Clinicopathologic Prognostic Factors in Locally Advanced Pancreatic Cancer Patients Treated with Radiation Therapy

Radyoterapi ile Tedavi Edilen Lokal İleri Evre Pankreas Kanserinde Klinikopatolojik Prognostik Faktörler

Pankreas Kanserinde Radyoterapi / Radiation Therapy in Pancreatic Cancer

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Özet

Giriş: Pankreas kanseri prognozu en kötü malignitelerdendir. Son zamanlarda yapılan randomize klinik çalışmalarda adjuvan kemoterapi (KT), adjuvan kemoradyoterapi veya sadece cerrahi sorularına yanıt aranmaktadır. Çalışmamızda kliniğimizde lokal ileri pankreas kanseri nedeniyle adjuvan ve definitif radyoterapi (RT) uygulanan hastalar değerlendirilmiştir. Gereç ve Yöntem: 2000-2008 yılları arasında Akdeniz Üniversitesi Radyasyon Onkolojisi Ana Bilim Dalı'nda takip edilen histopatolojik olarak tanısı doğrulanmış ve görüntüleme yöntemleri ile evrelendirme çalışmaları yapılmış pankreas kanserli hastalar retrospektif olarak değerlendirildi. Bulgular: Çalışmaya toplam 32 hasta alındı. Tümör çapına göre sağkalımı belirlemede ROC (Receiver Operating Characteristics) analizi kullanıldı. Hastalar tümor çaplarına göre Grup A, tm çapı 4 cm'den küçük, Grup B tm çapı 4 cm'den büyük olarak gruplara ayrıldı. Hastalarda ortalama sağkalım; 17.3 ay idi. Lenf nodu tutulumu olup olmamasının sağkalımla ilişkisi yoktu (p=0.009). Sağkalım açısından Grup A ve B arasında anlamlı fark vardı. (p=0.029). Tartışma: Pankreas kanseri nedeniyle radyoterapi alması planlanan hastalarda tümör çapı ve lenf nodu durumu prognostik faktörler olarak dikkate alınmalıdır.

Anahtar Kelimeler

Pankreas Kanseri; Radyoterapi; Lenf Nodu Durumu; Tümör Çapı

Abstract

Aim: The prognosis of pancreatic cancer is one of the worst malignancies. In randomized clinical trials done in recent times, the answer is researched for adjuvant chemotherapy, chemoradiotherapy. Our study investigated the clinicopathologic prognostic factors for pancreatic cancer. Material and Method: Patients diagnosed with histopathologically confirmed pancreatic cancer, followed by Akdeniz University School of Medicine, Department of Radiation Oncology between the years 2000-2008 were included in the study. Results: A total number of 32 patients were taken to the study. The tumor diameter values in predicting survival were analyzed using ROC (Receiver Operating Characteristics) curve analysis. Patients were grouped according to their tumor diameters: the tumor diameter lower than 4 cm (Group A), the tumor diameter higher than 4 cm (Group B). The mean survival of patients is determined as 17.3 months. The fact that there is whether or not lymph node involvement is found to be related with survival (p=0.009). A significant relationship between Group A and B in terms of survival is determined (p=0.029). Conclusions: While treatment is considered in patients who are planned to receive radiation therapy because of pancreatic cancer, the tumor diameter and the lymph node status should be taken into account as prognostic factors.

Keywords

Pancreatic Cancer; Radiation Therapy; Lymph Node Status; Tumor Diameter

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Introduction

The global pancreatic cancer ratio is approximately 8/100,000 person per year. It constitutes 2.2% of all the new cancer cases [1]. Men are more affected by this disease when compared to women (female: male ratio of about 1:1.5). The peak incidence is seen between the ages of 60-80 [2].

Despite the progress in surgical techniques, adjuvant chemotherapy and chemoradiotherapy, the pancreatic cancer is still one of the malignancies having worst prognosis. Just at the time of diagnosis, most of the patients are presented with a devastating disease, which is characterized by widespread tumor growth, vital organ dysfunction, uncontrollable pain, fast-growing cachexia and coagulopathy. Only 10-20% of the patients are suitable for surgery in the moment of diagnosis [3].

