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HIGHLIGHT ARTICLE

# Palliative Care from the Beginning of Treatment for Advanced Pancreatic Cancer

***Highlights from the "2010 ASCO Gastrointestinal Cancers Symposium". Orlando, FL, USA. January 22-24, 2010***

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**Summary**

Palliative care ought to be offered at the initiation of treatment for people who are diagnosed with pancreatic cancer, given the poor relative survival rate and the intractable symptom profile of those who have this life-limiting disease. In this article, we argue that palliative treatment of people with pancreatic cancer is not found in extending survival, but rather, in promoting quality of life. This argument is made by reviewing the literature on the state of palliative care in pancreatic cancer and by summarizing key studies presented at the "2010 ASCO Gastrointestinal Cancers Symposium" held in Orlando, FL, USA on January 22-24, 2010. The studies discussed here include: i) a study of a random sample of 564 patients with pancreatic cancer that found that the symptom cluster of fatigue and pain predicted survival (Abstract #265); ii) a retrospective study of 108 patients that identified anticoagulation therapy in those who developed portal vein thrombosis prolonged survival (Abstract #143); iii) a double-blind randomized control trial of 50 patients with gastrointestinal cancers who were cachexic in which a thalidomide-olanzapine-megasterol acetate combination attenuated the effects of cancer-anorexia-cachexia syndrome (Abstract #209); iv) a retrospective study on the role of adjuvant chemoradiation and chemotherapy in the treatment of advanced pancreatic cancer (Abstract #230); and v) the benefit of chemotherapy in patients with metastatic pancreatic cancer 80-year-old or more (Abstract #232). Based on the results presented at the meeting, we believe that the discussion of palliative care in the treatment of advanced pancreatic cancer must not conflate the notion of increased survival with increased quality of life, the latter of which is part and parcel of the goal of palliative care. We believe that future study on the effect on quality of life of early palliative-care interventions among people with pancreatic cancer is necessary.

## Introduction

While slightly fewer than 1.4% of people alive in the United States (US) today will face a diagnosis of pancreatic cancer, its low prevalence belies a poor relative survival rate: the overall 5-year relative survival rate for 1999-2005 US Surveillance, Epidemiology and End Results (SEER) data was 5.5% [1], though this varies according to stage and location of the neoplasm within the pancreas [1, 2]. If the neoplasm is suitable for resection, surgery offers a five-year survival rate of about 25% [3]. When viewed in chronological time, the median survival of people with metastatic pancreatic cancer is three to six months, while those with locally advanced disease have a median survival of six to nine months [4, 5].

These unfavorable figures make exigent the World Health Organization's (WHO) palliative-care guidelines that encourage the initiation of palliative care early in the course of treatment [6]. Palliative care, following WHO's definition, is the active total care of patients' body, mind, and spirit. By improving quality of life, palliative care affirms life through alleviating suffering and relieving pain, without remedying underlying causes [6]. Given the short survival of those with advanced pancreatic cancer, ensuring the highest quality of life possible is one of the foci of palliative-care interventions with pancreatic cancer patients.

The distressing symptoms people with pancreatic cancer experience heighten the importance of early palliative-care intervention. At diagnosis patients often present with fatigue, loss of appetite, impaired sense of well-being, and pain [7]. Crippa *et al*. found that those with a localized cancer present most commonly with jaundice, while those with locally advanced or metastatic disease more likely present with abdominal pain and weight loss [8]. By initiating palliative care at

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**Abbreviations** CACS: cancer anorexia-cachexia syndrome; HRQoL: health-related quality of life

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the beginning of treatment patients are familiar with the function of palliative-care providers, which is important as the disease progresses, for Labori *et al*. found that in the last eight weeks of life, these symptoms intensified [7], and may be accompanied by cancer anorexia-cachexia syndrome (CACS) [9], a syndrome that has been identified with a prognosis of less than 90 days [10].

