Journal of BUON **15:** 543-546, 2010

ORIGINAL ARTICLE

Does the tumor localization in advanced pancreatic cancer have an influence on the management of symptoms and pain?

C. Eyigor[1], B. Karaca[2], Y. Kuzeyli-Yildirim[3], R. Uslu[2], M. Uyar[1], A. Coker[4]

[1]Ege University Faculty of Medicine, Anesthesiology Department, Pain Clinic, Izmir; [2]Ege University Faculty of Medicine, Tulay Aktas Oncology Hospital, Division of Medical Oncology, Izmir; [3]Ege University Nursing School, Department of Internal Medicine Nursing, Izmir; [4]Ege University Faculty of Medicine, General Surgery Department, Izmir, Turkey

Summary

Purpose: *The symptoms and survival of patients with advanced pancreatic cancer show great variability according to tumor localization. The main purpose of this study was to see for any differences between the intensity of symptoms, mainly pain, and the need for analgesic treatment in advanced pancreatic cancer patients with different (head vs. body-tail) tumor localizations.*

Methods: *Ninety-six patients with histologically confirmed pancreatic cancer were enrolled in the study. The patients were divided into 2 subgroups according to tumor localization: group 1 (n=50) with head tumors and group 2 (n=46) with body and tail tumors. The demographic features of the patients as well as disease stages, onset of symptoms and necessity and consumption of analgesics were recorded. Patients were followed-up until death, and survival data was also analysed.*

Results: *At the time of diagnosis, patients with body and tail tumors had more advanced disease stages compared to head tumors (p=0.006). While jaundice was the most common initial symptom in head tumors (p <0.0001), it was pain in body and tail tumors (p <0.001). Patients with body and tail tumors had more analgesics consumption as compared to those with head tumors (p=0.009). No statistically significant difference in survival was detected between the 2 groups (p >0.05).*

Conclusion: *We believe that pancreatic cancer should be accepted as two diverse disease types according to tumor localization, and pain and symptom management should be organized based on this fact.*

Key words: pain, pancreatic cancer, symptom, tumor localization

Introduction

Pancreatic cancer is a major cause of cancer-related death and is associated with a particularly high mortality rate. The disease is generally asymptomatic at the early stages, thus the great majority of patients are often diagnosed at advanced stages [1-3]. Anatomically, pancreatic cancer is localized either in the head, body or tail. The head of pancreas is the most common site of tumor occurrence with a prevalence of 65%, and this is followed by body-tail and other combined localizations within the organ [4-6]. Surgery is the main standard of care for pancreatic cancer, which could be achieved in a very limited number of patients. That's why palliative care approaches - including pain management and improving the quality of life - generally come forward in the management of pancreatic cancer [7,8].

Both the symptoms at the time of diagnosis and tumor localization have an impact on the prognosis of pancreatic cancer. In addition, symptoms and the degree of pain show distinct features within different localizations of the tumor. The most common symptoms of pancreatic cancer at the time of diagnosis may be summarized as jaundice, abdominal and back pain, fatigue, nausea and loss of weight [9,10].

However, from the clinical point of view, the symptoms and survival of advanced pancreatic cancer patients show great variability. Our hypothesis is that this variability in clinical presentation may be associated with the primary tumor localization. Therefore, the main purpose of this study was to see for any difference between the grade of symptoms, mainly pain, and the patients' need for analgesic treatment in cases of advanced pancreatic cancer with different (head vs.

Correspondence to: Can Eyigor, MD. Ege University Faculty of Medicine, Anesthesiology Department, Pain Clinic, 35100 Bornova-Izmir, Turkey. Tel: +90 2323902190, E-mail: can.eyigor@yahoo.com.tr

Received 14-10-2009; Accepted 05-12-2009

body-tail) tumor localizations, from the time of diagnosis until death.

Methods

The medical records of 96 patients with histologically confirmed advanced or metastatic adenocarcinoma of the pancreas who were treated at the Ege University School of Medicine, T. Aktas Oncology Hospital and Department of Algology, from November 2005 to November 2008 were reviewed after approval of the local ethics committee. A team of physicians including surgeons specialized at hepatopancreaticobiliary system surgery, medical oncologists and algologists were in charge of taking care of these patients. At the time of data collection, both physicians and the patients were blinded to primary tumor localization to avoid bias. After all the necessary data were collected, the patients were divided into 2 subgroups according to tumor localization: group 1 included patients with head tumors, and group 2 patients with tumors in the body and tail of pancreas.

Demographic features, onset symptoms and tumor characteristics were recorded. In addition, the mean time interval between the onset of symptoms, mainly pain, and the usage of analgesics or other supportive treatments, were recorded. Tumor localization was detected with computed tomography (CT). Tumor staging was done according to the International Union Against Cancer (UICC), based on the pathological evaluation of the patients.

