Guideline Resource Unit
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Literature Review: Early Palliative Care in Advanced Cancer

Tumour Team: Supportive Care

Alberta Health Services

Literature Review SUPP-023
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Research Questions:

- What are the advanced cancer criteria and triggers for diagnosis?
- What is the mortality associated with the criteria?
- What are the indicators for Palliative Care?
- Documentation/recommendations in national/international guidelines

Table 1: Summary of Existing Guideline Recommendations for Early Palliative Care in Advanced Cancer

Guideline author, year	Recommendations
ASCO 2017	**Advanced cancer definition:** Patients with distant metastases, late-stage disease, cancer that is life limiting, and/or with prognosis of 6 to 24 months **Recommendations:** • Patients should be referred to interdisciplinary PC teams for consultation. These teams should provide inpatient and outpatient care early in the course of disease, along side active treatment of their cancer (*type: evidence based, benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong*) • PC should be delivered through interdisciplinary PC teams, with consultation available in both outpatients and inpatient settings. (*type: evidence based, benefits outweigh harms; evidence quality intermediate; strength of recommendation: moderate*) • PC services may include a referral to a PC provider. Essential components of PC: rapport and relationship building with patient and family caregivers; symptoms, distress, and functional status management (pain, dyspnea, fatigue, sleep disturbance, mood and nausea or constipation); exploration of understanding and education about illness and prognosis; clarification of treatment goals; assessment and support of coping needs (provision of dignity therapy); assistance with medical decision making; coordination with other care providers; and provision of referrals to other care providers as indicated. (*type: informal consensus; evidence quality: intermediate; strength of recommendation: moderate*). • Patients with high symptom burden and/or unmet physical or psychosocial needs, outpatient programs of cancer care should provide and use dedicated resources (PC clinicians) to deliver PC services to complement existing program tools. (*type: informal consensus, benefit outweigh harms; evidence quality: intermediate; strength or recommendation: moderate*) • Patients with early or advanced cancer for whom family caregivers will provide care in outpatient, home, or community settings, nurses, social workers, or other providers may initiate caregivers-tailored PC support, which could include telephone coaching, education, referrals, and face-to- face meetings. For family caregivers who may live in rural areas and/or are unable to travel to clinic and/por longer distances, telephone support may be offered (*type: evidence based; evidence quality; low; strength of recommendations: weak*)

	• Patients with new cancer diagnosis should receive early PC: within 8 wks of diagnosis (*type: informal consensus evidence quality: intermediate strength of recommendation: moderate*)
BCCA 2017	**Intended Patients:** Adult patients aged ≥ 19 years with incurable cancer and end stage chronic disease of many types and their families **Recommendations:** • Identify patients who would benefit from PC early in the illness trajectory: a palliative approach addresses the need for pain and symptom management, as well as psychosocial and spiritual support of patients and their families, beginning in disease management through to survivorship or EOL care. • Encourage patients to have an advance care planning discussion with family and caregivers. • Establish goals of care with the patient and families/caregivers. • Before ordering investigations, ensure that the results will change management to improve QOL and/or prognostication, consistent with the patient's goals of care • Organize care coordination around key illness transitions.

NCCN 2020	• PC can begin at diagnosis; be delivered concurrently with disease-directed, life-prolonging therapies; and facilitate patient autonomy, access to information and choice.
	• PC should be provided by primary oncology team and augmented as needed by collaboration with an interdisciplinary team of PC experts
	• All cancer patients should be screened for PC needs at their initial visit, at appropriate intervals and as clinically indicated
	PC indications:
	• ≥ 1of the following:
	  • uncontrolled symptoms
	  • moderate-to- severe distress related to cancer diagnosis and cancer therapy
	  • serious comorbid physical and psychosocial conditions
	  • complex psychosocial needs
	  • poor prognosis awareness
	  • potentially life-limiting disease
	  • metastatic solid tumours and refractory hematologic malignancies
	  • PC for all patients undergoing stem cell transplant
	  • patient/family/caregiver concerns about course of disease and decision-making
	  • patient/family/caregiver requests for PC
	  • patient request for hastened death
	Assessment:
	• Benefits/burdens of anticancer therapy→ natural history of specific tumor, potential for response to further treatment, potential for treatment-related toxicities, patient's understanding

	of disease prognosis, hopes for and understanding of anticancer therapy, impairment of vital organs, performance status, serious comorbid conditions • financial toxicity • decision-making capacity • coping strategies • personal goals/values /expectations→ shared decision-making with patient/family/caregivers, advance care planning, hopes for and understanding of anticancer therapy, QOL • symptoms • psychosocial or spiritual distress→ depression/anxiety, spiritual or existential needs, social support challenges or concerns (home, family, financial toxicity, community), resource needs • educational and informational needs → patient/family/caregiver values and preferences about information and communication, patients/family/caregivers perceptions of disease status • cultural factors affecting care • criteria for consultation with PC specialist PC interventions • anticancer therapy • appropriate treatment of comorbid physical and psychosocial conditions • coordination of care with other health care providers • symptom management • advance care planning • psychosocial and spiritual support • culturally appropriate care • resource management/ social support • consultation with PC specialist • hospice referral • response to request to withdraw or withhold life-sustaining treatment • response to requests for hastened death (physician assisted dying) • care of imminently dying hospitalized patient • palliative sedation After Death interventions: • Family caregivers: immediate after-death care, bereavement support, cancer risk assessment and modification • Health care team: general support (debriefing ect.) Criteria for consultation with PC specialist • Limited anticancer treatment options due to: limited success to anticancer treatment, advanced disease process, multiple and/or sever comorbid conditions, rapidly progressive functional decline or persistently poor performance status

	• decision-making capacity • need for clarification of goals of care • resistance to engage in advance care planning • high risk or poor pain management or pain that remains resistant to conventional interventions (eg: neuropathic pain, incident or breakthrough pain, pain with severe associated psychosocial and/or family distress, rapid escalation of opioid dose, multiple drug “allergies” or a history of multiple adverse reactions to pain and symptom management interventions, concerns regarding substance use disorder) • high non-pain symptom burden, especially those resistant to conventional management • high distress score (>4) • need for invasive procedures (palliative stenting or venting gastrostomy) • Frequent emergency department visits or hospital admissions • need for ICU-level care (especially involving multiorgan system failure or prolonged support) • communications barriers (language, literacy, physical barriers, cognitive impairment) • request for hastened death

EOL, end of life; ICU, intensive care unit; PC, palliative care; QOL, quality of life.

Table 2: Published literature on early palliative care for advanced cancer patients

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
Brain mets					
Habibi, A. 2018	Retrospective Review ***(Level IV)***	EPC (w/in 8 wks of diagnosis) vs late PC (after 8 wks) **PC:** inpatient or outpatient settings with an attending physician board certified in hospice and palliative medicine or nurse practitioner (NP) working in conjunction with an attending physician	Pts with newly diagnosed brain mets, n=92 Early PC, n=46 Late PC, n=46 **Referral Process:** diagnosis of a stage IV malignancy and ≥ 1 of the following conditions: (1) ICU admission of >3 days, (2) at pt or family request for health-care decision-making assistance, (3) unresolved pain by current treatment plan, (4) consideration for long-term tracheostomy or enteral feeding tube, (5) multiple readmissions, and/or (6) prognosis < 6 months.	**Early vs late:** • Inpatient visits per patient: 1.5 vs 2.9; p=0.004 • ED visits: 1.2 vs 2.1; p=0.005 • PET/ CT studies: 1.2 vs 2.7; p=0.005 • MRI scans**:** 5.8 vs 8.1; p=0.03 • Radiosurgery procedures**:** 0.6 vs 1.3; p<0.001 • OS (med): 8.2 vs 11.2 months; p=0.2 • Discharged home after inpatient admission: 59% vs 35%; p=0.04	Timely PC consultations are advisable in this patient population and can reduce health-care utilization
Gastrointestinal Cancers					
Maltoni, M. 2016	Multicenter RCT ***(Level I)***	Systematic vs on-demand EPC **Systematic:** Pts met a member of the PC team w/in 2 wks of enrolment and were seen thereafter q 2-4 wks until death	Metastatic or locally advanced inoperable pancreatic cancer; ECOG 0-2; life expectancy >2 months; and candidate for antitumoural treatment n=186 On demand EPC, n=97 Systematic EPC, n=89	• Changes in TOI and HCS score between baseline and 12 wks (± 3wks) were -4.47 and -0.63, with a different b/t groups of 3.83 (95% CI 0.10-7.57; p=0.041) and -2.23 and 0.28 (difference b/t groups of 2.51, 95% CI 0.40-4.61, p=0.013), in favour of systematic group. • QOL scores at 12wks (±3wks) of TOI scale and HCS were 84.4 vs 78.1 (p=0.022) and 52.0 vs 48.2 (p=0.008), respectively, for systematic vs on demand care • No difference in OS b/t treatment arms	Systematic EPC in advanced pancreatic cancer patients significantly improved QOL with respect to on-demand EPC.
Scarpi, E. 2018	Prospective multicenter RCT ***(Level I)***	Standard care + on-demand EPC (standard arm) vs Standard care + systematic EPC (intervention arm)	Newly diagnosed, inoperable, locally advanced, and/or metastatic gastric cancer, ECOG 0-2, prognosis > 2 months n=186 Standard arm, n= 95	**Standard vs intervention:** • PC visits (mean): 0.53 (SD 1.14) vs 54.28 (SD 1.87); p<0.0001 • Δ TOI scores (mean): -1.30 (SD 20.01) vs 1.65 (SD 22.38); difference	Our results indicated a slight, albeit not significant, benefit from EPC. Findings on EPC studies may be underestimated in