The pancreatic cancer has a low survival rate and surgical resection is still the only primary curative treatment. Recurrence is seen in 80% of the patients after surgery. Therefore, adjuvant combined therapy is a standard treatment after surgical resection in resectable pancreatic cancers [4]. In randomized clinical studies published in recent years, the answer is researched for adjuvant chemotherapy (CT), for adjuvant chemoradiotherapy or for surgery alone [5-7]. However, a consensus has still been not obtained on the optimal adjuvant treatment. The prognostic and/or the predictive clinicopathologic factors that will determine the benefit of the adjuvant treatment in these patients are also not well-defined [8-10].

Prognostic factors in patients with pancreatic cancer who receive adjuvant, definitive and palliative radiotherapy (RT) in our clinic are researched in this study.

Material and Method

Selection of patients

Pancreatic cancer patients who received radiotherapy in the Akdeniz University Department of Radiation Oncology between years 2000-2008 were evaluated. Tumor staging of patients was done according to the AJCC 7th edition criteria. A retrospective analysis of patients' files is accomplished and the demographical data (age, gender), tumoral lesion in the pancreas (head, neck, and tail), pathological features (tumor diameter, histological grade, nodal status, metastatic status) and information on the received treatment are obtained. Informed consents of all patients who participated the study are taken for the treatment.

Patients who fulfilled following criteria are included in the study: patients between ages of 18-80, whose staging studies are accomplished with imaging methods (ultrasonography, abdominal computerized tomography, magnetic resonance imaging) before the treatment and patients whose Eastern Cooperative Oncology Group (ECOG) performance score is between 0 and 1. The exclusion criterion was ECOG > 2. Patients were categorized according to their age; >65 and ≤ 65.

Radiation Therapy

A total of 45 Gy is applied with a Linear Accelerator device, by using 6-25 MV photon energy tumor bed in the classic box (AP-PA-Right Left lateral) area, 5 days a week with a fraction dose of 1.8 Gy. In addition to the tumor, tumor bed and regional lymphatic's, and volumes of the organs at risk (OAR) are also determined in the radiotherapy planning. The OAR described as liver, kidneys, spinal cord and small intestines. The doses of the OAR during entire treatment process are calculated and the treatment plans of the patients who do not exceed the tolerance dose are approved. Toxicities are evaluated according to RTOG (Radiation Therapy Oncology Group) criteria in weekly examinations.

Statistical Analysis

The statistical analyses are done by using the software program SPSS 15.0. By using the Chi-Square or Fisher test (in cases in which the values observed in cells do not satisfy the assumptions of the Chi-Square test), it is investigated whether there is a difference or not between patient groups in terms of gender, preoperative chemotherapy, operation type and taking simultaneous chemotherapy.

The tumor diameter values in predicting survival were analyzed using ROC (Receiver Operating Characteristics) curve analysis. According to result of this analysis, patients were grouped according to their tumor diameters: the tumor diameter ≤ 4 cm (Group A), the tumor diameter >4 cm (Group B).

The effects of the age (≤ 65 and >65) and gender of the patient's, tumor localization (head, body and tail), tumor invasion (T1 to T4), lymph node involvement (negative or positive), perineural invasion (negative or positive), and tumor grade (grade 1-3) and tumor diameter (≤4 cm and >4 cm) on the survival are investigated by using the log rank test. The survival rates are calculated by using the Kaplan-Meier survival analysis. The cases under 5% of the Type 1 error level are accepted as statistically significant.

Results

A total number of 32 patients, of which 18 (56.3%) are men and 14 (43.7%) are women, were taken to study. The average age of the patients was 59.4±11 (range 35-79). The first symptoms in the submission of the patients were stomach pain and loss of weight in 21 (68.6%) patients, icterus in 10 (31.3%) patients and a new diagnosis of diabetes in one (3.1%) patient.

The tumoral lesion was in the head of the pancreas in 23 (71.9%) patients, in the body in 3 (9.4%) patients, in the tail in 1 (3.1%) patient and it was dispersed in the pancreas in 5 (15.6%) patients. Fourteen (43.8%) of the patients were operated and 18 (56.2%) patients were qualified as inoperable. Among the patients who were operated, 6 were operated through palliative surgery and 8 received Whipple operation.

Eighty-one point five percent of the histopathological samples had adenocarcinoma histology. The disease is identified in stage I for 1 (3.1%) of the patients, in stage II for 2 (6.3%) of the patients, in stage III for 21 (65.6%) of the patients and in stage IV for 8 (25%) of the patients. All metastatic patients had liver metastasis. The tumor grade was identified in 15 of the patients and tumors were well-differentiated in 1 (6.2%) of the patients, moderately differentiated in 8 (50%) of the patients, poorly differentiated in 3 (18.8%) of the patients and tumor showing neuroendocrine differentiation in 2 (13.4%) of the patients were determined.

