

Palliative care and advance care planning for pancreas and other cancers

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Abstract: The principles of palliative care are fundamental to support and treat the physical, mental, and psychosocial health of patients living with pancreatic cancer. In addition to its proven advantages to help manage disease-related symptoms, improve accurate illness understanding, and enhance the quality of life and survival outcomes for patients with advanced disease, the inclusion of palliative care principles (whether by a specialist or by the primary oncology team) with standard oncologic care strengthens timely and quality advance care planning (ACP). The primary objective of this review article is to underscore the significant value of palliative care integration and ACP in oncology, including but not limited to care at the end of life, with a particular focus on its relevance to patients with advanced pancreatic cancer.

Keywords: Pancreas cancer; palliative care; advance care planning (ACP)

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Introduction

Palliative care is a key element of the multidisciplinary management of patients with pancreatic cancer. The added clinical benefit of palliative care along with cancer-directed treatment improves the physical and psychosocial well-being of patients, especially as the majority of newly diagnosed patients with pancreas adenocarcinoma present with advanced stage disease (1,2). Multiple studies have demonstrated that integration of palliative care with standard oncologic care is needed from the time of diagnosis to help control disease-related symptoms, alleviate distress, enhance prognostic discussions and illness understanding, and empower patients to think deeply about their personal values to guide the planning of their future medical care (3,4). The primary aims of this review article are (I) to highlight the significant merit and ongoing challenges of palliative care integration in our current

practice of oncology; and (II) to emphasize the need for further improvement in advance care planning (ACP) in patients with pancreatic cancer.

Goals and challenges of palliative care integration

Providing meaningful and quality palliative care in oncology entails a longitudinal assessment and treatment of the dynamic physical, social, and psychological needs of patients with cancer (5,6). Throughout the trajectory of each patient's disease, oncologists and palliative care specialists must seek to ameliorate the present and prevent the future burden of cancer-related symptoms. A multidisciplinary team approach can foster improved therapeutic and supportive care recommendations for patients with pancreatic cancer (7).

Physical complications experienced by patients with

advanced pancreatic cancer include malignant biliary and gastric-outlet obstructions, refractory pain as a result of tumor infiltration of upper abdominal retroperitoneal nerves, cancer anorexia-cachexia syndrome, malnutrition due to pancreatic exocrine insufficiency, and increased risk for thromboembolic disease (8-10). Procedural interventions such as EUS guided celiac plexus neurolysis for opioid refractory pain, endoscopic biliary metal stent placement for symptomatic biliary obstructions, or gastrojejunostomy tube or enteral stent placement for gastric-outlet obstructions are routinely needed to offset the mass effect of aggressive disease and improve patients' quality of life. Tumor involvement and damage of pancreatic parenchyma, either by direct extension or blockage of the main pancreatic duct, also impede excretion of digestive enzymes that are necessary for the absorption of key nutrients. Pancreatic enzyme replacement and gastric acid suppression to prevent enzyme inactivation can strengthen nutrition and are recommended for patients with ongoing weight loss, abdominal cramping, or steatorrhea who are suspected of having enzyme deficiencies. Additionally, patients with pancreatic cancer are more prone to develop venous thromboembolic disease (11,12). Based on data from the CLOT and CONKO-004 studies—two large, prospective, randomized controlled trials—current guidelines recommend use of low molecular weight heparin, such as dalteparin or enoxaparin, instead of oral anticoagulants for the treatment of venous thromboembolism (VTE) (13,14). Prophylactic use of low molecular weight heparin in patients with advanced pancreatic cancer is feasible and effective for reducing incidence of VTE; however, it does not significantly impact overall survival and therefore, is not considered standard of care (14).

In addition to caring for the above physical manifestations of pancreatic cancer, supportive care and continued empathetic discussions are needed to attend to the higher prevalence of psychosocial distress, anxiety, and depression in this patient population (15-17). In fact, a comprehensive review of the United States Surveillance, Epidemiology, and End Results (SEER) database discovered that male patients diagnosed with pancreatic cancer are at an 11-fold increased risk of committing suicide compared to the general population (18). Vigilance and frequent mental health screening are thus imperative for oncologists to recognize, counsel, and manage the psychological suffering that typically accompanies the diagnosis and medical treatment of pancreatic cancer.