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
		Intervention: Met w/ PC physician w/in 2 wks of enrollment. Pts seen q2-4wks until death	Intervention arm, n=91	between grps 2.95 (95% CI -4.43 to 10.32) p=0.430 • Δ GaCS score (mean): 0.91 (SD 14.14) vs 3.19 (SD 15.25); difference between groups 2.29 (95% CI-2.80 to 7.38) p=0.375 • NO difference in data regarding mood, HADS anxiety and depression subscales and family satisfaction with care. • OS (med): 9.9 mo (95% CI 8.4-11.5) vs 10.2 mo (95% CI 7.8-12.3) • OS (12 mo): 37.9% (95% CI 27.7-48.1) vs 41.3% (95% CI 31.0-51.7); p=0.657	the event of suboptimally managed issues: type of intervention, shared decision-making process between oncologists and PC physicians, risk of standard arm contamination, study duration, timeliness of assessment of primary outcomes, timeliness of cohort inception, and recruitment of patients with a significant symptom burden.
Schenker, Y. 2018	Mixed-methods pilot RCT ***(Level II)***	EPC + standard oncology care vs standard oncology care alone **EPC:** In-person PC visits with a specialty-trained PC physician in same building as oncology appointments and on the same day. Scheduled monthly for 1st 3 months then as needed.	Pathologically confirmed locally advanced or metastatic pancreatic adenocarcinoma pts with ECOG 0-2 patients and caregiver pairs, n=30	• 3-mo mortality rate was 13%. Patients attended a mean of 1.3 (SD 1.1) PC visits during the 3-mo period. • Positive experiences with PC included receiving emotional support and symptom management. • Negative experiences included inconvenience, long travel times, spending too much time at the cancer center, and no perceived PC needs. • Physicians suggested embedding PC within oncology clinics, tailoring services to patient needs, and facilitating face-to-face communication between oncologists and palliative physicians.	A randomized trial of EPC for advanced pancreatic cancer did not achieve feasibility goals. Integrating PC w/in oncology clinics may increase acceptability and perceived effectiveness.
Hematological Malignancies					
Freeman, A.T. 2018	Descriptive study ***(Level V)***	PC consultation, frequency, and components of	High risk leukemia diagnosis (acute leukemia occurring in any pt ≥ 65 years, or relapsed leukemia	• Reported pain in admission: 64% • Died w/in 3 mo of hospitalization: 22% • PC consultation: 24%	Despite a poor prognosis and high symptom burden, the frequency of PC

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		documented advance care planning (ACP)	occurring in any patient more than the age of 18), inpatient, n=50	• ACP: 24%	consultation and ACP documentation was low.
Porta-Sales, J. 2017	Retrospective study ***(Level IV)***	Outpatient-based EPC: clinic w/in the hematology clinic. Pts received consultation w/in 1 wk of referral after a screening call by PC nurse.	Patients diagnosed with MM or plasmocytoma who experienced any disease- or treatment-related symptoms or other comorbidities affecting well-being, n=67	• Follow-up: 11 months • Moderate-to-severe pain: deceased from 57% to 18% (p<0.0001) • Average pain: decreased 24% to 2% (p<0.0001) • No pain interference increase: physical activity (52% vs 82%; p=0.0001), sleep (73% vs 91%; p=0.01, and mood (52% vs 87.5%; p=0.0001) • Physical and emotional symptoms improved: depression (13% vs 5%; p=0.001) • OS: 86.6% alive after 11 months	These finings indicate that EPC is feasible in patients with multiple myeloma. Pain and other symptoms were well controlled
Lung Cancers					
Duggan, K.J. 2019	Retrospecti ve cohort ***(Level IV)***	PC and Psychosocial care (PSC) **PC:** Consult with a PC clinician or nurse and/or admission to public hospital or community-based nursing-led home **EPC:** w/in 8 wks of diagnosis **PSC:** receipt of care at any time after diagnosis from a social worker, psychology or psychiatry, specialist nursing coordinator and others like support groups, counselling, and pastoral care.	Newly diagnosed stage IV NSCLC, n=923	• Seen by PC: 83% • EPC (w/in 8 wks of diagnosis): 67% • PSC: 82% • RT treatment and residential area were associated with both PC and PSC • Increasing age was associated with EPC referral • OS (med): 4 mo • PC was associated with patient survival, but the effect carried over time.	The rate of PC and PSC in this population was high when compared with published data. Despite this, there were gaps in PC and PSC provision, notably with patients not receiving active treatment, and those receiving systemic therapy utilising these services less frequently. PSC and PC contact were not convincingly associated with improved patient survival.

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
Ferrell, B. 2015	Prospective, quasi-experimental study ***(Level III)***	Interdisciplinary PC vs usual care **PC:** personalized PC plan, pts discussed at wkly MDT meeting (MDT→ nurse, PC physicians, thoracic surgeons, oncologists, geriatric oncologist, pulmonologist, social worker, chaplain, dietitian, physical therapist), 4 educational sessions	Pathologically confirmed Stage I-IV NSCLC, n=491 Control, n=219 PC, n=272	**PC vs usual care:** • QOL: 109.1 vs. 101.4; p < 0.001 • Symptoms: 25.8 vs. 23.9; p < 0.001 • Spiritual well-being: 38.1 vs. 36.2; p= 0.001 • Psychological distress (@ 12 wks): 2.2 vs. 3.3; p < 0.001 • Completed advance care directives: 44% vs. 9%; p < 0.001 • Overall supportive care referrals: 61% vs. 28%; p < 0.001	Interdisciplinary PC in the ambulatory care setting resulted in significant improvements in QOL, symptoms, and distress for NSCLC patients
Goldwasser, F. 2018	Retrospective cohort study ***(Level IV)***	**PC:** Timely (91-31 days before death) Late (90-8 days before death) Very late (7-0 days before death) None or not reported	Metastatic lung cancer, n=64950	• Timely PC: 26.3% • Late PC: 31.5% • Very Late: 12.8% • Not reported: 29.4% • patients with timely PC had the earliest and most progressive decrease in the use of anticancer therapy • Use of invasive ventilation increase with a delay in PC needs	There is a clear association between the timing of PC needs reporting and the aggressiveness of care near the end of life.
Greer, J.A. 2016	Secondary analysis of RCT data ***(Level III)***	EPC integrated with standard oncology care vs standard care alone **EPC:** Board-certified PC physician or advanced practice nurse w/in 3 wks after enrollment, and monthly thereafter until death **Standard Care:** pts were able to access PC services upon request or at discretion of treating oncologist	Metastatic NSCLC, ECOG 0-2, n=138	• Early PC was associated with a lower mean total cost per day of $117 (p = 0.13) compared to SC. • In the final 30 days of life, patients in the early PC group incurred higher hospice care costs (mean difference = $1,053; p = 0.07), while expenses for ChT were less (mean difference = $757; p = 0.03). • Costs for ED visits and hospitalizations did not differ significantly between groups over the course of the study or at the EOL.	The delivery of early PC does not appear to increase overall medical care expenses for patients with metastatic NSCLC. Larger, sufficiently powered cost studies of early PC are needed.

