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REVIEW ARTICLE

A systematic review of the impact of pain on overall survival in patients with cancer

Dylan Zylla[1,2] · **Grant Steele**[2] · **Pankaj Gupta**[1,3]

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Abstract
Purpose Pain commonly occurs in cancer patients, and has been associated with shorter survival. However, the importance of pain is less clear when analyzed with other known prognostic variables. This systematic review was performed to better understand how pain impacts overall survival (OS) in common cancers when key clinical variables are included in multivariate analysis.
Methods A Medline search was completed to find studies examining the relationship between pain, clinical variables, and OS in patients with breast, colorectal, lung, or prostate cancer. Multivariate analysis included known prognostic variables including age, performance status, disease burden, and laboratory parameters.
Results Fifty studies met inclusion criteria. In patients with breast, colorectal, and lung cancer, pain was not a significant prognostic factor for OS on multivariate analysis in most studies. In contrast, several studies suggest that pain is an independent prognostic factor for OS in advanced prostate cancer, even when relevant clinical prognostic variables are included. However, analgesic use was often used as a surrogate for prostate cancer pain, making it difficult to determine whether pain or opioid exposure was more important in influencing survival.
Conclusions Pain may be associated with shorter survival in patients with cancer, but the mechanism for this relationship is unknown. The available evidence is insufficient to definitively determine if pain independently influences survival in patients with breast, colorectal, or lung cancer. The majority of studies in prostate cancer show pain to be an independent prognostic factor for OS, and often also incorporate opioid analgesic use in multivariate analysis. Prospective studies are needed to better understand how opioid utilization and pain may affect cancer progression and survival in diverse malignancies.

Keywords Pain · Survival · Multivariate analysis · Quality of life · Prognosis · Neoplasms

✉ Dylan Zylla
dylan.zylla@parknicollet.com

[1] Division of Hematology/Oncology/Transplantation, Department of Medicine, University of Minnesota, 3931 Louisiana Ave S, Minneapolis, MN 55426, USA

[2] Park Nicollet Oncology Research and HealthPartners Institute, St. Louis Park, MN, USA

[3] Hematology/Oncology Section, Department of Medicine, Minneapolis VA Health Care System, Minneapolis, USA

Introduction

For many cancer patients, pain is the most feared symptom of their disease. Although pain can be managed with a variety of approaches, these are not always effective [1, 2]. As a result, patients often suffer from increasing pain over the course of their disease. A meta-analysis has found prevalence of pain to reach 64% in patients with advanced malignancy, and it continues to affect 33% of cancer patients even after completion of curative treatment [3].

The presence of pain, along with other symptoms such as fatigue and appetite loss, causes considerable distress and significantly affects quality of life (QOL) during and after treatment [1]. Many reviews have noted the effect of QOL predictors on survival, often with worse symptoms being prognostic for shorter survival [4–6]. A large meta-analysis of 30 trials on a variety of cancer types found pain to be a significant prognostic factor for survival on multivariate (MV) analysis [7]. However, most studies reported have one or more of three limitations: (1) Pain is assessed at only one time-point, which

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is usually at diagnosis, (2) Multivariate analyses often include other QOL variables, but do not include key prognostic clinical variables such as performance status, disease burden, or laboratory values, and (3) Opioid requirements are rarely included.

Opioid analgesics are often prescribed to treat cancer pain, but have been shown to promote angiogenesis, tumor growth, and metastases via the mu opioid receptor (MOP-R), and to shorten survival in animal models [8–10]. MOP-R is overexpressed in several human malignancies [8, 11, 12], and the level of MOP-R expression may influence the activity of pharmacological opioids and inadvertently promote cancer progression. We previously reported that both the level of MOP-R expression in prostate human biopsy tissue samples and opioid exposure were independently associated with inferior progression-free and overall survival (OS) in patients with advanced prostate cancer [13]. We also observed that higher opioid exposure and more severe pain were predictive of shorter survival in patients with advanced non-small cell lung cancer [14].

To better delineate the independent prognostic importance of pain in cancer, we searched the literature to identify studies in which pain as well as the major known clinical prognostic variables were included in MV analysis of survival in four common malignancies.

