



Early Integrated Palliative Care Alongside Curative-Intent Chemotherapy: A Narrative Review of Timing, Symptom Burden and What Families Say Afterwards

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Abstract

Palliative care alongside cancer treatment improves quality of life, reduces depression, and in the landmark trial was associated with living longer. The obstacle to using it earlier is not the evidence but the word, which patients and clinicians alike hear as an announcement that treatment has stopped working.

Objectives: *To review the published evidence on early integrated palliative care delivered alongside active cancer treatment: what it changes, when it should begin, what families report afterwards, and how far the evidence extends beyond advanced disease.*

Material and Methods: *Narrative review of randomised and cluster-randomised trials, meta-analyses, society guidance and bereaved-caregiver studies indexed in PubMed and the major oncology and palliative medicine journals. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *In the landmark randomised trial of 151 patients with newly diagnosed metastatic non-small-cell lung cancer, early palliative care integrated with standard oncology improved quality of life at 12 weeks (mean FACT-L 98.0 against 91.5, $p = 0.03$), reduced depressive symptoms (16 against 38 per cent, $p = 0.01$), reduced aggressive care at the end of life (33 against 54 per cent, $p = 0.05$), and was associated with longer median survival (11.6 against 8.9 months, $p = 0.02$). Later cluster-randomised and multicentre trials reproduced the quality-of-life findings without consistently reproducing the survival difference.*

Conclusion: *The evidence supports early referral in advanced cancer and is strong enough to have changed guidelines. It does not extend to patients receiving treatment with curative intent, where no randomised trial has been conducted, and the survival finding in particular has not replicated reliably and should not be used as the reason for referral.*

Abbreviations: ECOG – Eastern Cooperative Oncology Group, ESAS – Edmonton Symptom Assessment System, FACT-L – Functional Assessment of Cancer Therapy - Lung, HADS – Hospital Anxiety and Depression Scale, NSCLC – Non-Small-Cell Lung Cancer, QOL – Quality of Life.

Keywords: Early Palliative Care; Integrated Oncology; Quality of Life; Caregiver Outcomes; Timing of Referral

Introduction

Palliative care was historically what happened when oncology stopped. That sequencing was never justified by evidence, and it produced a familiar pattern: referral in the final weeks, symptom burden addressed too late to matter, and a conversation about goals held when the patient was too unwell to participate in it [1,2]. Patients' understanding of their own prognosis shifts when palliative input begins early [29], and qualitative work describes what those consultations contain [30,31].

The alternative proposition is that specialist palliative input should run alongside cancer treatment from diagnosis, addressing symptoms, coping and understanding of prognosis while treatment continues [3,4]. This was tested formally in 2010, and the result was more striking than its proponents had predicted [5].

Society guidance now recommends early referral in advanced cancer [6,7,8]. Uptake remains inconsistent, and the barriers documented are as much linguistic as structural: the word itself is understood by patients, families and referring clinicians as signalling that active treatment has been abandoned [9,10,11]. This review sets out what the evidence establishes, and where it stops.

Material and Methods

Search strategy: PubMed and the archives of the major oncology, palliative medicine and general medical journals were searched for studies of palliative care delivered concurrently with cancer treatment. Search terms combined early palliative care, integrated palliative care and supportive care with randomised, quality of life, timing of referral, caregiver and bereavement. Reference lists of society guidance [6,7,8] were screened by hand for primary sources.

Eligibility: Studies were included if they compared early or integrated palliative care with usual oncological care, measured patient or caregiver outcomes with such models, or documented barriers to referral. Observational studies of end-of-life care intensity are cited for context and identified as such.

Data extraction and handling: Design, sample size, tumour type, disease stage, timing of the intervention and reported outcome were extracted as published. Disease stage and treatment intent are reported alongside every result, because the evidence base is almost entirely in advanced disease and the distinction is central to what can be claimed. No pooling or re-analysis was performed. Figures 1 to 4 and Tables 1 and 2 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The landmark trial: One hundred and fifty-one ambulatory patients with newly diagnosed metastatic non-small-cell lung

cancer were randomised to early palliative care integrated with standard oncological care, or to standard care alone. Twenty-seven died by 12 weeks and 107 of the remainder completed assessments. Quality of life at 12 weeks was better in the intervention group, with a mean FACT-L score of 98.0 against 91.5 ($p = 0.03$) (Figure 1) [5].