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
King, J.D. 2016	Retrospective Study ***(Level IV)***	EPC vs standard care **EPC**: partially integrated PC w/in thoracic oncology clinic by 1 specially trained physician	Advanced lung cancer (stage IIIB and IV NSCLC and extensive stage small-cell lung cancer), n=207 Early PC, n=82	**Early PC vs usual care:** • OS: 11.9 mo vs 10.1 mo, adjusted HR= 0.72, p=0.032 • no difference in numbers of lines of ChT within last 14 and 30 d of life • Clinical trail participation: 29% vs 19%, adjusted OR=2.54, p=0.014 • Hospice Resource Utilization: no sig. difference (adjusted OR: 0.109, p=0.113) • Hospice length of stay: 38.5 d vs 24 d, adjusted HR=0.70, p=0.041	Early PC in advanced lung cancer was associated with a nearly 2-month OS advantage compared to standard care. This finding provides supportive evidence to previously published reports or survival benefit with early PC intervention.
Lafitte, C. 2018	Retrospective analysis ***(Level IV)***	Non-pharmacological Supportive Care in Cancer (**SCC**): intervention of a nurse for the home-hospital network coordination, as well as socio-aesthetics, psychomotricity, art-therapy, adapted physical activity, and establishment of at-home hospitalization	Pathological diagnosis of lung cancer – NSCLC or SCLC histology-, advanced (not eligible to RT) or metastatic stage, and at least one delivery of systemic anti-cancer treatment, including chemotherapy, targeted therapy, and/or immunotherapy, n=309	• OS (med): 11.2 mo • Unplanned hospitalizations: 89% • Hospital stay (med): 19 d • Unplanned hospitalizations mostly occurred w/in 3 mo of advanced cancer diagnosis or last 3 mo b/f death • Optimized SCC w/in 8 wks (med):88% • Intervention of nurse for in- and out-patient network coordination: 46% • Intervention of nurse for at-home hospitalization: 25% • OS med: SCC (11.8 mo) vs non-SCC (6.9 mo); p=0.270	This study provides landmark data to support an early integration of optimized SCC for patients with advanced lung cancer, that includes multimodal supportive care interventions along the course of the disease.
Lammers, A. 2018	Retrospective cohort study ***(Level IV)***	EPC vs no EPC **EPC:** At least 1 specialty PC encounter w/in 90 days of diagnosis	Stage IIIB or IV lung cancer, n=23566 EPC, n=5420	**EPC vs none:** • ChT: 34% vs 51% (AOR=0.55, 95% CI:0.51-0.58 • High-intensity ChT: >4 cycles of platinum-based doublet (AOR=0.68, 95% CI: 0.60-0.77), ≥3 lines of ChT (AOR=0.61, 95% CI:0.53-0.71), triplet therapy (AOR=0.68, 95% CI: 0.56-0.82), use of erlotinib prior to 2011 (AOR=0.66, 95% CI: 0.55-0.79)\	EPC was associated with reduced receipt of both any ChT and high-intensity ChT. However, receipt of ChT at the very EOL was increased among patients with EPC compared to those without.

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
				• ChT in the last 14 days: AOR=1.65, 95% CI: 1.44-1.87 • ChT in the last 30 days: AOR:1.67, 95% CI: 1.51-1.85	
Nieder, C. 2016	Retrospective single center study ***(Level IV)***	EPC (≥ 3months before death) vs (< 3 months before death) late PC	Histology confirmed, terminal NSCLC, n=286 EPC, n=22	• Patients who received early (8 %) or late (27 %) additional PC were significantly younger than those who did not receive additional PC. • The likelihood of active anticancer treatment in the last month of life was lowest in the early additional PC group, p=0.03. • Patients who received early or late additional PC were significantly less likely to lack a documented resuscitation preference, p=0.0001. • Patients who received early additional PC were significantly less likely to become hospitalized in the last 3 mo of life, p=0.003. • Place of death was also numerically different, with hospital death occurring in 33 % of patients who received early additional PC, as compared to 48% in the late and 50% in the no PC group, p=0.35. • Anticancer treatment intensity was not reduced if the PC contributed to the overall management.	Early additional palliative care resulted in relevant improvements. The optimal timing of this intervention should be examined prospectively.
Nipp, R.D. 2016	Secondary analysis of data from a RCT ***(Level III)***	EPC integrated with oncology care VS oncology care alone **EPC:** met with PC team member w/in 3 wks after enrollment and monthly until death	Newly diagnosed (w/in 8 wks), pathologically confirmed metastatic NSCLC, ECOG 0-2 n=107	• Follow up: 12 wks • younger patients receiving EPC reported better QOL (TOI mean 62.04 vs. 49.43, p=0.001) and lower rates of depression (HADS–Depression 4.0% vs. 52.4%, p=0.001; PHQ-9 0.0% vs. 28.6%, p= 0.006) than younger patients receiving oncology care alone.	Males and younger patients who received EPC had better QOL and mood than those who received oncology care alone. However, these outcomes did not differ significantly between treatment

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				• Males receiving EPC reported better QOL (TOI mean 58.81 vs. 48.30, p=0.001) and lower rates of depression (HADS–Depression 18.5% vs. 60.9%, p=0.002; PHQ-9 3.8% vs. 34.8%, p=0.008) than males receiving oncology care alone. • At 12 weeks, QOL and mood did not differ between study groups for females and older patients	groups for females or older patients.
Sun, V. 2015	2-group, prospective, sequential, quasi-experimental study ***(Level III)***	Interdisciplinary PC intervention vs usual care **PC:** Personal PC plan, weekly MDT meetings (w/out pts), FCG - 4 education sessions with self-care planning	Family caregivers (FCGs) of patients diagnosed with stage I through IV NSCLC, n=366 Usual care, n=157 PC, n=197	**PC vs Usual care:** • Social well being score: 5.84 vs 6.86; p<0.001 • Psychological distress scores: 4.61 vs 4.20; p=0.010) at 12 weeks • Caregiver burden: 13% vs 24%; p=0.008	An interdisciplinary approach to PC in lung cancer resulted in statistically significant improvements in FCG's social well being and psychological distress and in less caregiver burden.
Multiple cancer types					
Ahluwalia, S.C. 2015	Retrospective cohort study ***(Level IV)***	Early EOL planning vs no planning	Veterans with advanced cancer (Stage IV colorectal, lung or pancreatic cancer), n=665 Eligibility: stage IV cancer and (2) documentation that the veteran was alive >30 days after diagnosis with >1 hospitalization >2 days OR >2 Veterans affairs encounters of any type	• OS after diagnosis (mean): colorectal (12.2 months), lung (7.6 months), pancreatic (5.0 months) • EOL care planning in 1st month following diagnosis: 46.8% • patients with EOL care planning were significantly less likely to receive acute care at EOL (OR: 0.67; p=0.025) • OS (mean): early care planning (9.7 months) vs no early care planning (6.8 months); p<0.0001	Early care planning discussions are associated with lower rates of acute care use at the EOL in a system with already low rates of intensive EOL care.
Bakitas, M.A. 2015 ENABLE III	RCT ***(Level I)***	EPC (within 30-60 days of diagnosis, recurrence, or progression) vs delayed PC (3 months)	Advanced cancer: Lung (Stage IIIB or IV non-small cell, or extensive stage small cell), Breast (Stage IV with poor prognostic indicators including but not limited to: a) >2 cytotoxic regimens for MBC (b) diagnosis of MBC ≤ 12	**Early vs delayed:** • QOL 3 months after enrollment: • FACIT-Pal: 129.9; 95% CI, 126.6 to 133.3 vs 127.2; 95% CI, 124.1 to 130.3; p=0.34	Early-entry patient-reported outcomes and resource use were not statistically different; however, their survival 1-year

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		PC: initial in-person standardized outpatient PC consultation by a board-certified PC clinician and 6 structured wkly telephone coaching sessions by an advanced practice nurse. After that, monthly follow-up calls	months since completion of adjuvant or neoadjuvant treatment (c) triple negative disease (ER/PR - and Her 2-) (d) parenchymal brain mets and/or carcinomatous meningitis), GI (unresectable stage III or IV), GU (Stage IV; for prostate cancer inclusion is limited to persons with hormone refractory), Brain (unresectable, grade IV), Melanoma (stage IV), Hematologic (Leukemia - acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL): advanced stage, treatment refractory, poor prognosis cell type or chromosomal abnormalities, "older age" –Lymphoma: Stage IV or treatment refractory Hodgkin's disease or non-Hodgkin's lymphoma) Multiple Myeloma(elevated β2-microglobulin, albumin <3.5, PCLI >1%, CRP >6µg/mL, elevated LDH, plasmablastic morphology, abnormal. chromosome 13) and prognosis 6-24 months. Total n=207 **Early PC,** n=104 **Delayed PC,** n=103	• Symptom impact: 11.4; 95% CI, 10.8 to 12.1 vs 12.2; 95% CI, 11.6 to 12.8; p=0.09 • CES-D: 11.2; 95% CI, 9.7 to 12.7 vs 10.8; 95% CI, 9.5 to 12.1; p=0.33 • OS (1yr): 63% vs 48%; p=0.038 • OS (med): 18.3 months vs 11.8 months; p=0.18 • Estimated relative rate of ChT in last 2 wks of life: 1.57; 95% CI, 0.37-6.7; p=0.54	after enrollment was improved compared with delayed group.

Brims, F. 2018	Multicentre, randomised, non-blinded, parallel group-controlled trial
	
	(Level II)
		Early referral to specialist PC (w/in 3 wks) vs standard care
		PC: 1st consult w/in 3 wks of allocation, then q4wks for at least 24 wks until death or end of trial.
		Standard Care: At discretion of medical
			Histological or cytological confirmation of malignant pleural mesothelioma (MPM), ECOG 0–1, diagnosis of MPM received w/in the last 6 wks, n=174
			Early PC, n=87
			Control, n=87
			
			Carers, n=145: Early PC (n=73), control (n=72)
				Early vs control:
				• Follow-up (med): All 41.1 wks (IQR 25.1-61.9)
				• Patient reported outcomes:
				  • QOL (12 wks): 60.2 (SD 23.6) vs 59.5 (SD 21.2); p=0.59
				  • QOL (24 wks): 61.3 (SD 20.7) vs 63.7 (SD 19.8); p=0.54
					There is no role for routine referral to PC soon after diagnosis of MPM for patients who are cared for in centres with good access to PC when required.

