

BMJ Open Treatment targeted at underlying disease versus palliative care in terminally ill patients: a systematic review

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ABSTRACT

Objective: To assess the efficacy of active treatment targeted at underlying disease (TTD)/potentially curative treatments versus palliative care (PC) in improving overall survival (OS) in terminally ill patients.

Design: We performed a systematic review and meta-analysis of randomised controlled trials (RCT). Methodological quality of included RCTs was assessed using the Cochrane risk of bias tool.

Data sources: Medline and Cochrane databases were searched, with no language restriction, from inception to 19 October 2016.

Eligibility criteria for selecting studies: Any RCT assessing the efficacy of any active TTD versus PC in adult patients with terminal illness with a prognosis of <6-month survival were eligible for inclusion.

Results: Initial search identified 8252 citations of which 10 RCTs (15 comparisons, 1549 patients) met inclusion criteria. All RCTs included patients with cancer. OS was reported in 7 RCTs (8 comparisons, 1158 patients). The pooled results showed no statistically significant difference in OS between TTD and PC (HR (95% CI) 0.85 (0.71 to 1.02)). The heterogeneity between pooled studies was high ($I^2=62.1\%$). Overall rates of adverse events were higher in the TTD arm.

Conclusions: Our systematic review of available RCTs in patients with terminal illness due to cancer shows that TTD compared with PC did not demonstrably impact OS and is associated with increased toxicity. The results provide assurance to physicians, patients and family that the patients' survival will not be compromised by referral to hospice with focus on PC.

INTRODUCTION

The diagnosis of a terminal illness for patients is shattering news.¹ Following the diagnosis, patients along with their families are faced with several complex decisions relating to medical, spiritual, legal, or existential issues.¹ The most concerning decision for patients and families alike following diagnosis of terminal illness relates to the choice

Strengths and limitations of this study

- This is the first systematic review of randomised controlled trials to assess the benefits and risks associated with active treatment targeted at underlying disease versus palliative in the end-of-life setting.
- One of the strengths of this study was the extensive, systematic literature search performed to identify all available randomised controlled trials in terminally ill patients.
- A limitation of this systematic review is the availability of small number of studies with overall survival data.

of medical strategy of either opting for active treatment targeted at underlying disease (TTD) which can potentially be life-prolonging or curative, versus palliative care (PC) where the primary focus is on providing symptomatic relief and improving quality of life (QOL).² The US Medicare regulations recommend PC for patients with terminal illness, ideally in hospice setting, if the expected survival is <6 months; conversely, PC or referral to hospice is considered inappropriate if expected survival is <6 months. However, findings from several studies show that application of these recommendations is far from optimal in real-life setting. For example, around 40% of patients with advanced lung cancer continued aggressive therapy through the final month of life.³ Overall, over 60% of patients with cancer receive aggressive TTD within the past 3 months of life.⁴⁻⁷ In fact, during the last decade, the number of patients receiving aggressive therapy within the last month of life grew⁸ which also reflects the increased healthcare spending in the past 6 months of life. On the other hand, use of hospice in the past 3 days of life minimally increased from 14.3% to 17%.^{2 9 10} In short, patients

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with terminal illness are not receiving care as per the professional societies' or Medicare recommendations.²

There are several reasons for not delivering the appropriate care to patients with terminal illness. One of the main reasons is lack of evidence or conflicting evidence related to benefits and harms associated with TTD versus PC.² Findings from a randomised controlled trial (RCT) assessing the role of supportive care versus supportive care in addition to TTD in patients with transitional cell carcinoma of urothelial tract demonstrated no survival advantage with a combination treatment approach.¹¹ Another study by Schmid *et al*¹² which assessed the role of radiotherapy or chemotherapy (ie, TTD) compared with no treatment in patients with inoperable squamous carcinoma of the oesophagus showed no survival advantage with TTD. However, results from a RCT comparing supportive care versus supportive care plus TTD in patients with metastatic non-small cell lung cancer showed a survival advantage with TTD.¹³

Given that physicians are not accurate in establishing patients' prognosis for course of disease or death,^{14 15} to make informed choice, patients and physicians alike need reliable evidence on benefits and risks associated with TTD versus PC. Accordingly, we performed a systematic review with a goal to synthesise all available evidence to reliably assess the efficacy and safety of TTD compared with PC in patients with terminal illness (with expected survival of <6 months).