In addition to traditional palliative measures of managing pain and symptoms, surgery and endoscopy may in some instances play a role in palliation. While Crippa *et al*. found that surgery can favorably affect quality of life [8], Neiveen van Dijkum *et al*. found that quality of life decreased after surgery, though it returned to baseline after three months [11]. If life expectancy is short, surgery may not, then, offer palliative benefits. Unequivocal, however, are proven palliative outcomes of endoscopy for placing metal stents for biliary or duodenal obstruction [7, 8, 12, 13, 14], as well as transhepatic portography for portal vein thrombosis [15, 16].

On the other hand, the literature does not suggest a clear palliative role for chemoradiation and chemotherapy alone. Crippa *et al*., who followed health-related quality of life (HRQoL) scores in patients who underwent chemoradiation and chemotherapy alone for treatment of pancreatic cancer, found that chemoradiation did not change HRQoL scores, but the HRQoL scores of those who received chemotherapy alone significantly decreased, a decrease perhaps explained by chemotherapy preferentially performed in patients with metastatic disease [8]. Recent literature on the role of chemotherapy in the treatment of advanced pancreatic cancer focuses on whether it results in significant survival benefit [17]. Little, however, has addressed the role of chemotherapy alone in the palliation of symptoms and improvement of HRQoL in advanced pancreatic cancer. Indeed, one review article made the logical category mistake of conflating prolonged survival through treatment with chemotherapeutic agents as having in and of itself a palliative effect [18]. Prolonged survival is not necessary and sufficient to claim palliative benefits such as improved HRQoL.

That there is a need to provide palliative care to patients with pancreatic cancer, thereby positively affecting their HRQoL, is uncontestable. To the end of reporting on the state of palliative care in pancreatic cancer, we review the data presented at the 2010 ASCO Gastrointestinal Cancers Symposium held on January 22 through 24 in Orlando, Florida, USA.

**Highlights on Issues in Palliative Care in the Treatment of Pancreatic Cancer**

Often a difficulty in determining whether to cease treatment for prolonged survival and to put all efforts into palliative care - or, if the patient is within six months of dying, hospice care - is complicated by not having clear and reliable prognostic indicators. However, Gupta *et al*. identified fatigue and pain at initial presentation as independent predictors of survival. In their study, Gupta *et al*. randomly sampled 564 pancreatic cancer patients treated between January 2001 and December 2009. Newly diagnosed participants were 324; 240 participants had no prior treatment history. Males accounted for 333 participants, and females 231. Mean age at presentation was 56.6 years. At presentation, 345 had metastatic disease. Median overall survival of participants was 7.5 months, with a range from 6.7 to 8.3 months. Researchers assessed participants' symptoms at presentation with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C 30 (EORTC QLQ-C30); assessed were fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, and diarrhea. Multivariate analysis found that, independent of age at presentation, gender, stage at diagnosis, and prior treatment history, fatigue (P=0.02) and pain (P=0.01) significantly predicted survival. Gupta *et al*. concluded that identifying the symptom cluster of fatigue and pain may aid decision-making vis-à-vis symptom management [19].

In a retrospective study of medical records, Price *et al*. determined the frequency and the natural history of portal vein thrombosis and venous thromboembolism in 108 patients with pancreatic cancer, and the effect of portal vein thrombosis on survival [20]. They also analyzed whether ten potential risk factors (age, gender, stage, primary tumor size, progression, venous thromboembolism development, prior surgery, prior radiation, and use of erythropoiesis-stimulating agents or transfusion support) for portal vein thrombosis had any prognostic significance. Portal vein thrombosis occurred in 30% (n=32) of all patients, including in 21% of patients who had had resection, 33% of patients with locally advanced pancreatic cancer, and 36% of patients with metastatic disease. From diagnosis, average time to development of portal vein thrombosis was 9.1 months, ranging from an average of 6.3 months for patients with metastatic disease, 12.1 months for patients who had had resection, to 15.8 months for patients with locally advanced pancreatic cancer. The average time to death from the development of portal vein thrombosis was 4.1 months: in patients with metastatic disease it was 2.2 months, 4.9 months in patients who had had resection, and 6.1 months in patient with locally advanced disease. On bivariate analysis, the ten potential risk factors did not predict portal vein thrombosis. However, Price *et al*. found that of the 32 patients who developed portal vein thrombosis, 8 had received therapeutic anticoagulation; the survival of these 8 was 4.2 months longer than those who did not receive anticoagulation (6.6 months *versus* 2.4 months, respectively) [20]. So though no potential risk factors were identified, Price *et al*. did find that development of portal vein thrombosis was associated with less than six months to live, an important prognostic tool when considering initiation of hospice care, and that therapeutic anticoagulation may benefit pancreatic cancer patients [20].