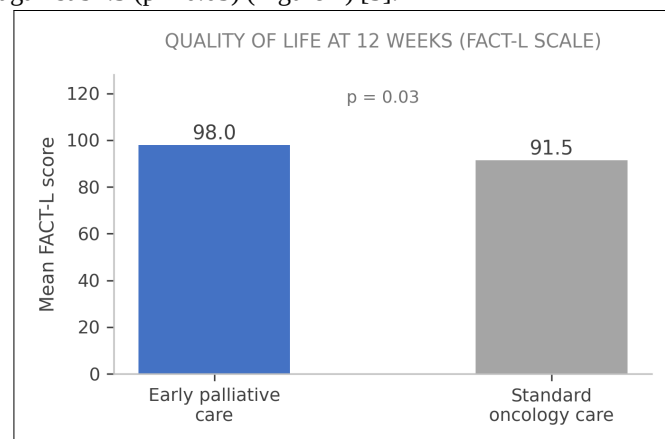


Figure 1: Quality of life at 12 weeks on the FACT-L scale, early palliative care against standard oncological care [5]

Mood and end-of-life care: Depressive symptoms were reported by 16 per cent of the intervention group against 38 per cent of the standard care group ($p = 0.01$), and aggressive care at the end of life, defined as chemotherapy within 14 days of death, no hospice care, or hospice admission within three days of death, occurred in 33 against 54 per cent ($p = 0.05$) (Figure 2) [5]. Patients receiving early palliative care also received less chemotherapy, made fewer emergency department visits and were more likely to die at home [12].

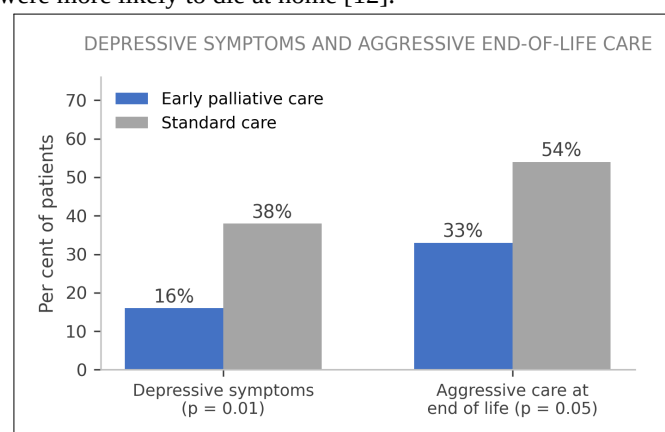


Figure 2: Depressive symptoms and aggressive care at the end of life in the landmark trial [5]

The survival finding: Median survival was 11.6 months (95% CI 6.4 to 16.9) in the early palliative care group against 8.9 months (6.3 to 11.4) with standard care ($p = 0.02$), and group assignment remained a significant predictor after adjustment for age, sex and performance status, with a hazard ratio for death of 1.70 in the standard care group (Figure 3) [5]. This is the finding that made the trial famous, and it is also the one that has proved least reproducible.

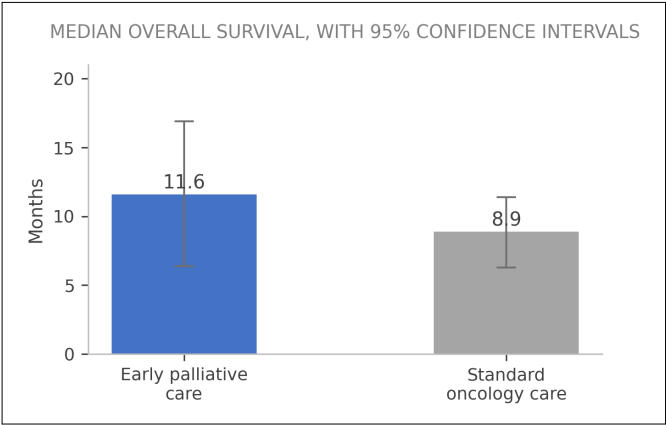


Figure 3: Median overall survival with 95% confidence intervals in the landmark trial [5]

What replicated: A cluster-randomised trial across 24 oncology clinics found improved quality of life and satisfaction with care at three months [13]. A trial of concurrent oncology palliative care in advanced cancer reported improved quality of life and mood [14,15], and a multicentre trial of early integration in advanced cancer reported improvements in patient-reported outcomes [16], as did European trials of systematic early integration [32,33]. Meta-analyses find consistent benefit for quality of life and symptom burden, and inconsistent or absent effect on survival [17,18,34]. The quality-of-life finding is the robust one.