METHODS

This systematic review was performed according to a pre-specified protocol and is reported according to PRISMA guidelines.¹⁶

Eligibility criteria

Any RCT enrolling patients with clearly stated predicted median survival of <6 months comparing an established TTD versus PC alone was eligible for inclusion. Studies of novel TTD treatments within a context of clinical trials were excluded. We also excluded trials comparing add-on PC to two active treatments. The distinction between PC versus TTD was made based on the original investigators intent (ie, symptom management vs curative or life prolonging intent) as stated in the introduction or methods of included studies.

Search and study selection

A comprehensive search of Medline and Cochrane electronic databases, with no language restriction, was undertaken from inception to 19 October 2016. Search strategy is provided in online supplementary appendix 1. Two authors (AK and TR) reviewed all retrieved titles/abstracts and full-text articles independently. A third author (BD) reviewed any disagreements to arrive at consensus.

Data collection

Data were abstracted on study and patient characteristics, treatment, and outcomes (overall survival (OS), QOL,

treatment-related mortality (TRM), and adverse events). Data extraction was performed independently by two authors (TR and FAK) using a standardised data extraction form. The corresponding author (BD) resolved any disagreement during the data extraction process. Risk of bias was assessed using Cochrane Risk of Bias Tool.¹⁷ The overall assessment of methodological quality was performed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.¹⁸

Statistical analysis

When appropriate, data were pooled for each outcome. Dichotomous data were summarised using risk ratio (RR) based on the number of events and total number of participants and pooled under random-effects model. In regards to time-to-event data, HR and 95% CIs were extracted, whenever reported. Otherwise, total number of participants and events per arm and the p value were obtained in order to calculate the observed minus expected value (O-E) and variance as per method by Tierney *et al*.¹⁹ Time-to-event data were pooled using generic inverse variance under the random-effects model. All data are reported with 95% CI. Calculation of the I² statistic was used to assess for heterogeneity. An I² <30% was considered low heterogeneity, between 30% and 50% moderate heterogeneity and over 50% high heterogeneity.²⁰ The analyses were performed using Review Manager software (Review Manager (RevMan) [program]. Version 5.3 version. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study selection

The initial search identified 8252 articles of which 10 RCTs (15 comparisons, 1549 patients) met the inclusion criteria.^{11–13 21–27} The study selection process is illustrated in figure 1.