Sanchetee, located in "a resource poor area" where at presentation 90% of the patients with pancreatic cancer have advanced disease for whom palliative care is the only treatment option, assessed in a single-center, double-blind study whether thalidomide or thalidomide with olanziapine and megastrol acetate were safe and effective treatments of the late symptom of CACS [21]. Fifty patients with GI cancers who had lost 10% of the body weight were included in the study. Sixteen patients were randomized to thalidomide 100 mg daily; and 17 patients to thalidomide 100 mg, olanzipine 5 mg, and megestrol acetate 80 mg daily. They were evaluated at four weeks. Twelve patients were randomized to a thalidomide only group, and eight to a control group; they were evaluated at eight weeks. At four weeks, patients in the thalidomide-olanzipine-megestrol group had gained 0.37 kg in weight and 1.0 $cm^3$ in arm muscle mass, compared with a loss of 2.21 kg of weight (absolute difference -2.59 kg; P=0.005) and 4.6 $cm^3$ in arm muscle mass (absolute difference -5.6 $cm^3$; P=0.002) in the thalidomide only group. At eight weeks, patients in the thalidomide-olanzipine-megestrol group had lost 0.06 kg in weight and 0.5 $cm^3$ in arm muscle mass, while patients in the thalidomide only group lost 3.62 kg in weight (absolute difference -3.57; P=0.034) and 8.4 $cm^3$ (absolute difference -7.9 $cm^3$; P=0.014). Improvement in physical functioning positively correlated with weight gain (P=0.001). Sanchetee concluded that the thalidomide-olanzapine-megestrol acetate combination attenuated weight loss and loss of lean body mass in patients with GI cancers who experienced CACS [21].

Two studies presented at the 2010 ASCO Gastrointestinal Cancers Symposium dealt with the vexing question of the roles of chemoradiation and chemotherapy in the treatment of advanced pancreatic cancer: Subbiah *et al*. [22] and Aldoss *et al*. [23]. Subbiah *et al*. retrospectively analyzed medical records from the Veterans Affairs Central Cancer Registry database of 742 patients who had resection for early-stage pancreatic cancer between the years 1995 and 2007[22]. Fifty-seven percent of patients had no adjuvant therapy, 11% had adjuvant chemotherapy, 28% had chemoradiation, and 4% had adjuvant radiation. Median overall survival in the adjuvant chemotherapy group was 1.36 years, and in the adjuvant chemoradiation group was 1.54 years. In the adjuvant chemotherapy group, 63%, 19%, and 13% survived one, three, and five years, compared with 72%, 28%, and 19% in the adjuvant chemoradiation group, respectively. Multivariate analysis associated decreased survival with advanced age, number of positive lymph nodes, and poorly differentiated tumors (P=0.0001). Race, gender, smoking history, and number of examined lymph nodes were not associated with survival [22].

The research question Aldoss *et al*. asked was whether chemotherapy played a palliative role for metastatic pancreatic cancer in the Veterans Affairs population aged 80 and above [23]. To answer the question, they retrospectively reviewed medical records from the Veterans Affairs Central Cancer Registry of all cases of metastatic pancreatic cancer from 1995 to 2005 in the age 80 and over population. Of the 440 eligible patients, 12% received chemotherapy alone, 2% received radiotherapy alone, 1% received chemoradiation therapy, and 2% underwent surgery. Aldoss *et al*. found that patients who received chemotherapy survived 4.9 months, whereas those who received no therapy (83%) survived 1.7 months; this difference in survival was significant (P<0.0001). Thirteen percent of patients who received chemotherapy survived one year, while 3% of patients who received no therapy survived one year. Current smoking was significantly associated with a decrease in median overall survival compared to past or never smoking status (P=0.001). However, tumor grade, race, or gender was not significantly associated with overall survival [23].