Every patient enrolled in the study was followed up routinely every 3 months until death. After the diagnosis of pancreatic cancer was histologically confirmed, patients found eligible for operation received oral preparations of exocrine pancreas enzymes (Kreon® 10000 or 25000 thrice a day), routinely. Patients with head localization and having obstructive jaundice were treated with endoscopic temporary placement of plastic stents. Patients whose bilirubin levels dropped below 15 mg/dl were operated.

During follow-up, the patients' analgesic need and consumption were recorded. Pain management was done according to the World Health Organisation (WHO) analgesic ladder system (1, 2, or 3 step). Depending on this guideline, patients who had mild pain visual analogue scale (VAS) <3 received paracetamol (max. 4 g/day) and/or non-steroid anti-inflammatory drugs (NSAIDs) at their highest doses, whereas those with moderate or severe pain (VAS ≥ 4) received tramadol (max. 400 mg/day) and/or third-step analgesics (morphine or fentanyl TTS).

During the follow-up period, 26 patients were lost to follow-up due to different reasons. The analgesic consumption of the patients was analysed in 70 patients (group 1: n=39, group 2: n=31), while survival analyses were carried out in 68 patients.

Statistical analysis

Descriptive tables and statistical analyses were carried out using SPSS 13 statistical program. Age and the time of diagnosis were evaluated with Students' t-test. Gender, disease stage at the time of diagnosis, WHO analgesic consumption, onset of symptoms, and analgesic consumption in the terminal stage were analysed with Pearson chi-square test. Survival analysis was done by Kaplan-Meier and log-rank test. For comparison of difference in analgesic consumption at the time of diagnosis and terminal stage the McNemar-Bowker test was used. A p-value <0.05 was considered as statistically significant.

Results

Ninety-six patients were enrolled in the study (group 1, n=50, and group 2, n=46). The demographic features of the patients are summarised in Table 1. The mean age of group 1 patients was statistically higher compared with group 2 patients ($p < 0.05$), but the pathologic disease stage at the time of diagnosis was statistically more advanced in group 2 patients as compared with group 1 ($p=0.006$). There was no statistically significant difference in time to diagnosis between the 2 groups ($p > 0.05$; Table 1).

The need for analgesic treatment in the initial phase of the disease was much more higher in group 2 patients ($p < 0.0001$; Figure 1).

When the onset of symptoms was compared, jaundice was the most common symptom in group 1 patients

Table 1. Baseline characteristics

Characteristics	*Group 1 (n=50) n (%)*	*Group 2 (n=46) n (%)*
Age (mean±SD)*	61.68±10.33	56.93±11.01
Sex		
Men	34 (68)	30 (65.2)
Women	16 (32)	16 (34.8)
Pathological stage*		
2	3 (6.3)	0
3	17 (35.4)	6 (13)
4	28 (58.3)	46 (87)
Time since diagnosis; months (mean±SD)	3.1±1.8	2.7±1.5

*p <0.05, SD: standard deviation

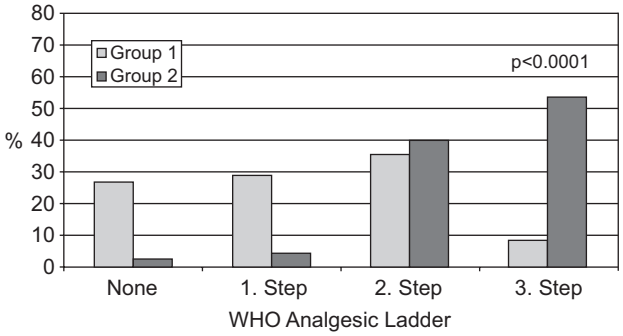

Figure 1. Need for analgesic treatment in the initial phase of the disease.

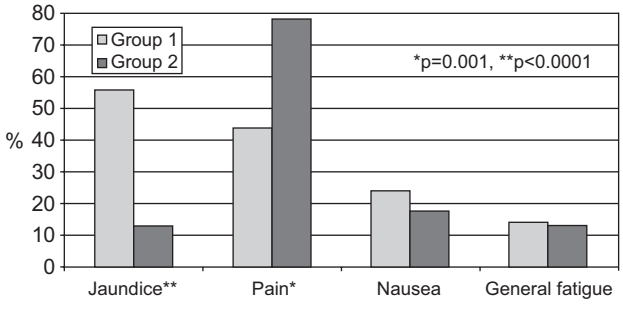

Figure 2. Onset of symptoms.