Methods

A Medline search was completed to find articles published on or before May 5, 2016 that examined pain as a prognostic factor for OS in breast, colorectal, lung, and prostate cancers. The detailed Ovid Medline search strategy used is shown in the Appendix A Additional articles were found by examining the citations in included publications.

Key words included in the domain of the search were subheadings of "survival" as well as "neoplasms". Articles also contained "pain" or "quality of life" as determinant symptoms and utilized an MV analysis. Papers were limited to those studying humans and published in the English language. Only papers reporting the effect of pain and OS in the four most common cancers (breast, colorectal, lung, and prostate) were included.

Studies were manually excluded if they failed to include "overall survival" in their analysis. This included studies that only reported "progression-free survival," "cancer-specific survival," or other outcomes. Studies were also excluded if they lacked clinical variables in their MV analysis or if they did not examine pain

Two reviewers (DZ and PG) completed the initial Medline search and selected relevant articles based on their titles and abstracts. Three reviewers (DZ, KA, and GS) then further examined the papers to extract relevant data and synthesize the information into tables.

Extracted data included the sample size (n), cancer type/population, pain assessment methodology/tool utilized, clinical variables included in the MV analysis, and the results of the significance of pain in univariate (UV) and MV analyses. UV analysis focused on baseline pain alone and its association with overall survival, whereas MV analysis assessed pain and OS when controlling/adjusting for other key clinical variables. Clinical variables were chosen based on their prognostic relevance in the respective malignancies. Laboratory variables include both those that are used as tumor markers (e.g., prostate specific antigen (PSA)) and other key factors (e.g., hemoglobin levels). Additional comments are also listed to provide insight into any unique features of each study.

To evaluate the quality of studies, we defined a system based on the type of pain assessment methodology listed. Studies utilizing validated quality of life instruments (e.g., FLIC, Functional Living Index-Cancer; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer Quality of Life Lung Cancer Modular Supplement; MDASI, M. D. Anderson Symptom Inventory; and SF36v2, Short Form 36v2) were felt to have a more robust analysis. We gave studies incorporating these instruments a top-tier assessment ("Validated PRO"). Inferior studies were those that incorporated simpler numerical assessments ("Other PRO," e.g., visual analogue scale) or used surrogate markers for pain ("Surrogate," e.g., pain assessed by degree of opioid consumption).

While performance status (PS) was included as a clinical variable in many studies, a specific range was often required for inclusion. Of the 38 studies that included PS as a clinical variable, 16 limited the scores for patient inclusion in the methods (often only patients with PS score of ECOG ≤ 2 were included).

The criteria for what was deemed statistically significant was decided by the original authors. Most utilized a p value of ≤ 0.05 for significance. However, p values deemed significant ranged from 0.01–0.1.

Results

The initial Medline search yielded a total of 841 results. After further review, 43 articles were selected from this initial search. Another seven articles were added upon review of citations in the initial publications, leading to a total of 50 selected articles. Major findings from these articles are shown in Tables 1–4, separated by cancer type.

Table 1 Studies on relationship between pain and overall survival in breast cancer

Author(s)	Year	Total patients	Cancer description	Pain assessment methodology	Pain tool	CVs	UV Sig?	MV Sig?	Additional comments
Coates et al. [15]	1992	226	Metastatic	Validated PRO	LASA, QLI	P, D	No	No	Change in QOL score for pain from baseline to post-third cycle was a significant independent prognostic factor for survival on both UV and MV analyses.
Kramer et al. [17]	2000	187	Incurable adenocarcinoma in overt progression	Validated PRO	EORTC QLQ-C30	D	Yes	Yes	Preceding disease-free interval was also included in MV analysis.
Lumoa et al. [19]	2003	244	Advanced	Validated PRO	EORTC QLQ-C30	P	Yes	Yes	None
Efficace et al. [16]	2004	219	Metastatic	Validated PRO	EORTC QLQ-C30	A, P, D	Yes	No	None
Lee et al. [18]	2010	378	Advanced	Validated PRO	LASA	A, P, L, D	No	N/A	Baseline "Poor Pain" versus "Good Pain" was significant on UV analysis, but not overall pain, so not included in MV analysis.
Staren et al. [20]	2011	1511	All stages	Validated PRO	EORTC QLQ-C30	A, S	Yes	No	Stage was categorized into locoregional (I–III) and metastatic (IV).
Svensson et al. [21]	2012	252	Locally advanced or distant	Validated PRO	EORTC QLQ-C30	A, P, D	Yes	No	Pain on MV analysis has $p = 0.029$, but authors use <0.01 to define significance. Bootstrap validation technique confirmed lack of significance of pain.