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		teams based on clinical need.		• Depression/Anxiety @ 12 wks: 2.2 (SD 3.0) vs 2.6 (SD 3.2); p=0.23 • Depression/Anxiety @ 24 wks: 1.8 (SD 2.5) vs 2.1 (SD 2.5); p=0.27 • OS (med): 50.0 (95% CI 42.2 to 69.0) vs 54.7 (95% CI 46.4 to 85.4); p=0.50 • Carers: no difference in HRQOL or mood at 12 or 24 wks	
Collins, A. 2018	Retrospective population cohort study ***(Level IV)***	PC: Acute hospital consultancy services and specialist inpatient PC units	Diagnosis of metastatic NSCLC, SCLC, prostate or breast cancer, n=29,680	• 80% died in hospital, • 83% had suboptimal EOL care outcomes • 59% received a palliative approach to care (med 27 d before death) • Transition points in the cancer illness course of all cases were identified as first admission with any metastatic disease (NSCLC: 3.8 mo [IQR 1.1, 16.0]; n =14,666; and SCLC: 4.2 mo [IQR 1.0, 10.6]; n =2914); first multiday admission with any metastatic disease (prostate: 6.0 mo [IQR 1.3, 26.4]; n = 7174); and first multiday admission with at least one visceral metastatic site (breast: 6.0 mo [IQR 1.2, 29.8]; n=7120).	Despite calls for integrated PC, this occurs late or not at all for many patients with cancer. Our findings demonstrate the application of targeted cancer-specific transition points to trigger integration of palliative care as a standard part of quality oncological care and augment clinician-based referral in routine clinical practice.
Costantini, M. 2018	Phase 2 mixed-methods study ***(Level II)***	Outpatient specialised PC intervention integrated with standard oncological care **PC:** specialised hospital-based unit with no beds; staffed by 2 physicians and 2 advance practice nurses with	New diagnosis of cancer (NSCLC or SCLC, stage IIIb–IV; mesothelioma, stage III–IV; pancreas, stage IV; gastric, stage IIIb–IV), no specific therapy for any cancer during the previous 12 months, ECOG 0-2 n=38	• The PC Unit performed 274 visits in 38 patients (med per patient 4.5), and 24 family meetings with relatives of 16 patients. • All patients and most relatives referred to the usefulness of the intervention, specifically for symptoms management, information and support to strategies for coping. • Oncologists highlighted their difficulties in informing patients on	Early integration of PC in oncological setting seems feasible and well accepted by patients, relatives and, to a lesser extent, oncologists. Some difficulties emerged concerning patient information and inter-

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
		psychologist involved in wkly meetings. 1st session w/in 30 days from consent, then monthly or more often if needed, until death.		palliative intervention, sharing information and coordinating patient's care with the PC team.	professional communication
Dionne-Odom, J.N. 2015 ENABLE III	RCT ***(Level II)***	Early (w/in 30-60 days of diagnosis, recurrence, or progression) vs delayed (3 mo) initiation of PC intervention PC: 1:1 telephone sessions between advanced-practice PC nurse coach and CG. 1st session addressed CG role, PC and Supportive care, and problem-solving framework of COPE attitude; session 2 addressed CG self-care and effective partnering in pt symptom assessment and management; session 3 addressed building a support team, decision making, decision support and ACP.	Family caregivers (CG) of patients with new diagnosis, recurrence, or progression of an advanced-stage cancer w/in ~ 30 to 60 days of the date the pt was informed of the diagnosis by oncology clinician and oncologist-determined prognosis of 6 -24 months, n=122 **Early PC**, n=61 **Delayed PC**, n=61	**Mean between-group differences from enrollment to 3 months:** • Depression score: -3.4 (SD1.5); d= -0.32; p=0.02 • QOL: -2 (SE 2.3); d= -0.13; p=0.39 • Burden: 0.3 (SE 0.7); d= 0.09; p=0.64 • Stress: -0.5 (SE 0.5); d= -0.2; p=0.29 • Demand: 0 (SE 0.7); d= -0.1; p=0.97 **Terminal decline analysis: mean between-group differences:** • Depression: -3.8 (SE 1.5);d= -0.39; p=0.02 • Stress burden: -1.1 (SE 0.4); d= -0.44; p=0.01 • QOL: -4.9 (SE 2.6); d= -0.3; p=0.07 • Objective burden: -0.06 (SE 0.6); d= -0.18; p=0.27 • Demand burden: -0.7 (SE 0.6); d= -0.23; p=0.22	Early-group caregivers had lower depression scores at 3 months and lower depression and stress burden in the terminal decline analysis. PC for caregivers should be initiated as early as possible to maximize benefits.
Dionne-Odom, J.N. 2018	A qualitative formative evaluation ***(Level V)***	EPC intervention	Patients with advanced cancer, (Stage III/IV lung, breast, gynecologic, GI, GU, brain, melanoma, and hematological cancers) n=18 and their primary family caregiver, n=20 and lay patient navigators, n=26	• Participants recommended that intervention topical content be flexible and have an adaptable format based on continuous needs assessment.	This evaluation elicited the following recommended modifications: adaptive content, regular needs assessment, mixed in-

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				• Sessions should be ≥20 minutes long and additional sessions should be offered if requested. • Faith and spirituality are essential to address but should not be an overarching intervention theme. • Content needs to be communicated in simple language. • Intervention delivery via telephone is acceptable but face-to-face contact is desired to establish relationships. Other internet-based technologies (e.g., videoconferencing) could be helpful but many rural-dwellers may not be technology savvy or have internet access. • Most lay navigators believed they could lead the intervention with additional training, protocols for professional referral, and supervision by specialty-trained PC clinicians.	person and telephone encounters, and flexibility in encounter length.
Einstein, D.J. 2017	Retrospective study ***(Level IV)***	Embedded PC vs usual care (separate PC clinic) **Embedded PC:** PC team saw pts in the Biologics clinic on 1 day of the wk.	Advanced cancer (kidney cancer or melanoma), with presence of automatic triggers: diagnosis of metastatic kidney cancer or melanoma, receiving anticancer therapy, and/or having a self-assessed EAS score >5 on one or more individual symptoms Total n= 114 Embedded PC, n=26 Usual Care, n=88	**Embedded vs Usual:** • Seen by PC: 73% vs 53%; OR 2.36; p=0.079 • PC duration (mean): 231 d vs 109 d; p<0.001 • Initial PC contact: outpatient 65% vs 27% and inpatient: 8% vs 26%; p<0.001 • Place of death: home 38% vs 35%, hospice facility 12% vs 9%, Hospital 15% vs 24%, ICU 8% vs 11%; p=0.505 (ICU vs non-ICU) • ChT w/in 2 wks death: 8% vs 14%; OR 0.43; p=0.204 • Enrolled in hospice: 58% vs 51%; OR 1.80; p=0.303 • Hospice duration (mean): 57 d vs 25 d; p=0.006	A model of embedded and automatically triggered PC among patients treated exclusively with targeted and immune-based therapies was associated with significant improvements in use and timing of PC and hospice, compared with usual practice.