To assist with early detection of disease-related

complications, recent clinical studies have shown promising results in using electronic-based patient reported assessments that enable patients to notify their healthcare teams with new or recurrent symptom development. In a randomized controlled trial by Basch *et al.*, patients with advanced solid tumor malignancies experienced higher quality of life, fewer emergency room visits, greater chemotherapy tolerance, and improved overall survival when they were afforded the opportunity to self-report interval symptoms while receiving chemotherapy (19). Similarly, in patients with high risk lung cancer, the use of patient-driven follow-up reports on symptom burden led to earlier supportive care with improved clinical outcomes (20). Patient reported outcomes and symptom assessment scales have the potential to be useful in addressing the specific palliative care needs in patients with pancreas cancer, but are yet to be validated in prospective studies (21,22).

Along with a dedicated focus on symptom management, palliative care in oncology embraces the task of improving illness understanding and clarifying the goals of treatment for patients, as they begin to cope with the reality of their disease. Inaccurate expectations of cure with chemotherapy in the metastatic setting can mislead patients to make treatment decisions that are discordant with their values, and thereby delay end-of-life ACP (23,24). Data analysis from the Cancer Care Outcomes Research and Surveillance (CanCORS) study showed that 81% of patients with stage IV colorectal and 69% of patients with stage IV lung cancers expected that receipt of systemic chemotherapy would cure their disease (24-26). Those patients who had accurate expectations for the role of chemotherapy to stabilize disease and control symptoms were more likely to utilize hospice services (27). Illness understanding can be improved with discussions on life expectancy and prognosis between patients and their oncologists (28-31). Specialty palliative care is a powerful adjunct to standard oncology that can enrich patient comprehension of the goals of treatment in the setting of advanced disease (32).

The integration of specialty palliative care by way of traditional in-hospital consultations and end-of-life discussions has durable impact on the quality of life, use of late chemotherapy, and healthcare associated costs for patients (33-37). For example, inpatient palliative care consultations for hospitalized patients with advanced gastrointestinal cancers, including stages III-IV pancreatic adenocarcinoma, increase the odds of home death and hospice utilization, while decreasing the likelihood of dying in a hospital (38). In a retrospective analysis of 5,381

patients with advanced pancreatic cancer, the 2,816 patients who received a palliative care consultation benefited from decreased chemotherapy use near death, with fewer subsequent hospitalizations, emergency room visits, and intensive care unit admissions compared to those patients who received standard care only. Higher intensity of palliative care, measured by the number of palliative care visits, was also associated with lower odds for aggressive end-of-life care (39). These findings collectively establish that palliative care consultations for hospitalized patients result in the improved utilization of healthcare resources and allow patients to die comfortably at home, without negatively impacting their overall survival (40). In order to guide when inpatient consultations should be requested, a prospective cohort from Adelson *et al.* defined a set of criteria that would trigger an automatic palliative care consultation when patients with solid tumor malignancies are hospitalized. The intervention group consisted of patients who met one of the following eligibility criteria: advanced solid tumor cancers, prior hospitalization within thirty days, hospitalization length of greater than seven days, or active physical or psychosocial symptoms. The results from this study indicated that patients who received criteria-driven automatic consultation with specialty palliative care had lower readmission rates, less chemotherapy use after hospital discharge, and increased hospice referrals (41). Tracking patient-specific data such as frequency and duration of hospital admissions, in parallel with symptom burden and overall prognosis, is a useful strategy to prompt an evaluation of a patient's unmet palliative care needs.

The clear synergy between inpatient palliative care consultations and standard oncologic care on symptom management, illness understanding, and appropriate healthcare utilization has ultimately led to research in the last decade that shows superior outcomes with the early integration of specialty palliative care (42–44). In a seminal study by Temel *et al.*, patients with metastatic non-small cell lung cancer who were randomized to receive early outpatient palliative care in addition to standard oncologic care had less depressive symptoms, better quality of life, and improved overall survival compared to patients who received standard oncologic care alone. Moreover, patients who derived benefit from concurrent palliative care received less aggressive end-of-life care (45). However, the efficacy of an early palliative care intervention may be tumor-specific, especially as the palliative needs, disease trajectories, and therapeutic options vary per cancer type.