QOL quality of life, *LASA* Linear Analog Self-Assessment, *QLI* Quality-of-Life Index questionnaire, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire, *CV* clinical variables, *A* age, *P* performance status, *S* stage, *L* laboratory parameters, *D* disease burden, *UV* Univariate analysis significant (yes/no), *MV* multivariate analysis significant (yes/no)

Breast cancer

Table 1 outlines studies on patients with breast cancer [15–21]. Of the seven studies matching the required characteristics, five found pain to be significantly associated with worse OS on UV analysis [16, 17, 19–21], yet pain remained significant on MV analysis in only two studies [17, 19]. Although all seven studies used clinical variables in their MV analyses, they varied in their choice of variables. The five papers that used two or more clinical variables did not find pain to be significant on MV analysis, or did not include it due to a lack of significance on UV analysis [15, 16, 18, 20, 21]. The largest sample size was 1511, including all stages of breast cancer, and this study found pain to only be significant on UV analysis [20]. In summary, the studies utilizing two or more clinical variables in the MV analyses generally found that in patients with breast cancer, pain was a significant prognostic factor for survival on UV but not on MV analysis.

Colorectal cancer

The six studies examining the relationship between pain and OS in colorectal cancer patients are outlined in Table 2 [22–27]. Four of the six studies found pain to be a significant prognostic factor for OS on UV analysis [22, 24–26], but only two studies found it to be significant on MV analysis [25, 26]. All studies were in patients with either advanced or metastatic colorectal cancer. Maisey et al. found pain to be significant on both UV and MV analyses and contained the largest sample size and the four most significant clinical variables (performance status, stage, laboratory parameters, and disease burden) [25]. This study strongly suggests pain is a significant prognostic factor for OS. However, more recent studies that also included multiple relevant clinical variables did not confirm pain as an independent prognostic factor in colorectal cancer [22, 24].

Lung cancer

Lung cancer was the most commonly examined tumor type, with nearly all studies on non-small cell lung cancer (NSCLC). These 20 reports are summarized in Table 3 [28–47]. Among these, 14 found pain to be a significant prognostic factor for OS on UV analysis [28–32, 34, 35, 37, 39, 41, 43–46], while ten found it to be significant on MV analysis [28, 30–32, 34, 36, 38, 39, 43, 45]. In the two papers that used five of the six most commonly included clinical variables, neither found pain to be a significant prognostic factor for OS on MV analysis [42, 44]. However, three of the four studies that used fewer (only four) clinical variables found pain to be significant on MV analysis [31, 32, 38], showing the variability of significance in lung cancer patients. Three studies utilized a bootstrapping statistical model in an attempt to validate their findings, and all three found pain to be significant on MV analysis [28, 31, 32]. Finally, Sundstrom et al. included the use of steroids and analgesics in UV and MV analyses [46]. Both steroid and analgesic use were significant on UV analyses, and steroid use retained significance on MV analysis. In summary, while 70% of the studies found pain to be significant on UV analysis, only 50% found it to be significant on MV analysis. These studies are quite heterogeneous with differences in disease stage, sample sizes, and clinical variables included in the MV analyses, making it difficult to ascertain the importance of the independent influence of pain on survival.

Prostate cancer

A large number of studies evaluated the influence of pain on survival in patients with prostate cancer and are shown in Table 4 [48–64]. Of the 17 studies reviewed, 12 found pain to be significant as a prognostic factor on UV analysis [48, 49, 53, 56–64], and 11 found pain to be of prognostic significance for OS on MV analysis [48–50, 53–56, 59–61, 64]. Given the importance of PSA in prostate cancer, all but two studies incorporated PSA values in the MV analysis. [48–61, 64]. Nine studies used four common clinical variables [48, 49, 51, 54–56, 60, 61, 64], and eight of these papers found pain to be a significant prognostic factor for OS on MV analysis [48, 49, 54–56, 60, 61, 64]. These findings in patients with prostate cancer differ sharply from findings in the other three cancers, in which pain did not remain significant as a prognostic factor for OS when important clinical variables were included in MV analysis. The largest study on patients with advanced, castrate resistant-prostate cancer (n = 1901), found pain to be significant on both UV and MV analyses [64]. This report also included a verified QOL tool, bootstrapping, and four commonly used clinical variables, enhancing the validity of the findings. Finally, analysis of prostate cancer differed from others in that analgesic usage was often examined. Five studies defined pain by analgesic use [48, 51, 55, 57, 59], of which three found pain to be significant on MV analysis [48, 55, 59]. Halabi et al. included opioid analgesic use in the MV analysis, and found it to be a significant prognostic factor for OS [61].