Study	Design and cohort	Principal reported finding
Temel et al. 2010 [5]	RCT, 151 patients, metastatic NSCLC	QOL 98.0 vs 91.5; depression 16% vs 38%; survival 11.6 vs 8.9 months
Greer et al. 2012 [12]	Secondary analysis of the same trial	Less chemotherapy near death; more likely to die at home
Zimmermann et al. 2014 [13]	Cluster RCT, 24 oncology clinics	Improved quality of life and satisfaction at 3 months
Bakitas et al. 2015 [15]	ENABLE III, early vs delayed referral	Compared timing directly; survival difference at one year
Temel et al. 2017 [16]	RCT, advanced lung and gastrointestinal cancer	Improved patient-reported outcomes with early integration
Kavalieratos et al. 2016 [17]	Systematic review and meta-analysis	Consistent QOL and symptom benefit; survival evidence weak
Ferrell et al. 2017 [6]	ASCO clinical practice guideline update	Recommends early referral in advanced cancer

Table 1: Principal studies reviewed, with the finding as reported by the original investigators

Does timing matter within advanced disease: The ENABLE III trial addressed this directly, randomising patients with advanced cancer to palliative care initiated immediately or three months later. Patient-reported outcomes did not differ substantially between the arms, while one-year survival favoured the earlier group [15]. That pattern, an effect on survival without a corresponding difference in the measured patient-reported outcomes, is difficult to explain mechanistically and should be treated cautiously.

What families report: Caregiver outcomes are measured less often than patient outcomes but point consistently in one direction. Bereaved caregivers of patients who received early palliative care report lower depression scores and better quality of life [19,20], and caregiver burden and distress are reduced when symptom management and prognostic communication occur earlier [21,22]. Observational work links aggressive treatment in the final weeks with worse bereavement outcomes in the family, independently of the patient's own experience [23,24]. Since aggressive end-of-life care is exactly what early referral reduces, this is a plausible pathway by which the intervention reaches people who were never the patient.

Why referral is late: The obstacles are documented and mostly not logistical. Oncologists report reluctance to raise palliative care for fear of removing hope or implying that treatment has failed [9,10]. Patients and families associate the term with imminent death, and services renamed supportive care receive earlier referrals than identical services that were not renamed [11,25]. Availability is genuinely constrained in many centres [26,27], but attitudinal barriers appear at least as important as capacity.

Outcome	Evidence status	Basis
Quality of life	Robust; replicated	Multiple RCTs and meta-analysis [5,13,16,17]
Depressive symptoms	Well supported	16% vs 38% in the landmark trial [5]
Aggressive care at end of life	Well supported	33% vs 54%; less chemotherapy near death [5,12]
Overall survival	Not reliably replicated	Significant in one trial; inconsistent since [5,17,18]
Caregiver and bereavement outcomes	Supported, less studied	Lower depression in bereaved caregivers [19,20]
Benefit in curative-intent treatment	Untested	No randomised trial in this population

Table 2: Outcomes attributed to early palliative care and the evidential status of each

Discussion

Three claims are commonly made for early palliative care, and they have very different evidential standing. That it improves quality of life and mood is established, replicated and the reason it belongs in guidelines [5,13,16,17]. That it reduces aggressive treatment at the end of life is well supported and, on the caregiver data, may be where much of the benefit to families originates [12,23]. That it makes people live longer rests principally on one trial of 151 patients [5].

The survival finding deserves specific handling because it is the one most often quoted. It was statistically significant, it survived adjustment, and it is biologically plausible through several routes: less toxic treatment near death, better symptom control, earlier recognition of complications. It has nonetheless not replicated consistently, and meta-analyses find the survival

evidence weak while the quality-of-life evidence holds [17,18]. Using it as the argument for referral is unwise. If a subsequent trial reports no survival difference, an oncologist who referred on that basis has lost their rationale, when the rationale that actually holds was never survival.

The more significant limitation for this article's question is one of population. The entire randomised evidence base concerns advanced, incurable disease. The landmark trial enrolled patients with newly diagnosed metastatic disease; subsequent trials enrolled advanced lung, gastrointestinal and mixed cancers [5,13,16]. Not one randomised trial has tested integrated palliative care alongside treatment given with curative intent (Figure 4). Patients receiving curative-intent chemoradiotherapy for head and neck, oesophageal or haematological malignancy carry symptom burdens comparable to those in the trials, and the argument that they would benefit is reasonable, and timing of referral is known to shape the quality of care received at the end of life [35]. It is an argument by extrapolation, and it should be labelled as one.