To expand on Temel's research, several studies now aim

to investigate the role of early palliative care in patients with advanced gastrointestinal cancers. Although patients often have locally advanced or metastatic disease at presentation, retrospective data demonstrate that most palliative care consultations continue to occur late in the disease course of patients with pancreatic cancer (46). The Early Palliative Care Italian Study Group (EPCISG) recently conducted a secondary analysis of a randomized controlled trial in patients with metastatic pancreatic cancer, who were assigned to receive early specialty outpatient palliative care versus on-demand palliative care. The early palliative care intervention group had increased number of palliative care visits, higher use of hospice services, and received less chemotherapy in the last 30 days of life; overall survival did not statistically differ between groups (47). Early specialty palliative care for patients with advanced colorectal and pancreatic cancers is also feasible and effective in its application in larger health care networks, such as the United States Veterans Affairs Health System (48). In spite of its potential advantages, patients with pancreatic cancer still may feel overwhelmed to participate and maintain attendance at additional outpatient palliative care clinics, especially as they cope with their new diagnoses and treatment plans (49). Moreover, in patients with incurable non-colorectal gastrointestinal cancers, changes in quality of life and mood over time did not significantly differ between patients who were randomly assigned to early integrated palliative care versus those who received usual care (50). These latest findings substantiate that patients with different cancers may require different approaches to palliative care integration.

While the concurrent use of cancer-directed therapy with non-hospice palliative care services is both feasible and advantageous, there are financial barriers that limit the ability of patients to enroll in hospice if they continue to receive chemotherapy for disease and symptom control. For example, current Medicare regulations in the United States stipulate that patients must forgo curative medical treatment in order to receive hospice support. Even though chemotherapy is not given with curative intent for patients with metastatic disease, its use has been traditionally prohibited once Medicare beneficiaries transition to hospice care. In 2015, the United States federal Centers for Medicare and Medicaid Services (CMS) proposed an innovative solution with the Medicare Care Choices Model. This initiative enables patients to benefit from hospice-like supportive care services and still receive disease-specific medical care, with a goal of improving overall quality

and patient satisfaction at the end of life (51). The results from this national endeavor will be critical for advancing healthcare policy and overcoming the financial constraints related to hospice integration for patients with advanced cancers.

Amid the strong advocacy and recognition for the integration of palliative care into standard oncology practice, the current workforce of palliative care specialists remains a limiting factor to meet the demands of a growing cancer population (52-55). Investment in the development of primary palliative care skills for oncologists can help compensate for this shortcoming, and in doing so, generate a sustainable model that delivers high quality palliative care that effectively triages needs that are complex and refractory to palliative care specialists (56-60). With this in mind, patients with advanced pancreatic cancer may benefit from a conceptual framework of graded responsibility, with their primary oncologists providing basic psychosocial support, symptom management, and initiating ACP. Physicians who are dual trained in medical oncology and palliative care can further promote a united effort to address the present and future palliative care needs of patients (61).

ACP

ACP is the multifaceted process by which patients make decisions regarding their future medical care. Oncologists and palliative care specialists have shared responsibility to candidly discuss prognosis and recommend end-of-life care options at appropriate times in a cancer patient's disease trajectory. When physicians engage in patient-centered discussions, they must be mindful of an individual's distinct cultural, spiritual, and moral values that underlie decision making, while also recognizing that such decisions are not static and can evolve with time (62,63). The primary objective of ACP is to enable patients to cogitate about their goals at the end of life, and in turn, make informed health care related choices that are congruent with and fulfill these wishes. For patients with incurable cancers, such as unresectable or metastatic pancreas cancer, ACP is therefore an integral component of oncologic care, and should be addressed frequently and in parallel with therapeutic recommendations.

Despite the increasing recognition for ACP in patients with advanced cancers, there are multiple barriers that prevent timely and high quality patient education, completion of advance directives or life-sustaining treatment forms, and incorporation of end-of-life care planning into

standard oncologic practice. Previous longitudinal results from the United States Health and Retirement Study from 2000–2012 demonstrate a trend for increasing assignment of durable healthcare power of attorneys among cancer patients. However, even though more cancer patients are selecting surrogates to make medical decisions on their behalf in the event that they are no longer able to do so, the number of end-of-life discussions and rates of terminal hospitalizations remain unchanged (64). This inconsistency highlights an important concept that patients may not be discussing or reflecting on their end-of-life care preferences with their oncologists, but rather are choosing surrogates who may mistakenly make decisions that are discordant with patients' individual goals.