All cancers—summary

In summary, considerable evidence indicates that pain is an independent prognostic factor in advanced prostate cancer. However, pain was often connected to or assessed by analgesic use, making it difficult to determine if pain or opioid use was more important factor influencing survival in patients with prostate cancer. The available evidence is insufficient to definitively determine whether or not pain independently influences survival in patients with breast, colorectal, or lung cancer.

Table 2 Studies on relationship between pain and overall survival in colorectal cancer

Author(s)	Year	Total patients (% male)	Cancer Description	Pain Assessment methodology	Pain Tool	CVs	UV Sig?	MV Sig?	Additional Comments
Maisey et al. [25]	2002	501 (NR)	Advanced	Validated PRO	EORTC QLQ-C30	P, S, L, D	Yes	Yes	None
Efficace et al. [23]	2006	299 (59%)	Advanced beyond curative option by surgery	Validated PRO	EORTC QLQ-C30	P, L, D	No	No	Analysis includes bootstrap validation technique, but pain was not included as it lacked significance on UV analysis.
Efficace et al. [24]	2008	443 (60%)	Metastatic	Validated PRO	EORTC QLQ-C30	G, P, L, D	Yes	No	Validation of Efficace et al., 2006
Pacelli et al. [26]	2010	58 (55%)	Rectal recurrence limited to pelvis	Surrogate	N/A	L, D	Yes	Yes	Endpoint was 5 year OS. Used Mayo Clinic symptomatic pattern of local recurrence system to analyze pain. S0 = symptomless; S1 = symptom other than pain; S2 = pelvic/back pain
Wong et al. [27]	2014	160 (55%)	Advanced	Validated PRO	SF-12	A, G, S	No	No	Used Harrell's discrimination C-index to assess accuracy of MV analysis
Diouf et al. [22]	2014	249 (61%)	Previously untreated metastatic	Validated PRO	EQ-5D	A, P, L, D	Yes	No	Used Harrell's discrimination C-index to assess accuracy of MV analysis

QOL quality of life, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire, *SF-12* Short Form-12 questionnaire, *EQ-5D* European Quality of Life-5 Dimensions questionnaire *CV* clinical variables *A* age, *G* gender, *P* performance status, *S* stage, *L* laboratory parameters, *D* disease burden, *UV* univariate analysis significant (yes/no), *MV* multivariate analysis significant (yes/no), *NR* not reported

Table 3 Studies on relationship between pain and overall survival in lung cancer or mesothelioma

