage nonsmall cell lung cancer. *J Palliat Med* 2017; **20:** 29–34.

34 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.

35 Gonsalves WI, Tashi T, Krishnamurthy J, et al. Effect of palliative care services on the aggressiveness of end-of-life care in the Veteran's Affairs cancer population. *J Palliat Med* 2011; **14:** 1231–35.

36 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.

37 Henson LA, Gomes B, Koffman J, et al. Factors associated with aggressive end of life cancer care. *Support Care Cancer* 2016; **24:** 1079–89.

38 Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer* 2014; **120:** 1743–49.

39 Jang RW, Krzyzanowska MK, Zimmermann C, Taback N, Alibhai SM. Palliative care and the aggressiveness of end-of-life care in patients with advanced pancreatic cancer. *J Natl Cancer Inst* 2015; **107:** dju424.

40 Lee SW, Jho HJ, Baek JY, et al. Outpatient palliative care and aggressiveness of end-of-life care in patients with metastatic colorectal cancer. *Am J Hosp Palliat Care* 2018; **35:** 166–72.

41 Li D, Prigerson HG, Kang J, Maciejewski PK. Impact of radiation therapy on aggressive care and quality of life near death. *J Pain Symptom Manage* 2017; **53:** 25–32.

42 Lopez-Acevedo M, Havrilesky LJ, Broadwater G, et al. Timing of end-of-life care discussion with performance on end-of-life quality indicators in ovarian cancer. *Gynecol Oncol* 2013; **130:** 156–61.

43 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:** 4387–95.

44 Magarotto R, Lunardi G, Coati F, et al. Reduced use of chemotherapy at the end of life in an integrated-care model of oncology and palliative care. *Tumori* 2011; **97:** 573–77.

45 Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: a randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *Eur J Cancer* 2016; **69:** 110–18.

46 Nakano K, Yoshida T, Furutama J, Sunada S. Quality of end-of-life care for patients with metastatic non-small-cell lung cancer in general wards and palliative care units in Japan. *Support Care Cancer* 2012; **20:** 883–88.

47 Nevadunsky NS, Gordon S, Spoozak L, et al. The role and timing of palliative medicine consultation for women with gynecologic malignancies: association with end of life interventions and direct hospital costs. *Gynecol Oncol* 2014; **132:** 3–7.

48 Nieder C, Tollåli T, Haukland E, Reigstad A, Flatøy LR, Engljähringer K. Impact of early palliative interventions on the outcomes of care for patients with non-small cell lung cancer. *Support Care Cancer* 2016; **24:** 4385–91.

49 Pellizzari M, Rolfini M, Ferroni E, et al. Intensity of integrated cancer palliative care plans and end-of-life acute medical hospitalisation among cancer patient in Northern Italy. *Eur J Cancer Care* 2018; **27**.

50 Rabow M, Small R, Jow A, et al. The value of embedding: integrated palliative care for patients with metastatic breast cancer. *Breast Cancer Res Treat* 2018; **167:** 703–08.

51 Sano M, Fushimi K. Association of palliative care consultation with reducing inpatient chemotherapy use in elderly patients with cancer in Japan: analysis using a nationwide administrative database. *Am J Hosp Palliat Care* 2017; **34:** 685–91.

52 Sato K, Miyashita M, Morita T, Sanjo M, Shima Y, Uchitomi Y. Quality of end-of-life treatment for cancer patients in general wards and the palliative care unit at a regional cancer center in Japan: a retrospective chart review. *Support Care Cancer* 2008; **16:** 113–22.

53 Scibetta C, Kerr K, Mcguire J, Rabow MW. The costs of waiting: implications of the timing of palliative care consultation among a cohort of decedents at a comprehensive cancer center. *J Palliat Med* 2016; **19:** 69–75.

54 Shao YY, Hsiue EH, Hsu CH, et al. National policies fostering hospice care increased hospice utilization and reduced the invasiveness of end-of-life care for cancer patients. *Oncologist* 2017; **22:** 843–49.

55 Sharma G, Wang Y, Graham JE, Kuo YF, Goodwin JS. Provider continuity prior to the diagnosis of advanced lung cancer and end-of-life care. *PLoS One* 2013; **8:** e74690.

56 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:** 733–42.

57 Triplett DP, LeBrett WG, Bryant AK, et al. Effect of palliative care on aggressiveness of end-of-life care among patients with advanced cancer. *J Oncol Pract* 2017; **13:** e760–69.

58 Wiesenthal A, Goldman DA, Korenstein D. Impact of palliative medicine involvement on end-of-life services for patients with cancer with in-hospital deaths. *J Oncol Pract* 2017; **13:** e749–59.

59 Yoo SH, Keam B, Kim M, Kim TM, Kim DW, Heo DS. The effect of hospice consultation on aggressive treatment of lung cancer. *Cancer Res Treat* 2018; **50:** 720–28.

60 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.

61 Kaasa S, Loge JH, Aapro M, et al. Integration of oncology and palliative care: a *Lancet Oncology* Commission. *Lancet Oncol* 2018; **19:** e588–653.

62 El-Jawahri A, Greer JA, Pirl WF, et al. Effects of early integrated palliative care on caregivers of patients with lung and gastrointestinal cancer: a randomized clinical trial. *Oncologist* 2017; **22:** 1528–34.

63 El-Jawahri A, Traeger L, Greer JA, et al. Effect of inpatient palliative care during hematopoietic stem-cell transplant on psychological distress 6 months after transplant: results of a randomized clinical trial. *J Clin Oncol* 2017; **35:** 3714–21.

64 Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial. *J Clin Oncol* 2017; **35:** 834–41.

65 Haun MW, Estel S, Rücker G, et al. Early palliative care for adults with advanced cancer. *Cochrane Database Syst Rev* 2017; **6:** CD011129.

66 UK Department of Health. End of life care strategy: quality markers and measures of end of life care. https://webarchive.nationalarchives.gov.uk/20130104173044/http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_101681 (accessed Feb 24, 2019).