Cancer patients who do have the opportunity to discuss their end-of-life care wishes with a physician are more likely to receive care at the end of life that honors these values and preferences (65). Speaking to the complexity of ACP, there is no established paradigm to guide the timing, approach, and content of such discussions, which therefore often occur late if at all. In a large, multi-center prospective cohort study of patients diagnosed with Stage IV lung or colorectal cancer, Mack *et al.* show that 55% of documented initial end-of-life care discussions occur in the hospital, with conversations taking place a median of only 33 days before death (66). Recent analysis of data from the United States Health and Retirement Study additionally confirms that patients with cancer have significantly higher odds of completing advance directives late in their disease course, specifically during the last 3 months of life (67).

The timing of advance directive completion is noteworthy because it directly relates to patient preferences, with late completion associated with more aggressive end-of-life care preferences (67). While this relationship may be the result of some patients who genuinely opt for aggressive treatment, it is likely influenced by patient distress, inaccurate expectations for recovery and prolonged life, and the inadequate quality of end-of-life conversations when being treated for acute disease-related complications. Patients and their family members may feel compelled to make urgent (and therefore, possibly uninformed) end-of-life care decisions that result in unwanted aggressive care, particularly if these discussions with their medical team are conducted in a de-personalized or hurried manner. Likewise, if advance directive completion is performed too early, patients may not appreciate the clinical context of a hypothetical scenario to accurately predict how they may feel when they are seriously ill (68,69). Oncologists must

thus work toward finding the optimal time to discuss end-of-life care options for each patient in order to achieve high quality ACP.

For example, patient preferences regarding “code status” or the use of life-sustaining interventions, such as cardiopulmonary resuscitation (CPR) and mechanical ventilation, are a fundamental component of advance directives and care planning. Analysis of data from the Coping with Cancer Study provides evidence to suggest that cancer patients who elect for do-not-resuscitate (DNR) orders have better quality of life and lower health-care associated costs during the last week of life (70). Yet, the decision for a patient to allow for a natural death and elect for a DNR order to be placed in his or her medical chart is not necessarily intuitive. Perceptions on the success and process of CPR may be shaped by the portrayal of CPR in society and entertainment, well before the physician-patient clinical encounter (71,72). Adding to this discrepancy between the medical reality and societal depiction of CPR, discussions about CPR held during a hospital admission are frequently without physician guidance, described with medical jargon, and framed in a way that is not specific to each patient’s medical condition (73-75). Code status discussions upon hospital admission may occur too late in the disease trajectory of cancer patients and cut too short the time for patients to make meaningful decisions, especially when this is the first time they are being asked to express their values and goals for their care. This simplifies a dynamic cognitive process into an instantaneous, sometimes hasty, decision. Instead, ACP with earlier, yet not too remote, end-of-life care discussions during a time of relative clinical stability can empower cancer patients to contribute to their future medical care, resulting in fewer hospitalizations, less chemotherapy, and increased utilization of appropriate hospice services during the last days of life (76,77).

Along with the difficulty of ACP timing, challenges in physician-patient communication due to poor health literacy, time constraints in the outpatient setting, inaccurate prognostic expectations, and gaps in illness understanding can impede patients from making well-informed decisions that are consonant with their goals and preferences for future care (78-83). Even though most cancer patients want to be knowledgeable of their end-of-life care options (84), oncologists may not be prepared to help patients navigate these options and engage in ACP due to lack of formal training (85). Fearful of losing their therapeutic alliance, oncologists may feel less inclined to

participate in end-of-life discussions or do so with poor communication, with concern that these conversations will negatively impact the mood and diminish hope for patients who are still actively receiving cancer treatment (86,87). Furthermore, accurate prognostication by oncologists about the life-expectancy of patients is strongly associated with greater patient acknowledgment of being terminally ill, and accordingly, improved ACP with higher DNR order completion rates and less aggressive care near death (88). Prognostic certainty is, however, difficult to achieve in our current era of rapid drug development. New treatment options can make it challenging for oncologists to help patients navigate their disease trajectories and appropriately time ACP discussions (89,90). Still, the act of prognostic disclosure enables patients to have a better sense of their life expectancy, as patients who have had discussions about prognosis with their oncologists have more realistic expectations and can thereby plan for their end-of-life care (28,91). Therefore, in a process that is often inherently complex and emotionally challenging for both oncologists and their patients, further work is needed to circumvent communication barriers and facilitate quality ACP.