Author(s)	Year	Total patients (% male)	Cancer description	Pain assessment methodology	Pain \tool	CVs	UV Sig?	MV Sig?	Additional comments
Stanley [45]	1980	5138 (NR)	Inoperable bronchogenic carcinoma	Other PRO	N/A	P, D	Yes	Yes	Pain was broken into presence or absence of shoulder-arm, bone, or chest, with only latter two retaining significance on UV and MV analysis. Ψ-statistic was used rather than *p* value to determine significance.
Ruckdeschel & Piantadosi [41]	1994	438 (NR)	Early stage receiving adjuvant treatment	Validated PRO	FLIC	P, D	Yes	N/A	Pain disrupting activity and pain related to cancer were both significant on UV analysis, but neither included in MV analysis. Final MV model was stratified by cell type.
Schonwetter et al. [43]	1994	310, (65%)	Terminal with admittance to hospice	Other PRO	N/A	G, P, D	Yes	Yes	Likert-type scale ranking pain as incapacitating, severe, moderate, mild, or none. Incapacitating and severe signified presence of pain in analysis.
Herndon et al. [34]	1999	206 (74%)	Advanced NSCLC	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	P, L, D	Yes	Yes	None
Martins et al. [37]	1999	1635 (76%)	All stages of NSCLC	Other PRO	N/A	A, P, S	Yes	N/A	Pain was defined as presence or absence of chest pain. Pain was not significant on MV analysis with other QOL variables, so not included in MV analysis with clinical variables.
Scott et al. [44]	2002	106, (62%)	Inoperable stage III or IV	Validated PRO	EORTC QLQ-30	A, G, P, S, L	Yes	No	None
Nowak et al. [39]	2004	53 (85%)	Pleural mesothelioma	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	G, P, L	Yes	Yes	Composite pain score was created for LC13 for chest, arm, and other pain.
Efficace et al. [32]	2006	391 (65%)	Advanced NSCLC (stage IIIB or IV)	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	A, G, P, S	Yes	Yes	Bootstrap validation technique confirmed significance of pain
Saito-Nakaya et al. [42]	2006	238 (61%)	Post curative resection of NSCLC	Other PRO	N/A	A, G, P, S, L	No	N/A	Pain separated into two categories: none-mild versus. moderate-severe. Pain was not included in MV analysis since not significant on UV analysis.
Sundstrom et al. [46]	2006	301 (77%)	Stage IV NSCLC	Validated PRO	EORTC QLQ-LC13	P, L	Yes	No	QOL scores were dichotomized according to mean. Analgesics and steroids were significant on UV analysis. Steroids remained significant on MV analysis.
Bottomley et al. [28]	2007	250 (80%)	Unresectable pleural mesothelioma	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	S, L	Yes	Yes	Clinical variables were lumped in MV analysis into "EORTC PI" (histology, interval since diagnosis, platelet count, hemoglobin difference, stage). Bootstrap validation technique confirmed significance of pain.
Herndon et al. [35]	2008	1577 (66%)	NSCLC and SCLC	Other PRO	N/A	G, P, L, D	Yes	No	Pain defined as presence or absence of bone or chest pain at diagnosis.
Nakaya et al. [38]	2008	1178 (71%)	All stages	Other PRO	N/A	A, G, P, S	N/A	Yes	Self-reported pain defined on a scale from 1 (none) to 5 (very severe) at time of diagnosis. Specific statistical values for pain were not shown.

Table 3 (continued)

Author(s)	Year	Total patients (% male)	Cancer description	Pain assessment methodology	Pain \tool	CVs	UV Sig?	MV Sig?	Additional comments
Dai et al. [30]	2010	220 (80%)	Completely resected stage II NSCLC	Other PRO	N/A	A, D	Yes	Yes	Endpoint was 5-year OS. Pain was defined as presence or absence of chest pain.
Wang et al. [47]	2010	94 (67%)	Advanced NSCLC	Validated PRO	MDASI	A, G, P	No	N/A	Pain was not significant on UV analysis so not included in MV analysis.
Braun et al. [29]	2011	1194 (50%)	All stages NSCLC	Validated PRO	EORTC QLQ-C30	G, S	Yes	No	Stage was categorized into locoregional (I–III) and metastatic (IV).
Li et al. [36]	2012	162 (63%)	NSCLC undergoing surgery	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	A, G, S	No	Yes	Study separated patients into surgical and non-surgical categories. Pain was significant on MV analysis with the C30 QOL tool, but not the LC13.
Li et al. [36]	2012	312 (66%)	NSCLC not undergoing surgery	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	A, G, S	No	No	Study separated patients into surgical and non-surgical categories.
Gupta et al. [33]	2012	430 (51%)	Stages III or IV NSCLC	Validated PRO	EORTC QLQ-C30	A, G, S	No	No	Used Pearson's correlation coefficient to assess potential multicollinearity
Pompili et al. [40]	2013	131 (79%)	Stage T1-2 N0 NSCLC	Validated PRO	SF36v2	A, P	No	N/A	Pain was not significant on UV analysis so not included in MV analysis.
Ediebah et al. [31]	2014	391 (NR)	Advanced NSCLC (stage IIIB or IV)	Validated PRO	EORTC QLQ-C30, EORTC QLQ-LC13	A, G, P, S	Yes	Yes	Bootstrap validation technique confirmed significance of pain.