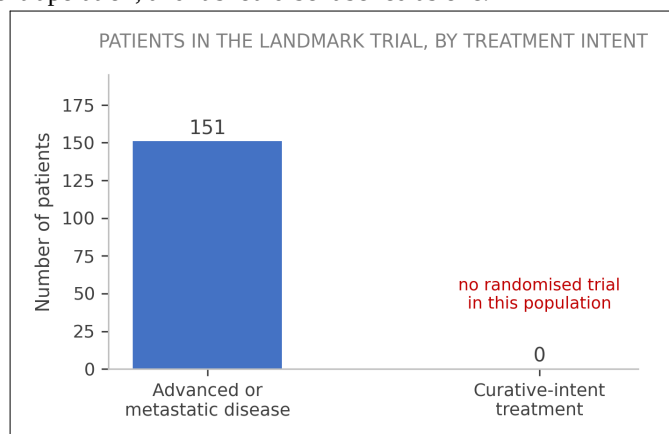


Figure 4: Patients randomised in the landmark trial by treatment intent, illustrating the gap in the evidence base [5]

There is also a specific risk in that extrapolation. In advanced disease, referral carries an implicit prognostic message that is, however unwelcome, accurate. In curative-intent treatment the same referral carries a message that is not accurate, and patients may reasonably infer that their clinicians have privately concluded the treatment will fail [9,11]. Services that address this by renaming, or by embedding symptom support within the oncology clinic rather than referring outward, appear to achieve earlier involvement [25,28].

Study limitations

The limitations belong to the underlying literature. The landmark trial randomised 151 patients at a single centre, in one tumour type, in an ambulatory and predominantly white population, and was not powered for survival [5]. Blinding is impossible in trials of a consultation, so patient-reported outcomes are vulnerable to expectation effects [13,17]. The intervention is heterogeneous between studies, ranging from monthly specialist visits to nurse-delivered telephone coaching,

which limits pooling [15,17]. Attrition is high and differential by definition in a dying population, and missing data handling varies. Caregiver outcomes are usually secondary and often collected only from those who consented to bereavement follow-up [19,20]. Comparator usual care differs substantially between health systems. And no randomised evidence exists for curative-intent populations, which is the principal gap [6,17].

Conclusion

Palliative care delivered alongside cancer treatment from the point of diagnosis improves quality of life and mood and reduces the intensity of treatment in the final weeks, and the family evidence suggests the benefit extends past the patient. Those findings are solid and should drive referral. The survival result from the landmark trial is the weakest part of the case and the part most often cited, which is the wrong way round. And the evidence stops at the boundary of incurable disease: for a patient receiving chemotherapy intended to cure them, integrating palliative care is a reasonable inference from adjacent evidence rather than a demonstrated benefit, and the conversation introducing it has to be handled with that in mind.

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Conflict of Interest

The authors declare no competing interests.

Ethics Statement

This article reviews previously published studies only. No new patient data were collected and no participants were recruited, so ethical approval was not required.

References

1. 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* 22(2004):315-321.
2. Hui D, Elsayem A, De la Cruz M, Berger A, Zhukovsky DS, Palla S, et al. "Availability and integration of palliative care at US cancer centers". *JAMA* 303(2010):1054-1061.
3. Meier DE, Beresford L. "Outpatient clinics are a new frontier for palliative care". *J Palliat Med* 11(2008):823-828.
4. Jacobsen J, Jackson V, Dahlin C, Greer J, Perez-Cruz P, Billings JA, et al. "Components of early outpatient palliative care consultation in patients with metastatic non-small cell