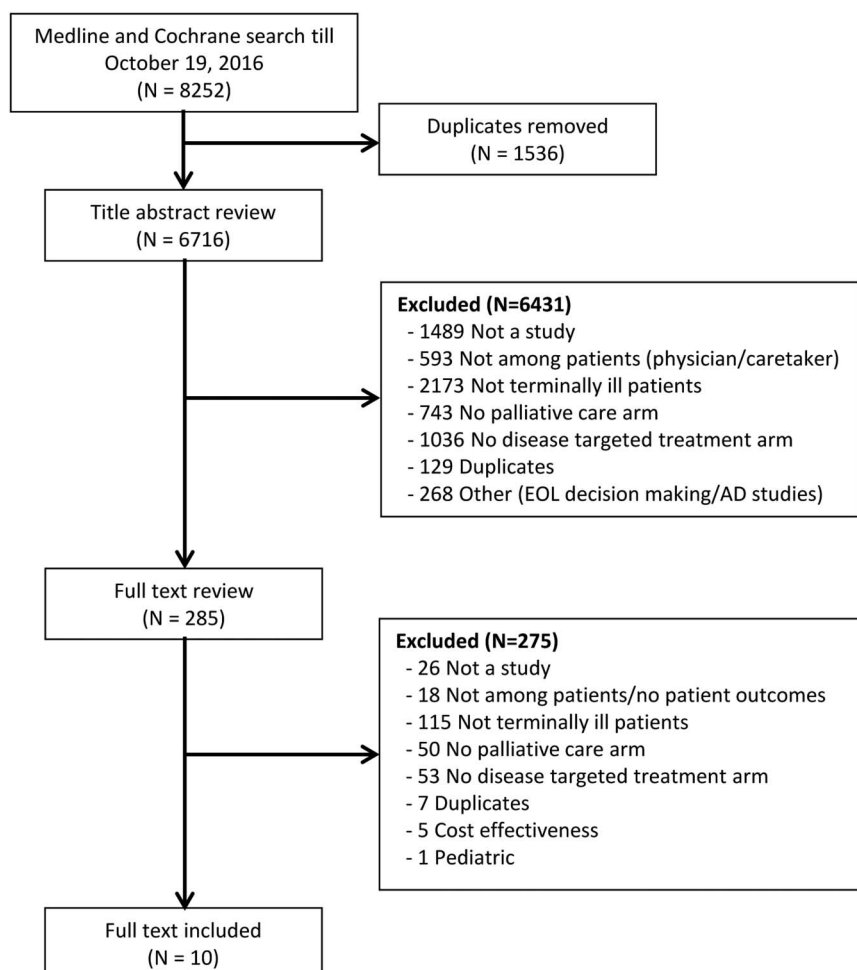
Characteristics of included studies

As illustrated in table 1, all included studies enrolled patients with cancer. The majority of studies compared disease-targeted chemotherapy (12/15 comparisons) to PC alone^{11–13 21–26} while the remaining three studies used targeted drug therapy,²⁷ radiotherapy,¹² and hormone therapy²⁶ on the TTD arm. The PC arm mainly consisted of analgesics (8/15 comparisons),^{11 13 22 25 26} blood product transfusions (7/15 comparisons),^{11 13 23 25–27} and palliative radiotherapy (5/15 comparisons).^{13 22 23}

Risk of bias in included studies

The overall methodological quality of included studies ranged from moderate to low. As shown in figure 2, 80% of included studies (8/10) reported method of randomisation sequence generation. However, only 20% (2/10) of included studies were judged to have adequate

Figure 1 Flow diagram depicting the identification and selection of eligible studies for inclusion in the systematic review and meta-analysis.



allocation concealment and only 10% (1/10) involved blinding of participants/personnel or outcome assessors. Ninety per cent of studies (9/10) performed analysis as per intention-to-treat principle and 70% (7/10) studies reported all outcomes and did not involve selective reporting of outcomes.

Outcomes

Patient outcomes are summarised in table 2. Figure 3 shows a forest plot comparing effects of TTD versus PC on the OS. OS was reported by seven RCTs (eight comparisons, 1158 patients).^{11–13 23–25 27} The pooled results showed no statistically significant difference in OS between TTD and PC (HR (95% CI) 0.85 (0.71 to 1.02)). The heterogeneity between pooled studies was high ($I^2=62.1\%$). Four studies included QOL as an outcome; however, data were not extractable for pooling.^{11 23 24 27} Only two RCTs (668 patients) reported TRM.^{11 25} There was no statistically significant difference in TRM between TTD and PC (RR (95% CI) 0.92 (0.31 to 2.76)). There was no heterogeneity between pooled studies ($I^2=0\%$). Seven RCTs (10 comparisons)^{11 13 22–26} discussed adverse events but only three (three comparisons)^{11 23 25} reported comparative data for both study arms. Overall, grade three or four

adverse events were significantly more common on the TTD arm compared with PC (see table 2).

DISCUSSION

The findings of this systematic review have several important implications for physicians, patients and policymakers. Physicians are obligated legally and ethically to provide patients with evidence on alternative management options in the end-of-life setting. Some states such as New York and California make the failure to discuss the management alternatives in terminal setting punishable by law (up to \$5000 for repeated offences, and wilful violations by a jail term of up to 1 year).²⁸ However, repeated assessments of the quality of decision-making in the end-of-life setting over the last two decades continue to show that is inadequate.¹ In 2014, 55 million people died worldwide, the vast majority of whom did not receive adequate end-of-life care.²⁹ The fundamental reason for this state of affairs is the lack of reliable estimates about the efficacy and safety of active treatment (TTD) versus PC in patients in terminal phase of their lives. Even though it is known that PC does improve survival when it is added to TTD,³⁰ it is not known if TTD is superior to PC alone. Our systematic review fills this void. To the best of our knowledge,