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El-Jawahri, A. 2017	Nonblinded RCT ***(Level I)***	EPC integrated with oncology care vs oncology care alone **EPC:** consult with bpard-certified PC physician or advanced-practice nurse w/in 4 wks of enrollment and at least q4wks until death. Telephone sessions also available.	Newly diagnosed with incurable lung (NSCLC, SCLC, or mesothelioma) or noncolorectal GI cancers (pancreatic, esophageal, gastric, or hepatobiliary); no prior therapy for metastatic disease; ECOG of 0–2 (n=275) and their caregivers (n=350) **Caregivers:** EPC, n=137 Control, n=138	• EPC led to improvement in caregivers' total distress (HADS-total adjusted mean difference= -1.45, 95% CI -2.76 to -0.15, p=0.029), depression subscale (HADS-depression adjusted mean difference= -0.71, 95% CI -1.38 to -0.05, p= 0.036), but not anxiety subscale or QOL at wk 12. • There were no differences in caregivers' outcomes at wk 24. • A terminal decline analysis showed significant EPC effects on caregivers' total distress (HADStotal), with effects on both the anxiety and depression subscales at 3 and 6mo before patient death.	Early involvement of PC for patients with newly diagnosed lung and GI cancers leads to improvement in caregivers' psychological symptoms. This work demonstrates that the benefits of early, integrated PC models in oncology care extend beyond patient outcomes and positively impact the experience of caregivers.
Franciosi, V. 2019	Multicenter RCT ***(Level II)***	EPC (w/in 2 wks of study start) vs standard oncology care (SOC) **EPC:** MTD→double board certified oncologists and PC physicians and full-time involved nurses, routine q 2 wks for 1st 24 wks then q3 wks or more often if requested	Pathologically confirmed NSCLC, pancreatic, gastric or biliary tract cancer diagnosed w/in 8 wks of study; ECOG 0-2; metastatic or locally advanced disease (but not susceptible to loco-regional treatments); prognosis >3 months; eligible for 1st line ChT and/or biological therapy, n=281 **Early PC**, n=142 **SOC**, n=139	**EPC vs SOC:** • QOL scores at baseline: 72.3 (SD 12.6) vs 71.7 (SD 14.7) • QOL scores at 12 wks: 70.1 (SD 15.5) vs 69.6 (SD 15.5)	In this study, early PC did not improve QOL in advanced cancer patients.
Gaertner, J. 2017	Systematic review and meta-analysis ***(Level I)***	Specialist PC	RCTs with adult inpatients or outpatients treated in hospital, hospice or community settings with any advanced illness, n=12 studies with 2454 patients, 72% had cancer	• In no trial was integration of specialist PC triggered according to patients' needs as identified by screening • Overall, there was a small effect in favour of specialist PC (SMD 0.16, 95% CI 0.01 to 0.31; QLQ-C30 global health/QOL 4.1, 0.3 to 8.2; n=1218, six trials). • Sensitivity analysis showed an SMD of 0.57 (−0.02 to 1.15; global health/	Specialist PC was associated with a small effect on QOL and might have most pronounced effects for patients with cancer who received such care early. It could be most effective if it is provided early and if it identifies though

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				QoL 14.6, −0.5 to 29.4; n=1385, seven trials). • The effect was marginally larger for patients with cancer (0.20, 0.01 to 0.38; global health/QOL 5.1, 0.3 to 9.7; n=828, five trials) and especially for those who received specialist palliative care early (0.33, 0.05 to 0.61, global health/QoL 8.5, 1.3 to 15.6; n=388, two trials). • The results for pain and other secondary outcomes were inconclusive. • Some methodological problems (such as lack of blinding) reduced the strength of the evidence.	screening those patients with unmet needs.
Greer, J.A. 2018	Secondary analysis of EIPC trial ***(Level III)***	Early integration of oncology and palliative care (EIPC) vs usual care EIPC: Pt met with board-certified PC physician or advanced- practice nurse w/in 4 wks of enrollment and at least monthly until death, with the option for additional visits. Usual Care: PC only at request of the oncologist, pt, or family.	Newly diagnosed incurable lung (NSCLC, small cell, or mesothelioma or non-colorectal GI cancer (pancreatic, esophageal, gastric, or hepatobiliary), with no history of treatment for metastatic disease, ECOG 0-2, n=350 EIPC, n=175 Usual care, n=175	• EIPC significantly increased patient use of approach-oriented coping strategies (B=1.09; SE = 0.44; p= 0.01) and slightly reduced use of avoidant strategies (B = 20.44; SE = 0.23; p= 0.06) from baseline to 24 weeks. • The increased use of approach-oriented coping and reduction in avoidant coping were associated with higher QOL and lower depressive symptoms at 24 wks. • The positive changes in approach-oriented coping, but not avoidant coping, significantly mediated the effects of EIPC on QOL (indirect effect, 1.27; 95% CI, 0.33 to 2.86) and depressive symptoms (indirect effect, 20.39; 95% CI, 20.87 to 20.08).	Patients with incurable cancer who received EIPC showed increased use of approach-oriented coping, which was associated with higher QOL and reduced depressive symptoms. Palliative care may improve these outcomes by providing patients with the skills to cope effectively with life threatening illness.
Groenvold, M. 2017 DanPaCT	Multicenter randomized clinical trial	Early referral to a specialist PC team + standard care vs standard care alone	Adult patients with advanced cancer (stage 4) or CNS cancer stage III/IV (no possibility of radical treatment) and have at least 1 palliative need	• Early specialist PC showed no effect on the primary outcome of change in primary need (−4.9 points (95% CI −11.3 to +1.5 points); *p*= 0.14). The	We did not observe beneficial or harmful effects of early specialist PC, but

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	(Level I)	PC: number and frequency of contacts with the PC team and the treatments and other interventions were determined by the pt's needs	(physical function, role function, emotional function, nausea/ vomiting, pain, dyspnoea, or lack of appetite), n=300 Early specialist PC, n=145 Standard Care, n=152	sensitivity analyses showed similar results. • Analyses of the secondary outcomes, including survival, also showed no differences, maybe except for nausea/vomiting where early specialist PC might have had a beneficial effect. • OS did not differ between groups: PC 323 days vs control 364 days, p=0.16	important beneficial effects cannot be excluded.
Grudzen, C.R. 2016	Single blind RCT ***(Level I)***	Emergency department (ED) initiated PC vs usual care (may or may not include PC) ED PC: PC team consulted w/in a few hours, followed by a full consultation by inpatient PC team on the same or following day. Team consists of physician, nurse practitioner, social worker, chaplain.	Advanced cancer: Laryngeal/ Throat/ Nasopharyngeal/ Mouth a.k.a Head and Neck (stage III or IV), Lung or NSCLC (Stage IIIb or IV), SCLC (extensive stage), Mesothelioma (Stage III or IV), Breast (Stage IV), Esophageal (Stage III, IV), Stomach/ gastric (Stage III,IV), Pancreatic (Stage III, IV), Gallbladder/ Bile Duct/ Cholangio/ Ampullary (stage II-IV), Liver/Hepatic, HCC (Stage III/IV), Colon/ Rectum/ Colo-rectal (Stage IV Dukes D), Kidney/ Renal Cell (stage IV), Ovarian (Stage III, IV), Cervical (stage IV), Prostate (stage IV), Melanoma (stage IV), Brain, Lymphoma (stage III,IV), MM (Stage III, IV), Sarcoma (stage IV), Anal (stage IV), Thyroid- eligible papillary or follicular or medullary or all anaplastic (Stage IV), Vulva (stage IV), Penis (stage IV), Osteosarcoma (stage IV), Carcinoid (stage IV). Total n=136 PC, n=69 Usual Care: 67	**PC vs UC:** • OS (1yr): 40% vs 34% • OS (med): 289 days (95 % CI, 128-453 days) vs 132 days (95 % CI 80-302 days); p=0.20 • QOL at wk 6: +4.78 points (SD 12.00) vs – 1.52 points (SD 15.00); p=0.054 • QOL at wk 12: +5.91 points (SD 16.65) vs +1.08 (SD 16.00); p=0.03 • Major depressive disorder: no significant difference from baseline for both groups (p=0.82) • Hospice use: 28% vs 25% • Hospital days: No sig. difference b/t groups p=0.67 • ICU admission: No sig. difference b/t 2 groups p>0.99	ED-initiated PC consultation in advanced cancer improved QoL in patients with advanced cancer and does not seem to shorten OS; the impact on health care utilization and depression is less clear and warrants further study
Haun, MW 2017	Cochrane Systematic	EPC vs standard care	Diagnosis of a malignant tumour entity at an advanced stage (as	• early PC sig. improved HRQOL at a small effect size (SMD 0.27, 95% CI	This systematic review of a small

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	Review and meta analysis ***(Level I)***		assessed by the oncologist and based on disease stage and tumour type) and without curative treatment options: 7 RCT and cRCT, n=1614 Systematic reviews 1) Bakitas 2009: life-limiting cancer (prognosis approximately 1year); and within 8 to 12 weeks of a new diagnosis of gastrointestinal tract(unresectable stage III or IV), lung (stage IIIB or IV non-small cell or extensive small cell), genitourinary tract (stage IV, prostate cancers limited to persons with hormone refractory), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor (ER) negative, human epidermal growth factor receptor 2 (Her 2 neu) positive)) cancer 2)Bakitas 2015: See above 3)Tattersall 2014: newly detected incurable metastatic cancer (just diagnosed or relapsed with metastatic disease after previous adjuvant chemotherapy), prognosis < 12 months 4) Zimmermann 2014: stage IV cancer (refractory to hormonal therapy as additional criterion for breast or prostate cancer, patients with stage III cancer and poor clinical prognosis were included at the discretion of the oncologist), prognosis 6-24 months	0.15 to 0.38; participants analysed at post treatment= 1028; evidence of low certainty) • HRQOL scores increased by mean 4.59 (95% CI 2.55 to 6.46) points more among participants given early PC than among control participants. • Death HR 0.85, 95% CI 0.56 to 1.28; evidence of very low certainty • Levels of depressive symptoms did not differ significantly (five studies; SMD -0.11, 95% CI -0.26 to 0.03; participants analysed at post treatment = 762; evidence of very low certainty) • Results from 7 studies that analysed n=1054 post treatment suggest a small effect for sig. lower symptom intensity in early PC compared with the control condition (SMD -0.23, 95% CI -0.35 to -0.10; evidence of low certainty) • The type of model used to provide early palliative care did not affect study results • 1 RCT reported potential AEs of early PC, such as a higher % of participants with severe scores for pain and poor appetite; the remaining 6 studies did not report adverse events in study publications. For these 6 studies, principal investigators stated upon request that they had not observed any AEs	number of trials indicates that early palliative care interventions may have more beneficial effects on quality of life and symptom intensity among patients with advanced cancer than among those given usual/standard cancer care alone.
Hoerger, M. 2017	Internet - based study used a pre-post	Intervention grp received a summary of an EPC study vs control group did not.	Patients currently in oncology care, self-reporting a past or present cancer diagnosis (prostate n=306, breast n=118, lung n=66, colon/rectal	• Intervention had a favorable impact on pts' preferences for outpatient PC relative to controls (d=1.01, p< 0.001), while controlling for covariates.	Educating patients about the EPC Study increases preferences for early outpatient PC