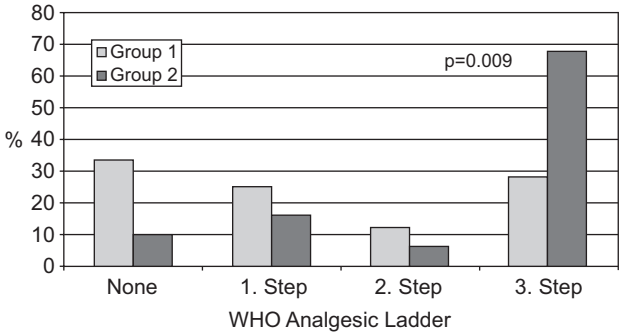

Figure 3. Analgesics consumption in the terminal stage of disease.

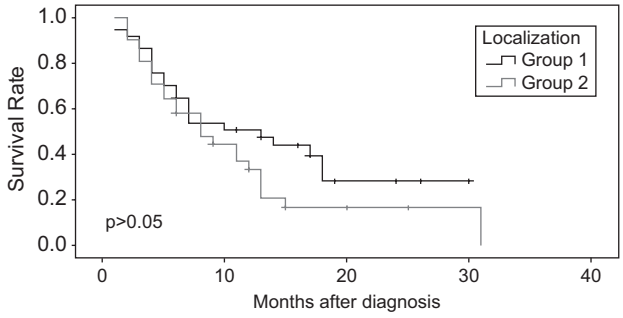

Figure 4. Kaplan-Meier survival curves of head and body-tail tumors.

($p < 0.0001$), whereas it was pain in group 2 patients ($p=0.001$). This diversity of the onset of symptoms between the 2 groups was statistically significant (Figure 2).

From group 1 patients (n=49) 24 (51%) were eligible for operation, while only 11 (24.4%) of 45 group 2 patients were operated ($p=0.019$).

The analgesic consumption in the terminal stage of disease was much more higher in group 2 patients as compared to group 1 ($p=0.009$; Figure 3). In addition, while there was no change in analgesic consumption of group 1 patients from the time of diagnosis till the terminal stage of disease ($p > 0.05$), the analgesic consumption of group 2 patients was ever increasing with the passing of time ($p=0.017$).

Regarding survival, there was no statistically significant difference between the 2 groups (group 1: 14.5±1.9 months, group 2: 11.4±1.8 months; $p > 0.05$; Figure 4).

Discussion

To the best of our knowledge, this is the first study in the literature searching for pain management of advanced pancreatic cancer patients from the time of diagnosis till death. Relevant studies that divide pancreatic cancer patients according to the localization of the primary tumor had only searched for either the prognosis [9] or the efficacy of sympathetic blockage [10,11]. On the contrary, in our study pancreatic cancer patients had been followed-up from the time of the diagnosis till death, and we noticed some important differences between symptoms and analgesic needs according to the localization of the primary tumor.

Pancreatic cancer patients with different tumor localization show versatile clinical presentation, and this may alter the time gap from the onset of symptoms till diagnosis. In a study by Watanabe et al. [9] the mean time gap between the onset of symptoms till diagnosis was 75 days. However, this time gap was shorter (58 days) in patients with jaundice, and the authors claimed that the patients presented with jaundice had better outcome because of early diagnosis, as compared to the others. The same study also showed that patients without symptoms had the best prognosis. But, in our study, the time gap was 3.1±1.8 months in group 1 patients, whereas it was 2.7±1.5 in group 2 patients, showing no statistically significant difference between these two groups having different onset of symptoms at diagnosis. Although jaundice was more frequent in group 1, it didn't have any influence on earlier diagnosis in our

study. This may be due to the ignorance of symptoms in Turkish patients, and may be related with low socioeconomic and educational status.

Pancreatic cancer is a devastating disease with a dismal prognosis and early detection remains a challenge [10,12]. Surgery remains the primary therapy for the minority of patients who are candidates for resection. This group amounts to only 10-15% of those diagnosed with the disease. Even with a successful complete resection (R0), long-term survival remains poor, typically amounting to one-fifth of patients at 5 years [13]. Besides, due to frequent perineural invasion regardless of stage or size of the tumor and anatomical proximity to the celiac plexus, pain may occur at any tumor stage. The relief of pain due to pancreatic cancer, as well as the maintenance of quality of life in preterminal patients, remains a therapeutic challenge [14]. Pharmacologic management is usually regarded as the cornerstone of care in most patients with pancreatic cancer pain [15].

Pain in pancreatic cancer may be related to different reasons e.g. invasion of the celiac plexus, or obstruction and distention in the pancreatic canal, or inflammation and ischemia [16-18]. The early clinical picture of the disease is usually vague, but the localization of cancer in the head or tail and body of the gland is connected with some differences in clinical symptoms and pain characteristics. Patients with body and tail tumors and advanced tumor infiltration and metastatic spread to the neighboring neural plexuses present with severe pain as compared to head tumors [5,9,10], necessitating analgesic treatment soon after disease diagnosis till their terminal stage.