Table 1 Study and patient characteristics

Study, year	Years	Patients enrolled	Cancer type	Age (TTD vs PC)	TTD	PC offered in addition to TTD	PC	Expected median survival <6 months
Bellmunt, 2009	2003–2006	337	Urothelial	NR	Chemotherapy	Yes	Pain medication, palliative chemotherapy, supportive care, antibiotics, corticosteroids	Yes
Cartei, 1993	NR	102	Lung	Median (range): 57 (39–71) vs 56 (41–73)	Chemotherapy	Yes	Pain medication, radiotherapy, supportive care	Yes
Ciuleanu, 2009	2004–2006	303	Pancreatic	Median (range): 58 (27–78) vs 57 (29–80)	Chemotherapy	Yes	Pain medication, supportive care, appetite stimulators	Yes
De Marinis, 1999a	1990–1993	61	Lung	NR	Chemotherapy	Unclear	Pain medication, radiotherapy, steroids, progestins	Yes
De Marinis, 1999b	1990–1993	63	Lung	NR	Chemotherapy	Unclear	Pain medication, radiotherapy, steroids, progestins	Yes
De Marinis, 1999c	1990–1993	64	Lung	NR	Chemotherapy	Unclear	Pain medication, radiotherapy, steroids, progestins	Yes
Lissoni, 1994a	NR	50	Pancreatic	Median (range): 56 (39–71) vs 57 (50–74)	Chemotherapy	Yes	Pain medication, supportive care, steroids, antiemetics, ansioliticos	Yes
Lissoni, 1994b	NR	50	Solid tumors	Median (range): 56 (38–72) vs 58 (42–71)	Drug therapy	Yes	Supportive care	Yes
Ranson, 2000	1995–1997	157	Lung	Median (range): 65 (37–78) vs 64 (23–82)	Chemotherapy	Yes	Radiotherapy, supportive care, corticosteroids, antibiotics, antiemetics	Yes
Schmid, 1993a	1987–1989	87	Esophageal	Median: 55 vs 53	Radiotherapy	Unclear	Intubation only	Yes
Schmid, 1993b	1987–1989	86	Esophageal	Median: 55 vs 53	Chemotherapy	Unclear	Intubation only	Yes
Selawry, 1977a	NR	150	Lung	Median: 62 vs 59	Chemotherapy	Unclear	NR	Yes
Selawry, 1977b	NR	152	Lung	Median: 59 vs 59	Chemotherapy	Unclear	NR	Yes
Xinopoulos, 2008	NR	73	Pancreatic	Mean (range): 66.5 (59–73) vs 66.6 (58–73)	Chemotherapy	Unclear	Plastic biliary endoprosthesis placement as needed	Yes

NR, not reported; PC, palliative care; TTD, treatment targeted at underlying disease.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bellmunt 2009	?	?	?	+	+	+	?
Cartei 1993	+	?	?	?	+	-	?
Ciuleanu 2009	+	?	?	?	+	+	-
De Marinis 1999	+	?	?	?	-	-	+
Lissoni 1994	?	?	?	?	+	+	?
Lissoni 1994 (pancreatic)	+	?	?	?	+	+	+
Ranson 2000	+	+	?	?	+	+	?
Schmid 1993	+	?	?	?	+	+	+
Selawry 1977	+	+	+	+	+	-	?
Xinopoulos 2008	+	?	?	?	+	+	?

Figure 2 Risk of bias in included studies.

this is the first systematic review assessing the role of TTD compared with PC in patients with terminal illness with expected survival of <6 months. The findings showed that overall TTD compared with PC does not improve survival and is associated with significantly higher incidence of fatigue, nausea/vomiting, mucositis, grade III/IV neuropathy, anaemia, leukopenia, neutropaenia, and myalgia leading to poor QOL.

Decisions to discontinue with TTD and focus on PC are accompanied by an assessment that such treatments would be ineffective, potentially harmful or medically futile.² Therefore, for patients and physicians our systematic review provides a long-awaited empirical answer on benefits and harms associated with TTD compared with PC. Based on research synthesis of all available randomised evidence, we found that patients with terminal illness and their physicians can avoid the impulse to 'try anything or everything' in desire to potentially prolong survival due to uncertainty if TTD is superior to PC. We demonstrated that this is not the case, and, in fact, TTD is typically more toxic. Our results, therefore, can be used to facilitate shared decision-making in end of life

care setting, which is often difficult for physicians, patients and families. Our results may assist patients and physicians when making a decision on whether to continue or discontinue TTD and make an informed choice between TTD versus PC. Given that unrealistic patient and physician expectations are key barriers to improving the quality of end-of-life care,³¹ providing reliable evidence to 'serve as a neutral arbiter',³² our results may help assure patients, physicians and family members that focus on PC and hospice referral may not compromise the patient life expectancy but, in fact, result in higher quality of end-of-life care. If acted on, our findings may help improve referral to hospice; as stated above, over 16% of patients with cancer who die in hospice care are in hospice for <3 days while many do not receive hospice care at all.^{33 34} Similarly, our results may minimise unnecessary suffering as many patients with a terminal prognosis receive chemotherapy in the last month of life.³⁵ Therefore, the findings from our systematic review may inform the referral to hospice for patients with terminal illness and avoid the late referrals to hospice; early referrals to hospice can help patients enjoy the full benefits of hospice care, more fulfilling remaining days of their lives while avoiding toxicity of unnecessary treatment. For policymakers, the evidence from this systematic review should promote a discussion on reimbursement practices where providers are more likely to be reimbursed for shared conversations with patients instead of administering aggressive therapy.³⁶