- lung cancer". *J Palliat Med* 14(2011):459-464.
5. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. "Early palliative care for patients with metastatic non-small-cell lung cancer". *N Engl J Med* 363(2010):733-742.
 6. Ferrell BR, Temel JS, Temin S, Alesi ER, Balboni TA, Basch EM, et al. "Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update". *J Clin Oncol* 35(2017):96-112.
 7. Jordan K, Aapro M, Kaasa S, Ripamonti CI, Scotte F, Strasser F, et al. "European Society for Medical Oncology (ESMO) position paper on supportive and palliative care". *Ann Oncol* 29(2018):36-43.
 8. Kaasa S, Loge JH, Aapro M, Albreht T, Anderson R, Bruera E, et al. "Integration of oncology and palliative care: a Lancet Oncology Commission". *Lancet Oncol* 19(2018):e588-e653.
 9. Schenker Y, Crowley-Matoka M, Dohan D, Rabow MW, Smith CB, White DB, et al. "Oncologist factors that influence referrals to subspecialty palliative care clinics". *J Oncol Pract* 10(2014):e37-e44.
 10. Hui D, Cerana MA, Park M, Hess K, Bruera E. "Impact of oncologists' attitudes toward end-of-life care on patients' access to palliative care". *Oncologist* 21(2016):1149-1155.
 11. Zimmermann C, Swami N, Krzyzanowska M, Leighl N, Rydall A, Rodin G, et al. "Perceptions of palliative care among patients with advanced cancer and their caregivers". *CMAJ* 188(2016):e217-e227.
 12. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, 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* 30(2012):394-400.
 13. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. "Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial". *Lancet* 383(2014):1721-1730.
 14. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, et al. "Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial". *JAMA* 302(2009):741-749.
 15. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, 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* 33(2015):1438-1445.
 16. Temel JS, Greer JA, El-Jawahri A, Pirl WF, Park ER, Jackson VA, et al. "Effects of early integrated palliative care in patients with lung and GI cancer: a randomized clinical trial". *J Clin Oncol* 35(2017):834-841.
 17. Kavalieratos D, Corbelli J, Zhang D, Dionne-Odom JN, Ernecoff NC, Hanmer J, et al. "Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis". *JAMA* 316(2016):2104-2114.
 18. Haun MW, Estel S, Rucker G, Friederich HC, Villalobos M, Thomas M, et al. "Early palliative care for adults with advanced cancer". *Cochrane Database Syst Rev* 6(2017):CD011129.
 19. El-Jawahri A, Greer JA, Pirl WF, Park ER, Jackson VA, Back AL, et al. "Effects of early integrated palliative care on caregivers of patients with lung and gastrointestinal cancer: a randomized clinical trial". *Oncologist* 22(2017):1528-1534.
 20. McDonald J, Swami N, Hannon B, Lo C, Pope A, Oza A, et al. "Impact of early palliative care on caregivers of patients with advanced cancer: cluster randomised trial". *Ann Oncol* 28(2017):163-168.
 21. Dionne-Odom JN, Azuero A, Lyons KD, Hull JG, Tosteson T, Li Z, et al. "Benefits of early versus delayed palliative care to informal family caregivers of patients with advanced cancer: outcomes from the ENABLE III randomized controlled trial". *J Clin Oncol* 33(2015):1446-1452.
 22. Higginson IJ, Evans CJ. "What is the evidence that palliative care teams improve outcomes for cancer patients and their families?". *Cancer J* 16(2010):423-435.
 23. Wright AA, Zhang B, Ray A, Mack JW, Trice E, Balboni T, et al. "Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment". *JAMA* 300(2008):1665-1673.
 24. Wright AA, Keating NL, Balboni TA, Matulonis UA, Block SD, Prigerson HG. "Place of death: correlations with quality of life of patients with cancer and predictors of bereaved caregivers' mental health". *J Clin Oncol* 28(2010):4457-4464.
 25. Dalal S, Palla S, Hui D, Nguyen L, Chacko R, Li Z, et al. "Association between a name change from palliative to supportive care and the timing of patient referrals at a comprehensive cancer center". *Oncologist* 16(2011):105-111.
 26. Hui D, Bruera E. "Integrating palliative care into the trajectory of cancer care". *Nat Rev Clin Oncol* 13(2016):159-171.
 27. Rocque GB, Cleary JF. "Palliative care reduces morbidity and mortality in cancer". *Nat Rev Clin Oncol*

- 10(2013):80-89.
28. Hui D, Hannon BL, Zimmermann C, Bruera E. "Improving patient and caregiver outcomes in oncology: team-based, timely, and targeted palliative care". *CA Cancer J Clin* 68(2018):356-376.
 29. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, et al. "Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of early palliative care". *J Clin Oncol* 29(2011):2319-2326.
 30. Yoong J, Park ER, Greer JA, Jackson VA, Gallagher ER, Pirl WF, et al. "Early palliative care in advanced lung cancer: a qualitative study". *JAMA Intern Med* 173(2013):283-290.
 31. Greer JA, Jackson VA, Meier DE, Temel JS. "Early integration of palliative care services with standard oncology care for patients with advanced cancer". *CA Cancer J Clin* 63(2013):349-363.
 32. Vanbutsele G, Pardon K, Van Belle S, Surmont V, De Laat M, Colman R, et al. "Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial". *Lancet Oncol* 19(2018):394-404.
 33. Maltoni M, Scarpi E, Dall'Agata M, Zagonel V, Berte R, Ferrari D, et al. "Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial". *Eur J Cancer* 63(2016):1339-1347.
 34. Hoerger M, Wayser GR, Schwing G, Suzuki A, Perry LM. "Impact of interdisciplinary outpatient specialty palliative care on survival and quality of life in adults with advanced cancer: a meta-analysis of randomized controlled trials". *Ann Behav Med* 53(2019):674-685.
 35. Hui D, Kim SH, Roquemoire 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* 120(2014):1743-1749.

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