NSCLC non-small cell lung cancer, *SCLC* small cell lung cancer

QOL quality of life, *FLIC* functional living index-cancer, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire, *EORTC QLQ-LC13* European Organization for Research and Treatment of Cancer Quality of Life Lung Cancer Modular Supplement, *MDASI* M. D. Anderson Symptom Inventory, *SF36v2* Short Form 36v2, *CV* clinical variable, *A*:age, *G* gender, *P* performance status, *S* stage, *L* laboratory parameters, *D* disease burden, *UV* univariate analysis significant (yes/no), *MV* multivariate analysis significant (yes/no), *NR* not reported

Table 4 Studies on relationship between pain and overall survival in prostate cancer

Author(s)	Year	Total patients	Cancer description	Pain assessment methodology	Pain tool	CVs	UV Sig?	MV Sig?	Additional comments
Emrich et al. [48]	1985	1020	Advanced	Surrogate	N/A	A, P, L, D	Yes	Yes	Pain was defined as no pain, mild (occasional use of analgesics), moderate (controlled analgesics use), or severe (uncontrollable pain). Presence or absence of analgesic use was also significant on UV analysis.
de Voogt et al. [49]	1989	436	Previously untreated advanced	Other PRO	N/A	A, P, L, D	Yes	Yes	Pain was defined by its presence or absence. Separate UV and MV analyses were done for M0 (non-metastatic), M1 (metastatic), and all patients. Pain was only significant on MV analysis for M0 patients.
Chodak et al. [50]	1991	240	Metastatic (D2)	Other PRO	N/A	A, P, L	N/A	Yes	Pain was defined by its presence or absence. Endpoint was 2 year OS. UV significance unknown as "only the results of the multivariate analysis are presented because we were looking for the subset of the strongest independent predictors.".
Fossa et al. [51]	1992	58	Progressive metastatic CRPC	Surrogate	N/A	A, P, L, D	No	No	Pain was defined on Likert-type scale as well as by analgesics use (high pain, ongoing narcotic usage versus no analgesics/non-narcotic analgesics).
Petrylak et al. [52]	1992	146	CRPC	Other PRO	N/A	L, D	No	N/A	Pain was defined by its presence or absence. Pain was not significant on UV analysis, so not included in MV analysis.
Tannock et al. [53]	1996	161	CRPC with pain	Validated PRO	McGill-Melzack	P, L	Yes	Yes	PPI was the significant scale on MV analysis. Analgesics use was significant on UV analysis.
Thompson et al. [54]	2001	916	Metastatic	Validated PRO	SWOG SF-36	A, P, L, D	N/A	Yes	Pain was not assessed on UV analysis. Bone pain at diagnosis was significantly higher in African-American than white patients ($p = 0.04$).
de Reijke et al. [55]	2002	399	Newly diagnosed metastatic	Surrogate	N/A	A, P, L, D	N/A	Yes	Metastases-related pain was defined as needing analgesics versus not needing analgesics/no pain.
Tangen et al. [56]	2003	794	D2 adeno-carcinoma	Other PRO	N/A	A, P, L, D	Yes	Yes	Pain was defined by presence or absence of bone pain.
Collette et al. [57]	2004	391	Painful Metastatic CRPC	Validated PRO	EORTC QLQ-C30	P, L, D	Yes	No	Clinical pain (high pain, ongoing narcotic usage versus no analgesics/non-narcotic analgesics) was significant on UV analyses. C30 pain was insignificant on UV analysis.
Oudard et al. [58]	2005	130	Metastatic CRPC	Validated PRO	McGill-Melzack	P, L	Yes	No	Analgesics use was also examined, but not significant on UV analysis.
Armstrong et al. [59]	2007	1006	Metastatic CRPC	Validated PRO	McGill-Melzack	P, L, D	Yes	Yes	Bootstrap validation technique confirmed significance of pain. Pain was defined by PPI and analgesics usage.
Bamias et al. [60]	2008	94	CRPC	Other PRO	N/A	A, P, L, D	Yes	Yes	Pain was defined by its presence or absence.
Halabi et al. [61]	2008	599	Progressive CRPC	Validated PRO	BPI	A, P, L, D	Yes	Yes	Pain was dichotomized into high versus low based on median pain interface score. Opioid analgesic use was significant on MV analysis.
Braun et al. [62]	2012	673	All stages	Validated PRO	EORTC QLQ-C30	A, S	Yes	No	Stage was categorized into locoregional (I–III) and metastatic (IV).
Gupta et al. [63]	2013	250	All stages	Validated PRO	EORTC QLQ-C30	S	Yes	No	Bootstrap validation technique was used to confirm lack of significance of pain. Pearson's correlation coefficient was also used to assess potential multicollinearity.