Our study has several limitations, mainly due to selective outcome reporting and methodological quality of the primary studies eligible for this analysis. For example, of the 10 RCTs that met the inclusion criteria only 7 (eight comparisons) reported survival as an outcome, which is surprising, given that life expectancy is the most important outcome for patients with terminal illness.³⁷ Additionally, QOL was also measured and reported in only 4 of the 10 studies; these studies used different QOL measures making comparisons more difficult. However, despite selective reporting in individual studies, these findings represent the totality of the currently available evidence. The overall methodological quality of included studies ranged from moderate to low, which can be attributed to lack of allocation concealment and blinding. Whether, the lack of allocation concealment is an artefact of reporting or conduct³⁸ could not be determined since study protocols were not available. Regarding the lack of blinding, we believe this issue is not a major concern because survival was the main outcome for our study; mortality is an objective outcome and blinding is important in cases where the outcome is subjective.

In summary, our systematic review of available RCTs in patients with terminal illness shows that TTD compared with PC does not impact survival and is associated with increased toxicity. The results provide assurance to physicians, patients, and family that the patients with estimated survival of <6 months would be better off by

Table 2 Evidence table for TTD versus PC alone in terminally ill adults GRADE evidence profile

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)†	Number of participants (studies)	Quality of the evidence (GRADE)
	Risk with PC	Risk with TTD			
Overall mortality (OS)	500 per 1000	445 per 1000 (389 to 507)	HR 0.85 (0.71 to 1.02)	1158 (7 RCTs)	⊕⊕⊕⊕ moderate ¹
TRM	Study population 22 per 1000	20 per 1000 (7 to 61)	RR 0.92 (0.31 to 2.76)	668 (2 RCTs)	⊕⊕⊕⊕ moderate ²
Fatigue (grade 3/4)	Study population 212 per 1000	286 per 1000 (222 to 364)	RR 1.35 (1.05 to 1.72)	813 (3 RCTs)	⊕⊕⊕⊕ moderate ²
Nausea/vomiting (grade 3/4)	Study population 12 per 1000	42 per 1000 (14 to 124)	RR 3.58 (1.22 to 10.54)	813 (3 RCTs)	⊕⊕⊕⊕ low ²³
Mucositis/stomatitis (grade 3/4)	Study population 0 per 1000	0 per 1000 (0 to 0)	RR 3.57 (0.42 to 30.68)	527 (2 RCTs)	⊕⊕⊕⊕ low ²³
Abdominal pain (grade 3/4)	Study population 76 per 1000	60 per 1000 (33 to 108)	RR 0.78 (0.43 to 1.41)	656 (2 RCTs)	⊕⊕⊕⊕ moderate ²
Neuropathy (grade 3/4)	Study population 0 per 1000	0 per 1000 (0 to 0)	RR 5.42 (0.68 to 43.04)	527 (2 RCTs)	⊕⊕⊕⊕ low ²³
Anaemia (grade 3/4)	Study population 41 per 1000	92 per 1000 (51 to 163)	RR 2.23 (1.25 to 3.97)	813 (3 RCTs)	⊕⊕⊕⊕ moderate ²
Leukopenia (grade 3/4)	Study population 0 per 1000	0 per 1000 (0 to 0)	RR 13.32 (1.75 to 101.24)	443 (2 RCTs)	⊕⊕⊕⊕ low ²³
Neutropaenia (grade 3/4)	Study population 5 per 1000	287 per 1000 (58 to 1000)	RR 56.02 (11.32 to 277.30)	527 (2 RCTs)	⊕⊕⊕⊕ low ²³
Myalgia (grade 3/4)	Study population 15 per 1000	91 per 1000 (30 to 271)	RR 5.89 (1.97 to 17.61)	527 (2 RCTs)	⊕⊕⊕⊕ low ²³
QOL	<ul style="list-style-type: none"> ► One study reported positive change in the global health status score on TTD and continuous decrement on PC. ► Second study reported significantly better QOL on TTD compared with PC at baseline (p value=0.028) which was reversed by the end of the study (p=0.0003). ► A third study reported a significant improvement in performance status among 29% (7/24 patients) of patients in TTD arm and in none of the patients in the PC arm (p<0.01). ► A fourth study reported improvement only in the functional activity subscore that favoured TTD vs PC; there was no significant difference in other QOL subscales. 			(4 RCTs)	⊕⊕⊕⊕ moderate ²