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	between-group randomized design ***(Level III)***	**All:** pts completed baseline assessment of preferences for PC, followed by additional survey measures.	n=57, and skin cancer n=73 were recruited but all cancers were able to participate (other cancer n= 78) Control, n=289 Intervention, n=309	• Intervention pts came to view PC as more efficacious (d=0.79, p< 0.001) and less scary (d=0.60, p< 0.001) and exhibited stronger behavioral intentions to utilize outpatient PC if referred (d=0.60, p< 0.001) • Findings were comparable in pts with metastatic disease, those with less education, and those experiencing financial strain	
Huen, K. 2019	Prospective study ***(Level III)***	Integrated PC-Urology care: Pts had choice to be seen on the same day by the PC team in the urology clinic with the urologist present or in the PC clinic, or to be seen on a different scheduled date. Family caregivers were included in consultation at the pt's discretion, and their inclusion was generally encouraged	Metastatic Urological Cancer (stage IV): first diagnosed or recurrent post treatment, metastatic bladder and kidney cancer→ evidence of disease to lymph nodes or viscera; metastatic prostate cancer→ evidence of disease to lymph nodes, bones or viscera, or with evidence of biochemical recurrence post treatment (refractory to hormonal therapy), n=53	• Time (med) for the first and second follow-up visits: 2.9mo (IQR 2.1-5.8) and 7.8 mo (IQR 5.1-10.6) • There were no significant differences in HRQOL and satisfaction between baseline and subsequent follow-up visits. • A total of 36 (68%) of 53 participants who were enrolled at the start of the study, died • Of those, 29 (81%) expired within a home or inpatient hospice.	Rates of hospice use were high in an integrated PC-urology model. Health-related quality of life and satisfaction did not worsen over time.
Hui, D. 2016	Systematic Review ***(Level I)***	Outpatient PC clinics	21 articles included. All but 1 were specific to oncology.	• Identified 20 unique referral criteria. • 6 major categories for referral: physical symptoms (n=13 [62%]), cancer trajectory (n=13 [62%]), prognosis (n=7 [33%]), performance status (n=7 [33%]), psychosocial distress (n=6 [29%]), and EOL care planning (n=5 [24%]). • Significant variations on the definition of advanced cancer and the assessment tools for symptom/distress screening. • The Edmonton Symptom Assessment Scale (n =7 [33%]) and the distress thermometer (n=2 [10%]) were used most often.	This systematic review identified 20 criteria including 6 recurrent themes for outpatient cancer PC referral. It highlights the significant heterogeneity regarding the timing and process for referral and the need for further research to develop standardized referral criteria.

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				• 14 other criteria: patient request, initiation of IV or tumor specific ChT, family concerns, serious comorbidities and multiple hospitalizations • Lack of consensus in the cutoffs in symptom assessment tools and timing for outpatient palliative care referral.	
Hui, D. 2019	Retrospective study ***(Level IV)***	Outpatient PC clinic: operated 5 days/ wk, staffed by physicians, bnnurses, psychologists, counselors, pharmacist, Chaplains, child life counselors, dieticians, physical therapist available as needed.	Advanced cancer (locally advanced n=56, metastatic n=111, or recurrent n=33): Breast (n=23), GI (n=36), Gynecological (n=21), Head and neck (n=32), Hematological (n=10), Respiratory (n=36), Other (n=26) Total n=200	• OS (med): 14 mo (95% CI 9.2, 17.5 mo) • 85% met ≥1 major referral criterion • 28% met 1, 30% met 2, 20% met 3, and 8% met ≥ 4 criteria • 70% had severe physical symptoms, 18% emotional symptoms, 13% decision-making needs, and 13% brain/ leptomeningeal metastases • 27% were referred ≤ 3 months of advanced cancer diagnosis • 32% referred after progression from ≥ 2 lines of palliative systemic therapy. • Timing b/t patient first meeting any criterion to PC referral (med): 2.4 (IQR 0.1, 8.6) mo	Patients were referred early to our PC clinic and a vast majority (85%) of them met ≥ 1major criteria. Standardized referral based on these criteria may facilitate even earlier referral/
Kavalieratos, D. 2016	Systematic review and meta-analysis ***(Level I)***	PC intervention	43 RCTs (only 30 with cancer pts) Patients, n=12731 Caregivers, n=2479	• 35 trials used usual care as the control, and 14 took place in the ambulatory setting. • PC was associated with statistically and clinically significant improvements in patient QOL at the 1- to 3-month follow-up (standardized mean difference, 0.46; 95%CI, 0.08 to 0.83; FACIT-Pal mean difference, 11.36] and symptom burden at the 1- to 3-month follow-up (standardized mean difference, −0.66; 95%CI, −1.25 to −0.07; ESAS mean difference, −10.30).	PC interventions were associated with improvements in patient QOL and symptom burden. Findings for caregiver outcomes were inconsistent. However, many associations were no longer significant when limited to trials at low risk of bias, and there was no significant

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				• When analyses were limited to trials at low risk of bias (n = 5), the association between PC and QOL was attenuated but remained statistically significant (standardized mean difference, 0.20; 95%CI, 0.06 to 0.34; FACIT-Pal mean difference, 4.94), the association with symptom burden was not statistically significant (standardized mean difference, −0.21; 95%CI, −0.42 to 0.00; ESAS mean difference, −3.28). • There was no association between PC and OS (HR, 0.90; 95%CI, 0.69 to 1.17). • PC was associated consistently with improvements in advance care planning, patient and caregiver satisfaction, and lower health care utilization.	association between palliative care and survival.
May, P. 2015	Prospective Cohort Study ***(Level III)***	PC consultation vs usual care (UC) **PC:** specialist-led MDT that assists in the treatment of seriously ill patients through identification and treatment of pain and other symptoms, clarifying treatment options, establishing goals of care and advance plans, and helping patients and family members select treatments that match their goals.	Advanced cancer diagnosis: metastatic solid tumor, CNS malignancy, locally advanced head, neck, or pancreatic cancers, metastatic melanoma, or transplant-ineligible lymphoma or multiple myeloma, n= 969 PC, n=256 UC, n=713	• Earlier PC consultation is associated with a larger effect on total direct cost. Intervention within 6 days is estimated to reduce costs by -$1,312 (95% CI, -$2,568 to -$56; P=0.04) compared with no intervention and intervention within 2 days by -$2,280 (95% CI, -$3,438 to -$1,122; P =0.001) • these reductions are equivalent to a 14% and a 24% reduction, respectively, in cost of hospital stay	Earlier PC consultation during hospital admission is associated with lower cost of hospital stay for patients admitted with an advanced cancer diagnosis. These findings are consistent with a growing body of research on quality and survival suggesting that EPC should be more widely implemented.
May, P. 2016	Prospective and observational	PC consult w/in 2 days of hospital admission vs usual care	Inpatient with advanced cancer diagnosis: stage 3 or 4 laryngeal, throat, nasopharyngeal, mouth, or	• PC consultation was significantly associated with lower total direct	Targeting early specialist palliative care to