**Discussion**

Aldoss *et al*. entitled their paper "Benefit of chemotherapy in very elderly patients … with metastatic" pancreatic cancer [23]. In the body of the abstract of their paper, they state that their interest lay in the palliative role of chemotherapy. The conclusions they draw, however, focus solely on survival benefit. While they do acknowledge in their concluding remarks that "increased survival with chemotherapy could have been at the cost of excessive toxicity … and poor quality of life," they still imply that increased survival is a benefit [23]. This is the philosophical mistake of question-begging, that is, the mistake in which the conclusion is contained in the premise: for by "benefit" they seem to mean increased survival, and by "benefit" they seem to imply "palliative". But HRQoL must be studied to determine whether the 3.2 months of survival gained by the administration of chemotherapy was, as they noted, associated with unbearable toxicity and untenably poor HRQoL. Until the effect of therapies on the cancer are evaluated in the context of the therapies' effects on the whole patient - body, mind, and spirit - then one cannot imply that increased overall survival is a palliative benefit. While increased survival through therapies is not to be begrudged in pancreatic cancer, a cancer type that is associated with poor survival rates, future research into whether care that does not aim at life-prolonging treatment but rather improvement of HRQoL is itself associated with increased survival rates must be undertaken. Subbiah *et al*. [22] make the same conceptual mistake. More tellingly, however, Subbiah *et al*. have no novel finding: their finding that decreased survival is associated with increased age, number of positive nodes, and poorly differentiated tumors is so commonplace a statement that it borders on being hackneyed.

Important and interesting, however, is the finding by Sanchetee that CACS can be ameliorated by the combination of thalidomide, olanziapine and megastrol

acetate [21]. CACS affects not only pancreatic cancer patients who live in poorly resourced areas, but pancreatic cancer patients worldwide, rich or poor. Sanchetee's study, though its strength lies in that it is a double-blind randomized control trial, needs to be replicated, and what is meant by saying that the thalidomide-olanziapine-megastrol acetate combination is well tolerated needs to be explicated; but Sanchetee's finding is important to the aims of palliative care, for by reducing the effects of CACS, HRQoL is indeed increased. Likewise, the finding by Price *et al*. [20] that anticoagulation therapy can reduce the incidence of portal vein thrombosis in the pancreatic cancer population merits further study; for the practice of palliative care among patients with pancreatic cancer needs safe and effective anticoagulation strategies to address portal vein thrombosis. Finally, Gupta *et al*. identify the cluster of pain and fatigue as a predictor of survival [19], a finding that can be a useful prognostic indicator, especially when making the decision to change the goal of care from life-prolonging to enhancing the quality of life.

In pancreatic cancer, with poor relative survival rates, palliative care, with its attention to improving HRQoL, needs to be initiated at the onset of treatment. Future research needs to understand the effect of early palliative care interventions not only on HRQoL but also on survival.

**Conflict of interest** Authors report no conflict of interest

**References**

1. Horner MJ, Ries LAG, Krapcho M, Neyman N, Aminou R, Howlader N, et al (eds). SEER Cancer Statistics Review, 1975-2006, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2006/, based on November 2008 SEER data submission, posted to the SEER web site, 2009.