GRADE Working Group grades of evidence High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. High heterogeneity between studies.

2. Majority of studies not reporting data on outcome.

3. Wide CIs.

Any text which is either bold or in grey shading represents the risk associated with TTD.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†<1: Poorer results with PC; >1: poorer results with TTD; 1=no difference between effects of PC and TTD.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; OS, overall survival; PC, palliative care; QOL, quality of life; RCTs, randomised controlled trials; RR, risk ratio; TRM, treatment-related mortality; TTD, treatment targeted at underlying disease.

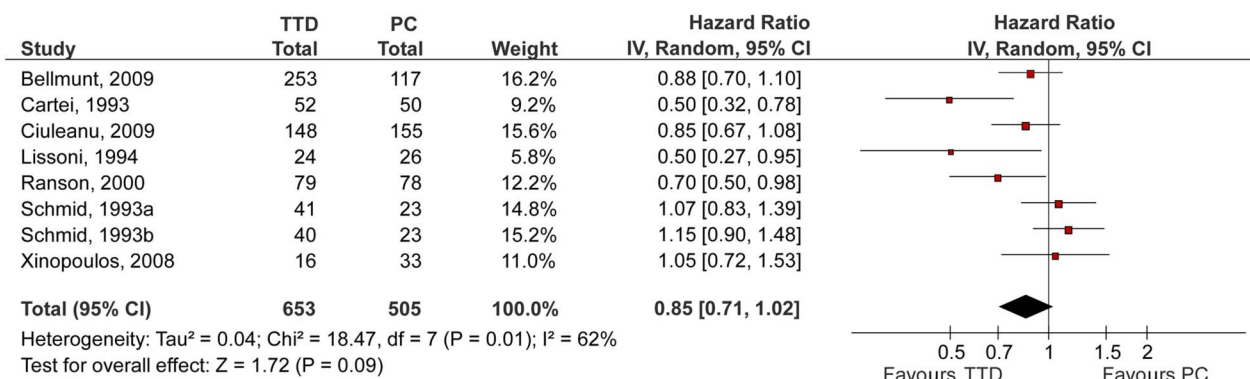


Figure 3 Forest plot for overall survival. The summary estimate (HR) from individual studies is indicated by rectangles with lines representing the 95% CIs. The summary pooled estimate from all studies is represented by the diamond and the stretch of the diamond indicates the corresponding 95% CI. Summary estimates that fall to the left of the line ($HR < 1$) indicate favourable survival on the treatment targeted at underlying disease (TTD) arm. Summary estimates that fall to the right of the line ($HR > 1$) indicate favourable survival on the palliative care (PC) arm.

referral to hospice. Whether new drugs with potentially life prolonging potential and safer toxicity profile will challenge these findings can only be determined in future well designed RCTs with adequate power. The average sample size in included studies was 124, which provides 15% power to detect a 15% survival difference (HR of 0.85 observed in this meta-analysis). To detect a 15% survival difference with 80% power and a 0.05 level of significance, a sample size of 1194 patients is needed. In the mean time, the physicians should be judicious in actively treating patients whose estimated survival is <6 months and provide information on benefits and risks associated with TTD versus PC to facilitate shared decision-making.

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Contributors TR, AK and BD contributed to the study concept and design. TR, AK and FAK performed the data abstraction, analysis and interpretation. TR and AK participated in the drafting of the manuscript. TR, AK, FAK and BD performed the critical revision of the manuscript for important intellectual content. TR performed the statistical analysis. BD obtained funding. "TR and FAK were responsible for procurement of full text of all articles for data abstraction, printing of data abstraction forms and entering of data for analysis." AK and BD were involved in the study supervision. TR, AK, FAK and BD approved final version of the manuscript for submission.

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Competing interests None declared.

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