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	multisite study design ***(Level III)***		head and neck cancer; NSCLC; mesothelioma, esophageal, stomach or gastric, pancreatic, gallbladder, bile duct, cholangio, ampullary, liver, hepatic, hepatocellular, or ovarian cancer; stage 4 breast, kidney, renal cell, endometrial, uterine, cervical, sarcoma, prostate, or melanoma cancer; Dukes' stage D colon cancer; extensive stage small-cell lung cancer; transplant-ineligible multiple myeloma; relapsed or transplant-ineligible lymphoma; and glioblastoma multiforme, n=906 PC, n=193	hospital costs for patients with multimorbidity. • Effect size increased as # of comorbidities increased: comorbidity score 2-3= reduction in costs $2321 (22%), comorbidity score 4+= reduction in cost of $3515 (32%) • Earlier consultation was also found to be systematically associated with a larger cost-saving effect for all subsamples defined by multimorbidity	hospitalized patients with advanced cancer and higher numbers of serious concurrent conditions could improve care while complementing strategies to curb the growth of health spending.
May, P. 2017	Prospective multisite cohort study ***(Level III)***	EPC vs LPC vs usual care **EPC:** MDT included a physician, nurse, social worker, with support from other professionals including psychiatry and chaplaincy **usual care:** PC provided by the primary attending physician and their support staff.	Advanced cancer: Solid tumour, Hematological, Gynecological, CNS, Lymphoma, n=863 Usual care, n=637 EPC, n=177 LOC, n=49	• Total direct cost mean: Usual care ($10171) vs EPC ($8632) vs LPC ($17968) • Room and board mean cost: Usual care ($3165) vs EPC ($3143) vs LPC ($5765) • Pharmacy mean cost: Usual care ($2101) vs EPC ($2233) vs LPC ($3346) • Laboratory mean cost: usual care ($611) vs EPC ($353) vs LPC ($811) • Imaging mean cost: usual care ($834) vs EPC ($699) vs LPC ($1324) • Mean LOS: usual care (7.8 days) vs EPC (6.37cdays) vs LPC (13.6 days) • Cost-savings from EPC are due to both reduced length of stay and reduced intensity of treatment, with an estimated 63% of savings associated with shorter length of stay. • A reduction in day-to-day costs is observable in the days immediately	Reduced length of stay is the biggest driver of cost-saving from early consultation for patients with advanced cancer. Patient- and family-centred discussions on goals of care and transition planning initiated by PC consultation teams may be at least as important in driving cost-savings as the reduction of unnecessary tests and pharmaceuticals identified by previous studies.

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				following initial consult but does not persist indefinitely. • A comparison of EPC and LPC consultation team cost-effects shows negligible difference once the intervention is administered. **All in US $	
McCorkle, R. 2015	Cluster Randomized Trail ***(Level II)***	Advanced practice nurse -coordinated multidisciplinary intervention (**intervention group**) vs usual multidisciplinary care plus a copy of the symptom management toolkit with instructions on its use (**enhanced usual care group**)	Adult, late stage cancer diagnosis w/in 100 days, post biopsy or surgery with additional treatment recommended and at least 1 chronic condition, n=92 -gynecologic and lung clinics to the intervention group, n=36 -head and neck and gastrointestinal clinics were randomized to the enhanced usual care, n=56	**Δ over 3 months: Enhanced usual care vs intervention:** • Symptom Distress Scale: -0.887± 0.788 (p=0.27) vs -0.235 ± 0.951 (p=0.80); p=0.61 • Health Distress: -0.3221 ± 0.142 (p=0.03) vs -0.312 ± 0.173 (0.07); p=0.97 • Patient Health Questionnaire-Depression Scale: -0.213 ± 0.529 (p=0.69) vs -0.135 ± 0.654 (0.84); p=0.9268 • Enforced Social Dependency Scale-personal: -0.276 ± 0.058 (p<0.0001) vs -0.197 ± 0.071 (0.25); p=0.3899 • Enforced Social Dependency Scale-social: -1.468 ± 0.366 (p<0.001) vs -0.514 ± 0.446 (p=0.25); p=0.10 • Self-rated health: -0.455 ± 0.144 (p=0.002) vs -0.590 ± 0.175 (p=0.001); p=0.55	Patients newly diagnosed with late-stage cancer were managed by disease-specific multidisciplinary teams who palliated their symptoms, providing whole patient care, patient outcomes remained stable or improved.
McDonald, J. 2017	Cluster Randomized Trial ***(Level II)***	EPC vs standard oncology care with PC only as needed **EPC:** consultation and monthly follow up in the outpatient PC clinic by a PC physician and nurse. Follow-up phone calls a week	Caregivers of patients with advanced cancer: stage IV cancer (those with breast and prostate had hormone-refractory disease), or stage III advanced cancer with poor prognosis; an ECOG performance status of 0–2; a clinical prognosis of 6–24 months, n= 151 EPC, n=77	• Satisfaction of care improved in EPC group compared to standard group over 3 months (p=0.007) and 4 months (p=0.02) • No difference over time b/t groups for QOL: SF-36-Physical QOL over 3 months (p=0.83) or 4 months (p=0.20), mental QOL over 3 months (0.87) or 4 months (p=0.60), CQOL-C	Early palliative care increased satisfaction with care in caregivers of patients with advanced cancer

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		after each visit; 24-h telephone support was provided by PC physicians.	Standard, n=74	over 3 months (p=0.92) or 4 months (p=0.51)	
McDonald, J. 2018	Qualitative grounded theory study ***(Level III)***	EPC (right at diagnosis) vs standard oncology care with PC only as needed **EPC:** specialised physician and nurse and monthly follow-up for 4 months; as well, participants had 24-h access to the PC team by telephone	Caregivers of patients with advanced cancer: Stage IV cancer (breast and prostate cancer had hormone-refractory disease) or stage III with poor prognosis; had ECOG performance status 0–2; had a clinical prognosis of 6–24 months, n=23 Intervention, n=14 Control, n=9	• Participants in the intervention group engaged in open discussion about the end of life, balanced hope with realism and had increased confidence from a range of professional supports. • Controls tended to engage in 'deliberate ignorance' about the future, felt uncertain about how they would cope and lacked knowledge of available supports.	Caregiver QoL is influenced profoundly by the interaction with the patient and should be measured with specific questionnaires that include content related to confronting mortality and professional supports. This would improve delineation of QoL for caregivers and allow greater sensitivity to change.
Nipp, R.D. 2018	Secondary analysis of data from a randomized trial ***(Level III)***	EPC intervention (w/in 4 wks) integrated with oncology care or usual oncology care alone **EPC:** outpatient MDT PC met pt at least monthly until death **Usual care:** Not referred to PC until request by pt, family or oncologist	Newly diagnosed (within the previous 8 wks) incurable, advanced lung and non-colorectal GI cancer, ECOG 0-2, n=350 EPC, n=175 Usual, n=175	• Follow-up: 24 wks • younger patients with lung cancer receiving EPC reported increased use of active coping (B=1.74; P=0.02) and decreased use of avoidant coping (B=−0.97; P=0.02), but the effects of EPC on these outcomes were not significant for older patients. • Male patients with lung cancer assigned to EPC reported better QOL (FACT-G: B=9.31; P=0.01) and lower depression scores (PHQ-9: B=−2.82; P=0.02), but the effects of EPC on these outcomes were not significant for female patients. • At 24-wks, we found no age or sex moderation effects within the gastrointestinal cancer subgroup	Age and sex moderate the effects of EPC for patients with advanced lung cancer. EPC may need to be tailored to individuals' unique sociodemographic and clinical characteristics.

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
Paiva, C. E. 2020	Longitudinal observational study, divided into 2 phases **(Level III-IV)**	Oncology referred outpatient PC vs screening criteria referred outpatient PC PC: w/in 90 days, w/in 45 days, w/in 15 days	Advanced, uncurable (distant metastasis or unresectable locoregional recurrence) breast and gynecological cancer outpatients, undergoing antineoplastic treatment or no treatment. Referral criteria: 1) Refractory pain 2) AEs of difficult management (secondary to opioid use) 3) Opioid rotation needed 4) CNS/leptomeningeal mets', 5) spinal cord compression or cauda equina 6) Severe physical symptoms 7) Assistance needs in decision making and care planning 8) severe emotional symptoms 9) delirium 10) Pts request to be referred 11) existential crisis 12) suicide risk 13) More than 3 unscheduled visits to ED or hospitalisation during last month 14) time of antineoplastic treatment (treatment line) 15) Emotional suffering of family caregiver 16) Poor ECOG-PS (2-4), Phase 1, n=120 Phase 2, n=251	Phase 1: • 23 (19.2%) pts were referred to PC by clinical oncologists • 82 (68%) referred by screening criteria • Med OS 451 days, 95% CI: 113.3-788.7 (screening criteria vs 178 days, 95% CI: 101.1-254.9 (oncologist referral); p<0.001 Phase 2 • 97 (38.6%) pts met at least 1 criterion • med number of criteria met: 2 • 45 (46.4%; 45 of 97), 30 (30.9%; 30 of 97), 15 (15.5%; 15 of 97), 5 (5.1%; 5 of 97), 1 (1%; 1 of 97) and 1 (1%; 1 out of 97) patient met 1, 2, 3, 4, 5 and 6 criteria	The use of referral criteria has the potential to significantly increase the number of timely PC referral. Further research is needed to test the implementation of these criteria.
Prescott, A.T. 2017	Secondary analysis of data from 2 RCTs (ENABLE	EPC vs LPC (12 wk delay) vs usual care **PC:** initial in-person PC consult, 4 or 6 semi-structured	New advanced solid tumor or hematological cancer, recurrence, or new disease progression following stable disease, prognosis of 6–24 months: Lung (n=205), GI (n=183),	• Higher baseline CES-D scores were significantly associated with greater mortality risk (HR = 1.042, 95% CI 1.017 to 1.067, p= 0.001). • Patients with higher CES-D scores who received PC had a lower	This study is the first to demonstrate that patients with advanced cancer who also have depressive