2. Lau MK, Davila JA, Shaib YH. Incidence and Survival of Pancreatic Head and Body and Tail Cancers: A Population-Based Study in the United States. Pancreas 2009 Nov 16. [PMID 19924019]

3. Hackert T, Büchler MW, Werner J. Surgical options in the management of pancreatic cancer. Minerva Chir 2009; 64:465-476. [PMID 19859037]

4. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. Surg Oncol Clin N Am 2004; 13:491-503. [PMID 15236731]

5. Sohn TA, Lillemoe KD, Cameron JL, Huang JJ, Pitt HA, Yeo CJ. Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. J Am Coll Surg 1999; 188:658-666. [PMID 10359359]

6. World Health Organization. Cancer: Palliative care. WHO Programmes and Projects.

7. Labori KJ, Hjermstad MJ, Wester T, Buanes T, Loge JH. Symptom profiles and palliative care in advanced pancreatic cancer-a prospective study. Support Care Cancer 2006; 14:1126-33. [PMID 16601947]

8. Uomo G, Gallucci F, Rabitti PG. Anorexia-cachexia syndrome in pancreatic cancer: recent development in research and management. JOP. J Pancreas (Online) 2006; 7:157-62. [PMID 16525199]

9. Crippa S, Domínguez I, Rodríguez JR, Razo O, Thayer SP, Ryan DP, et al. Quality of life in pancreatic cancer: analysis by stage and treatment. J Gastrointest Surg 2008; 12:783-94. [PMID 18317851]

10. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations--a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol 2005; 23:6240-8. [PMID 16135490]

11. Nieveen van Dijkum EJ, Kuhlmann KF, Terwee CB, Obertop H, de Haes JC, Gouma DJ. Quality of life after curative or palliative surgical treatment of pancreatic and periampullary carcinoma. Br J Surg 2005; 92:471-7. [PMID 15672431]

12. Freitas D, Dos Santos Fernandes G, Hoff P, Cunha, JE. Medical management of pancreatic adenocarcinoma. Pancreatology 2009; 9:223-32. [PMID 194209891]

13. Mortenson MM, HO HS, Bold RJ. An analysis of cost and clinical outcome in palliation for advanced pancreatic cancer. Am J Surg 2005; 190:406-11. [PMID 16105527]

14. Artifon EL, Sakai P, Cunha JE, Dupont A, Filho FM, Hondo FY, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. Am J Gastroenterol 2006; 101:735-42. [PMID 16968509]

15. Ellis CM, Shenoy S, Litwin A, Soehnlein S, Gibbs JF. Effective endovascular stenting of malignant portal vein obstruction in pancreatic cancer. HPB Surg 2009; 2009:426-36. [PMID 19826629]

16. Yamakado K, Nakatsuka A, Tanaka N, Fujii A, Terada N, Takeda K. Malignant portal venous obstructions treated by stent placement: significant factors affecting patency. J Vasc Interv Radiol 2001; 12:1407-15. [PMID 11742015]

17. Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 2009; 27:5513-8. [PMID 19858379]

18. Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D. WITHDRAWN: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. Cochrane Database Syst Rev 2009; 3:CD002093. [PMID 19821291]

19. Gupta D, Rodeghier M, Grutsch JF, Lis CG. Predicting survival in advanced pancreatic cancer: The role of symptom clusters. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 265.

20. Price LH, Nguyen MB, Picozzi VJ, Kozarek RA. Portal vein thrombosis in pancreatic cancer: Natural history, risk factors, and implications for patient management. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 143.

21. Sanchetee SC. Thalidomide versus thalidomide with olanziapine and megastrol acetate in treatment of cachexia in gastrointestinal cancer: A randomized trial. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 209.

22. Subbiah S, Aldoss I, Gonsalves W, Tashi T, Al-Howaidi I, Silberstein PT. Adjuvant chemotherapy versus chemoradiation therapy in resectable pancreatic cancer: Retrospective analysis from the VA Central Cancer Registry (VACCR) database. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 230.

23. Aldoss I, Subbiah S, Gonsalves W, Fang X, Silberstein PT. Benefit of chemotherapy in very elderly patients (≥ 80) with metastatic pancreatic cancer: VA Central Cancer Registry (VACCR) database analysis. 2010 ASCO Gastrointestinal Cancers Symposium. Abstract No. 232.