The use of informational video tools is a proven method that addresses some of the above shortcomings in physician-patient communication, with the aim to enrich patient understanding of end-of-life care options. Volandes *et al.* first showed that among 120 older patients, a video depiction of care options for a patient with advanced dementia led to significant changes in end-of-life care preferences, from life-sustaining treatments (CPR, mechanical ventilation) to basic care (acute hospitalizations, antibiotics, no CPR) or comfort care (symptom relief). The respective pre-video preferences for life-sustaining, basic, and comfort care were 20.8%, 18.3%, and 50%, and shifted to post-video preferences of 0%, 8.3%, and 89.2%. Viewing the video also decreased the number of patients who were unsure of their preferences (92). Compared to a verbal description of future care options, video tools increased the likelihood of electing comfort care in the setting of advanced dementia and resulted in more durable preferences over time (93). In patients with progressive cancer, multiple randomized controlled trials and surveys have established that the use of an informational video aid allows for better visualization of CPR and end-of-life care options, informing cancer patients to make lasting decisions that may be better aligned with their value systems. Those patients randomized to watching goals-of-care videos were less likely to opt for CPR, mechanical ventilation, and

aggressive care at the end of life (94-96). Examples of video support tools for patients and healthcare providers can be viewed on the website www.acpdecisions.org of the non-profit organization ACP Decisions.

As patients with pancreas cancer tend to have poor prognoses, with the majority of patients presenting with either metastatic or locally advanced disease, there is an ongoing need to evaluate advance directive completion and ACP in this patient population. In fact, in a large retrospective chart review of 1,186 consecutive unresectable exocrine pancreas cancer patients at the Mayo Clinic, only 15% of patients had documented advance directives as part of the medical record (97). Epstein *et al.* showed in a randomized controlled study designed specifically for patients with advanced pancreatic adenocarcinoma and hepatobiliary cancers that the use of validated informational videos resulted in a trend towards increased ACP documentation within one month of intervention. Moreover, patients randomized to the video arm instead of receiving a verbal narrative were significantly more likely to change their preferences regarding CPR, with 24% of patients no longer desiring CPR after watching the video. Though knowledge scores and preferences for life-sustaining measures did not differ between study groups, more patients in the video arm ultimately died in hospice settings (98). The findings from this study suggest that informational video aids are effective vehicles for augmenting ACP discourse between patients and their oncology teams. Subsequent analysis of the cohort also describes the common themes based on the content of patients' responses, namely that in spite of patient apprehension, early ACP is ideal, desired, helpful, and should be a necessary component of shared conversations with clinicians (99). Additional research incorporating innovative methods of communication using technology is warranted to help patients plan for and make educated decisions about their care at the end of life.

In order to better define and create a gold standard for patient-centered ACP, a recent model has been piloted to address the biopsychosocial themes of ACP in patients with advanced gastrointestinal cancers. The patient-centered oncologic care and choices (P-COCC) framework uses both introspective narrative and video information to target the myriad factors that contribute to patients' specific end-of-life care decisions. This process ultimately demands reflection of one's personal values, spirituality, symptom burden, social circumstances, family relationships, and comprehension of care options (100). Another instrument to help optimize ACP for patients with advanced cancers utilizes patient reported outcomes to guide the timing of

end-of-life care discussions. In patients receiving non-curative therapy, a seven item "Living with Cancer" survey was administered and focused on outcomes of interest, including performance status, personal desires, cancer-related pain, financial and family burden, and depression. Scores were then compared between two groups—patients whose oncologists deemed it appropriate to continue cancer treatment versus patients whose oncologists were actively engaged or considering ACP due to progression of disease and overall worsening clinical status. Outcome scores significantly differed between groups, suggesting not only that patient reported outcomes correlate with physician assessment of the appropriateness of continuing cancer therapy, but if used longitudinally, patient reported outcomes can help stratify patients into groups with differing ACP needs and facilitate proper timing of end-of-life care discussions (101).

Oncologists must therefore balance the principles of patient autonomy with guidance in order for cancer patients to make informed decisions regarding their end-of-life care. Advancements as above in technology, patient-centered models, and use of patient reported outcomes have shown promising results that can foster optimal planning.

Conclusions

High quality palliative care and ACP are essential for the comprehensive care of patients with pancreatic cancer, and any other serious illnesses. Thoughtful and well-timed integration of both primary and specialty palliative care into standard oncologic care can improve patient outcomes, quality of life, and overall survival. As patients with pancreatic cancer often have unresectable or metastatic disease at diagnosis, ACP helps to elicit end-of-life care preferences and prepare patients for their future medical and palliative needs. Further research is warranted to overcome the modern challenges of integration and to optimize the delivery of supportive care in patients with pancreatic cancer.

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Footnote

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