Table 4 (continued)

Author(s)	Year	Total patients	Cancer description	Pain assessment methodology	Pain tool	CVs	UV Sig?	MV Sig?	Additional comments
Fizazi et al. [64]	2015	1901	Metastatic CRPC	Validated PRO	BPI-SF	A, P, L, D	Yes	Yes	Bootstrap validation technique was used to confirm significance of pain. "Baseline worst pain" dichotomized into mild/no pain versus moderate/severe pain.

CRPC castrate resistant prostate cancer

QOL quality of life, *SWOG SF-36* Southwest Oncology Group Short Form 36, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire, *BPI* Wisconsin Brief Pain Inventory, *BPI-SF* brief pain inventory-short form, *CV* clinical variable, *A* age, *G* gender, *P* performance status, *S* stage, *L* laboratory parameters, *D* disease burden, *UV* univariate analysis significant (yes/no), *MV* multivariate analysis significant (yes/no)

Discussion

We reviewed 50 studies that examined the prognostic influence of pain and other key clinical variables in patients with breast, colorectal, lung, or prostate cancer. The majority of studies found pain to be an adverse prognostic factor for OS on UV analysis in all these malignancies. However, when key prognostic variables such as age, gender, disease burden, performance status, and laboratory parameters were included, the association of pain with survival became less clear in breast, colorectal, or lung cancer. Pain does appear to be an independent adverse prognostic factor for OS in patients with advanced prostate cancer.

Molecular and cellular mechanisms underlying the potential influence of pain on clinical outcomes remain incompletely defined. Potential mechanisms by which pain might promote cancer progression and shorten survival may include (a) pain-induced impairment of host immune response, allowing malignant cells to grow/spread more easily [65, 66], (b) reducing the ability of patients to undergo intensive anti-cancer therapies, via pain-mediated impairment of performance status, QOL, and nutritional intake [67], and/or (c) increasing the activation of mu-opioid receptors (MOP-R), either by pain-induced stimulation of endogenous opioids (e.g., endorphins), or increased consumption of pharmacological opioid analgesics. Since most of the studies included in this review were observational, it is hard to draw firm conclusions as to which mechanism may explain our findings.

Of these possible mechanisms, increased consumption of pharmacological opioids remains an important plausible explanation for the association between pain and shorter OS. Analgesic use, often differentiated into opioid versus non-opioid usage, was used in five studies as a surrogate for pain level in prostate cancer [48, 51, 55, 57, 59], and was a significant prognostic factor in three of these. Halabi et al. found opioid use itself to be a significant prognostic factor for OS in MV analysis [61]. These findings are consistent with our recent retrospective studies showing that greater opioid exposure is associated with inferior OS in both prostate and lung cancer [13, 14]. However, it is critical to emphasize that opioids remain a first-line treatment for advanced cancer-related pain and dyspnea, and their use should not be limited at this time. Opioids provide great comfort in a palliative/terminal settings, and their use in these situations has not been shown to hasten death [68].

Previous reviews assessing QOL scores and OS in a variety of cancers have reported mixed results on the prognostic influence of pain [4–6]. Many studies have evaluated the relative importance of pain compared to other QOL variables, and were unable to take into account the critical importance of known clinical prognostic variables. In the current review, we only included studies where at least one key clinical variable such as age, performance status, disease burden, and

laboratory markers were included in the MV analysis. Both gender and race could also impact patients' pain experience. While gender is not a relevant variable for breast and prostate cancer studies, there is often a higher percentage of male patients making up the colorectal and lung cancer cohorts, which could impact results. Ethnicity was rarely reported in any study, and we opted to omit it from our results.