In the present study, the analgesic consumption of patients with body and tail tumors increased significantly from the time of diagnosis till the terminal stage [10,19]. However, no change was found in analgesic consumption of patients with head tumors. This may be related to the higher probability of diagnosing patients with head tumors at early stages as compared to those with body and tail disease, thus making more patients with head tumors eligible for operation at the time of diagnosis.

Besides, in concordance with the literature, patients with head tumors in our study presented with earlier disease stages as compared with those with body and tail tumors, thus increasing their chance to undergo operation at the time of diagnosis. However, this did not have any significant impact on survival (group 1: 14.4±1.9 months vs. group 2: 11.4±1.8 months, $p>0.05$). This may be due to the rather low number of patients in both groups, and should be further investigated with larger patient numbers.

In conclusion, we demonstrated that the primary tumor localization had strong influence on pain of patients with pancreatic cancer. Initial symptoms, pain intensity, and need for analgesics consumption were significantly different, depending on the localization of the primary tumor. We believe that pancreatic cancer should be accepted as two diverse types according to tumor localization on diagnosis, and pain and symptom management should be organized based on this fact.

References

1. Lebovits AH, Lefkowitz M. Pain management of pancreatic carcinoma: a review. Pain 1989; 36: 1-11.
2. Bockman ED, Buchler MW. Pain mechanisms. In: Beger H, Warshaw A, Buchler MW et al (Eds): The Pancreas. London: Blackwell Science, 1998, pp 698-701.
3. Ischia S, Polati E, Finco G, Gottin L, Benedini B. 1998 Labat lecture. The role of the neurolytic celiac plexus block in pancreatic cancer pain management: Do we have the answers? Region Anesth Pain Med 1998; 23: 611-614.
4. Ventafridda GV, Caraceni AT, Sbanotto M, Barletta L, De Conno F. Pain treatment in cancer of the pancreas. Eur J Surg Oncol 1990; 16: 1-6.
5. Lillemoe KD, Cameron JL, Kaufman HS, Yeo CJ, Pitt HA, Sauter PK. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. Ann Surg 1993; 217: 447-457.
6. Freelove R, Walling AD. Pancreatic Cancer: Diagnosis and Management. Am Fam Physician 2006; 73: 485-492.
7. Amann ST, Toskes PP. Analgesic Treatment. In: Beger H, Warshaw A, Buchler MW et al (Eds): The Pancreas. London: Blackwell Science, 1998, pp 766-771.
8. Kawamata M, Ishitani K, Ishikawa K et al. Comparison between celiac plexus block and morphine treatment on quality of life in patients with pancreatic cancer pain. Pain 1996; 64: 597-602.
9. Watanabe I, Sasaki S, Konishi M et al. Onset Symptoms and Tumor Locations as Prognostic Factors of Pancreatic Cancer. Pancreas 2004; 28: 160-165.
10. Rykowski JJ, Hilgier M. Efficacy of neurolytic celiac plexus block in varying locations of pancreatic cancer: influence on pain relief. Anesthesiology 2000; 92: 347-354.
11. Ozyalcin NS, Talu GK, Camlica H, Erdine S. Efficacy of coeliac plexus and splanchnic nerve blockades in body and tail located pancreatic cancer pain. Eur J Pain 2004; 8: 539-545.
12. di Mola FF, di Sebastiano P. Pain and pain generation in pancreatic cancer. Langenbecks Arch Surg 2008; 393: 919-922.
13. Kleeff J, Michalski C, Friess H, Büchler MW. Pancreatic cancer: from bench to 5-year survival. Pancreas 2006; 33: 111-118.
14. Beger HG, Rau B, Gansauge F, Poch B, Link KH. Treatment of pancreatic cancer: challenge of the facts. World J Surg 2003; 27: 1075-1084.
15. Fazal S, Saif MW. Supportive and palliative care of pancreatic cancer. JOP 2007; 8: 240-253.
16. Ceyhan GO, Demir IE, Altintas B et al. Neural invasion in pancreatic cancer: a mutual tropism between neurons and cancer cells. Biochem Biophys Res Commun 2008; 374: 442-447.
17. Collins D, Penman I, Mishra G, Draganov P. EUS-guided celiac block and neurolysis. Endoscopy 2006; 38: 935-939.
18. Schmulewitz N, Hawes R. EUS-guided celiac plexus neurolysis-technique and indication. Endoscopy 2003; 35: 49-53.
19. Doucas H, Sutton CD, Zimmerman A, Dennison AR, Berry DP. Assessment of pancreatic malignancy with laparoscopy and intraoperative ultrasound. Surg Endosc 2007; 21: 1147-1152.