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
	and ENABLE II) ***(Level III)***	psychoeducational phone coaching sessions, monthly check-in calls until death	GU (n=55), Breast (n=56), Hematological (n=10), Other (n=20) n=529 EPC, n=265 LPC, n=103 Usual care, n=161	mortality risk (HR = 0.963, CI 0.933–0.993, p= 0.018) even when controlling for demographics, cancer site, and illness-related variables	symptoms benefit the most from EPC.
Romano, A.M. 2017	Retrospective cohort study ***(Level IV)***	EPC vs standard care **EPC:** Outpatient clinic in the Cancer Center; inpatient consultation, PC unit and home hospice components. Met with pts as early in cancer course as possible. Weekly MDT meetings to coordinate care. **Standard:** received PC and/or hospice planning services at the very EOL	Incurable advanced cancer: Stage I (n=22), Stage II (n=34), Stage III (n= 72), Stage IV (n=331), NSCLC (n=84), Head and neck (n=37), Nonovarian genitourinary (36), Breast, N=28), Colorectal (n=34), Pancreatic (n=29), Ovarian (n=24), SCLC (n=24), Esophageal/gastric (n=19), other (n=154) Total n=470 EPC, n=275 Standard care, n=195	**EPC vs Standard Care:** • ICU is last 6 mo of life: 17.5% vs 31.8%; p<0.001. OR 3.07 • ICU in last month of life: 11.3% vs 24.6%; p<0.001, OR 3.59 • ICU during terminal admission: 6.6% vs 20.0%; p<0.001, OR 4.69 • Died in Hospital:16.0% vs 35.9%; p<0.001, OR 4.14 • Died in ICU: 2.9% vs 11.8%, p<0.001, OR 5.57 • Enrolled in hospice, n=76.0% vs 38.5%; p<0.001 OR 0.13 • Use of RT of ChT did not sig. differ between groups • Length of ICU stay, code status, ICU procedures, disposition location and outcomes after ICU admission did not sig. differ between groups	EPC significantly reduced ICU use at the end of life but did not change ICU events.
Scibetta, C. 2016	Retrospective review ***(Level IV)***	EPC (> 90 days prior to death) vs LPC (<90 days prior to death **PC:** board-certified palliative care physician or nurse practitioner in a stand-alone palliative care clinic OR inpatient, MDT with board-certified PC clinicians	Advanced cancer (solid tumors): Breast (n=43), GI (n=91), Gynecologic (n=28), GU (n=44), Other (n=91) Total n=297: EPC, n=93 LPC, n=204	**EPC vs LPC:** • Inpatient: 33% vs 66%, p<0.01 • ICU: 5% vs 20%, p<0.01 • ED utilization: 34% vs 54%, p=0.04 • Direct costs of inpatient care in the last 6 mo of life: $19, 067 vs $25, 754, p<0.01 • Direct outpatient costs: $13, 040 vs $11, 549, p=0.85 • EPC mainly delivered in outpatient setting (84%)	EPC is associated with less intensive medical care, improved quality outcomes, and cost savings at the end of life for patients with cancer. Despite recommendations that EPC be offered to all patients with metastatic cancer, palliative care

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
				• LPC mostly delivered in hospital (82%) • Patients with urologic or gynecologic cancers were more likely to have EPC than patients with breast, gastrointestinal, or other cancers. •	services remain underutilized.
Shamieh, O. 2017	Prospective study ***(Level III)***	Outpatient PC (consultation and follow-up visit 14-34 days) with MDT	Advanced cancer: Stage 3 (n=9) or 4 (n=173); Breast (n=40), Lung (n=37), GI (n=31), GU (n=14), Skin and soft tissue (n=13), Head and Neck (n=17), Hematology (n=10), Gynecology (n=8), CNS (n=4), Other (n=8) Total n=182	• Duration between clinic visits (med): 21 days (IQR 15–28) • KPS between visits (mean): 68 vs. 66 %, p= 0.004 • ESAS pain: 5.9 vs. 5.1, p= 0.004 • ESAS sleep: 4.6 vs. 4.1, p= 0.007 • Pts with moderate to severe symptom intensity: pain (7 vs. 6, p< 0.0001), fatigue (7 vs. 6, p= 0.003), nausea (7 vs. 4, p< 0.0001), depression (7 vs. 5, p= 0.0008), anxiety (7 vs. 5, p< 0.0001), drowsiness (6 vs. 5, p< 0.001), appetite (7 vs. 6, p= 0.0007),well-being (7 vs. 6, p< 0.0001), dyspnea (6 vs. 5, p= 0.0006), and sleep (7 vs. 5, p< 0.0001)	Our outpatient palliative care consultation was associated with improvement in ESAS, particularly for patients who presented with moderate to severe symptoms.
Temel, J.S. 2017	Non blinded RCT ***(Level I)***	Integrated EPC + oncology care vs usual care **EPC:** Consult with outpatient PC team member w/in 4 wks and continued monthly until death. Extra visits at discretion of patient, oncologist or PC clinician. Inpatients observed by PC team. **Usual Care:** PC by request of oncologist, patient, family	Newly diagnosed uncurable lung (NSCLC, small-cell or mesothelioma) or non-colorectal GI (pancreatic, esophageal, gastric or hepatobiliary) cancer, ECOG 0-2, n=350 EPC, n=175 Usual care, n=175	**EPC vs usual care:** • Δ QOL over 12 wks: 0.39 vs 21.13; p= 0.339 • Δ QOL over 24 wks: 1.59 vs -3.40; p=0.10 • Depression at wk 24 (adjusted mean difference): -1.17; 95% CI, -2.33 to -0.01; p=0.048 • Discuss their wishes with MD if they were dying (30.2% vs 14.5%; p= 0.004).	For patients with newly diagnosed incurable cancers, integrated EPC improved QOL and other salient outcomes, with differential effects by cancer type.

Author, year	Study Type (EL)	Methods	Patient Characteristics, n	Results	Conclusions
Vanbutsele, G. 2018	Non-blinded RCT ***(Level II)***	Systematic EPC + oncology care vs standard oncology care **Standard care:** 1 intro consult with MDT and follow up at patient's discretion. **EPC:** consult with PC nurse w/in 3 wks and then monthly until death. PC nurse could refer to others and participated in weekly MDT oncology meetings.	Incurable, advanced cancer (histologically or cytologically confirmed) due to solid tumour, prognosis of 12 mo (new or progression), ECOG 0-2, n=186 EPC, n=92 Standard, n=94	**EPC vs standard care:** • Compliance at 12 wks: 71% vs 72% • Overall QOL score at 12 wks (EORTC QLQ C30): 61·98 (95% CI 57·02–66·95) vs 54·39 (95% CI 49·23–59·56); difference 7·60 [95% CI 0·59–14·60]; p=0·03); • Overall QOL score at 12 wks (MQOL Single Item Scale): 7·05 (95% CI 6·59–7·50) vs 5·94 (95% CI 5·50–6·39); difference 1·11 [95% CI 0·49–1·73]; p=0.0006	Our findings show that early and systematic integration of PC is more beneficial for patients with advanced cancer than PC consultations offered on demand, even when psychosocial support has already been offered.

ACP, advanced care planning; AOR, adjusted odds ratio; b/f, before; b/t, between; ChT, chemotherapy; CI, confidence interval; cRCT, cluster-randomized controlled trial; d, day(s); EL, evidence level; ED, emergency department; EIPC, early integration of oncology and palliative care; EOL, end of life; EPC, early palliative care; FCGs, family caregivers; GI, gastrointestinal; GU, genitourinary; HR, hazard ratio; HRQOL, health related quality of life; ICU, intensive care unit; IQR, interquartile range; KPS, Karnofsky Performance Scale; mo, month(s); MPM, malignant pleural mesothelioma; NSCLC, non small cell lung cancer; OR, odds ratio; OS, overall survival; PC, palliative care; PSC, psychosocial care; QOL, quality of life; RCT, randomized control trial; RT, radiotherapy; SCC, supportive care in cancer; SCLC, small cell lung cancer; SD, standard deviation; SE, standard error; SOC, standard oncology care; UC, usual care; w/in, within; wk(s), week(s).

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Appendix A: Search Strategy

Database	Date	Search Strategy	Limits	Results
PubMed	Mar. 3 2020	("advance"[All Fields] OR "advanced"[All Fields] OR "advancement"[All Fields] OR "advancements"[All Fields] OR "advances"[All Fields] OR "advancing"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("Early"[All Fields] AND ("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]) OR "palliative care"[All Fields]))	In the last 5 years, Humans, English, Adolescent: 13-18 years, Adult: 19+ years.	230, 45 after title abstract screen

Appendix B: Levels of Evidence

- Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity
- Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity
- Level III – prospective cohort studies
- Level IV – retrospective cohort studies or case-control studies
- Level V – studies without a control group, case reports, or expert opinions