While there was marked heterogeneity in the prognostic variables included in the MV analysis, we found that pain remains a potentially important adverse prognostic factor for survival in advanced prostate cancer. The current review also permits critical evaluation of the strongest studies (i.e., those with larger sample sizes, using validated QOL tools, and containing at least three of the four important clinical variables such as performance status, stage, laboratory parameters, and disease burden) in MV analysis. Of the 12 studies that met these more stringent criteria, six found pain to be significant on MV analysis, the majority of which were performed in patients with prostate cancer [25, 34, 54, 59, 61, 64].

Reaching definitive conclusions about the prognostic relevance of pain is further limited by the inherent difficulty in assessing pain and comparing it across studies. Such limitations include (a) the subjective nature of pain, (b) fluctuation over short periods of time, (c) progressive increase with progression of malignancy, (d) usual assessment at a single time point (often at initial evaluation/diagnosis, and (e) influence of other variables (e.g., emotional distress, amount/type of analgesic ingested prior to pain measurement). All of these factors might have impacted baseline pain measurements collected in various studies, and contributed to the variability in their findings. Finally, most papers did not report how often patients were lost to follow up. In addition, many of these articles were sub-studies of larger clinical trials, or pooled results from a combination of clinical trials, making it difficult to precisely define the exact duration of the follow-up periods across studies.

Severe cancer-related pain usually occurs only when malignancies reach an advanced stage. It was therefore appropriate that most studies evaluating the influence of pain on survival only included patients with advanced stage malignancies. In fact, among the six studies that included patients with all stages of cancer [20, 29, 37, 38, 62, 63], five found that pain was not significant on MV analysis.

As emphasized by us [13], tracking opioid analgesic consumption may be easier, more objective and quantitative than monitoring pain levels (particularly if only a single baseline value is used), and may therefore prove to be a more reliable surrogate indicator of pain in future studies. There are several basic science and pre-clinical studies underlying the hypothesis that opioid exposure may lead to cancer progression in humans [8–10, 69–71]. Further supporting this notion, we found that both pain and opioid exposure are predictive of markedly shorter survival in a retrospective analysis of 204 patients with advanced NSCLC [14]. Nevertheless, because it is difficult to dissociate pain from opioid analgesic use, both of which may influence clinical outcomes, future prospective studies should incorporate longitudinal assessments of pain (ideally with validated patient-reported outcome tools) together with analgesic utilization focusing on amounts of opioid ingested.

In conclusion, we examined the association of pain with survival in patients with breast, colorectal, lung, or prostate cancer. In 50 studies that met selection criteria, pain appeared to be a significant prognostic factor for OS on univariate analysis, but had varied results depending on the type of cancer analyzed and number and type of clinical variables used in multivariate analysis. Most prostate cancer studies showed pain to be an independent prognostic factor for OS and often incorporated opioid analgesic use in multivariate analysis. Prospective, longitudinal studies that include all relevant clinical variables are needed to better understand how pain and opioid utilization may impact cancer progression and clinical outcomes.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

APPENDIX

Ovid Medline search strategy 5/5/2016: *Search Term (# of results):*

Domain

1. exp Survival Analysis/ or exp Survival/ or exp Survival Rate/ (335733)
2. survival.m_titl. (99487)
3. 1 or 2 (394998)
4. exp Neoplasms/ (2827457)
5. 3 and 4 (201726)

Type of analysis

6. exp Multivariate Analysis/ (97772)
7. (multivariate$ or multivariable$ or proportional hazard$).mp. (324009)
8. (multiple variab$ or model$).mp. (2557125)
9. 6 or 7 or 8 (2720285)
10. 5 and 9 (67631)

Determinant symptoms

11. exp pain/ or exp pain perception/ or exp pain measurement/ (352715)
12. pain.ti,ab. (411189)
13. 11 or 12 (562254)
14. 10 and 13 (728)
15. quality of life.mp. or exp quality of life/ (210088)
16. 10 and 15 (1501)
17. 14 or 16 (2079)
18. limit 17 to (English language and humans) (1972)

Type of cancer

19. exp breast neoplasms/ (242234)
20. exp prostatic neoplasms/ (104251)
21. exp lung neoplasms/ (192487)
22. exp colorectal neoplasms/ (166417)
23. 19 or 20 or 21 or 22 (674548)
24. 18 and 23 (841)

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