Perineural invasion is identified in a ratio of 17.9% in the histopathological examination. The tumor was T1 for 1 (3.1%) of

the patients, T2 for 2 (6.3%) of the patients, T3 for 5 (15.6%) of the patients and T4 for 24 (75%) of the patients. Lymph node metastasis is identified in 45.2% of the patients (Table 1).

Table 1. Patient characteristics

Demografic and clinical features	Number (%)
Gender	
Female	14 (43.7)
Male	18 (56.3)
Primary Tumor	
Head	**23 (71.9)**
Body	**3 (9.4)**
Tail	**1 (3.1)**
Diffuse	**5 (15.6)**
T stage	
T1	**1 (3.1)**
T2	**2 (6.3)**
T3	**5 (15.6)**
T4	**24 (75)**
N status	
N0	**17 (53.1)**
N1	**14 (43.7)**
NX	**1 (3.1)**
Stage	
Stage 1	**1 (3.1)**
Stage 2	**2 (6.3)**
Stage 3	**21 (65.6)**
Stage 4	**8 (25)**
Tumor Size	
Group A (>4 cm)	**17 (53.1)**
Group B (≤4 cm)	**15 (46.9)**

The tumor diameter is determined as ≤4 cm for 17 (53.1%) of the patients (Group A) and >4 cm for 15 of the patients (Group B). There was no difference between Group A and B in terms of gender, age and tumor grade (p=0.755, p=0.863, p=0.338). There was no correlation between tumor size and location of the tumor in the pancreas (p=0.101). On the other hand, while the 88.2% of the tumors in Group A were in the head of the pancreas, this ratio was 53.3% in Group B. Distant metastasis is identified in one of the patients in Group A and in 7 of the patients in Group B.

The groups were different in terms of preoperative chemotherapy (p=0.005). Preoperative chemotherapy is applied to 17.6% of the patients in Group A and to 66.7% of the patients in Group B. Preoperative chemotherapy is applied to 13 (40.6%) patients among all. While 3 of applied chemotherapy regimens were 5-Fluorouracil based, 10 of them were Gemcitabine based. Simultaneous chemotherapy is applied to 22 (71%) of the patients. All of the simultaneous chemotherapy regimens were 5-Fluorouracil based regimens.

The mean survival of patients is identified as 17.3 months (%95confidence interval 10.2-24.4). The overall survival of patients is determined as 12.5% for 2 years, 9.4% for 3 years and 6.3% for 5 years (Figure 1).

No effect on the overall survival is identified for gender, age, tumor localization in the pancreas, perineural invasion and tumor grade in the survival analysis with one variable (p=0.887, p=0.692, p=0,912, p=0.568, p=0.322). Whether there is lymph node involvement or not is found to be related with survival (p=0.009). While the median survival is identified as 22.7±8.6 (%95 confidence interval 5.8-39.6) months in patients with no lymph node involvement, the median survival in lymph node involvement is identified as 10.4± 2.4 (%95 confidence interval 5.8-15) months.

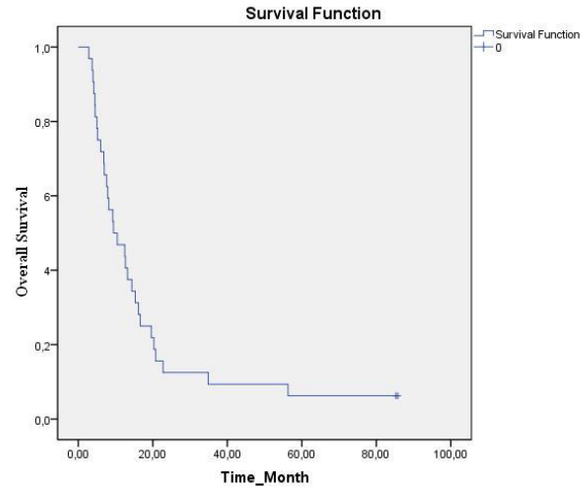

Figure 1. Overall survival for all patients

A significant relationship between Group A and B in terms of survival is determined (p=0.029) (Figure 2). While the median survival in Group A was 16.2±2.8 (%95 confidence interval 10.6-21.7) months, the median survival in Group B was 6±1.6 (%95 confidence interval 2.9-9.1) months.

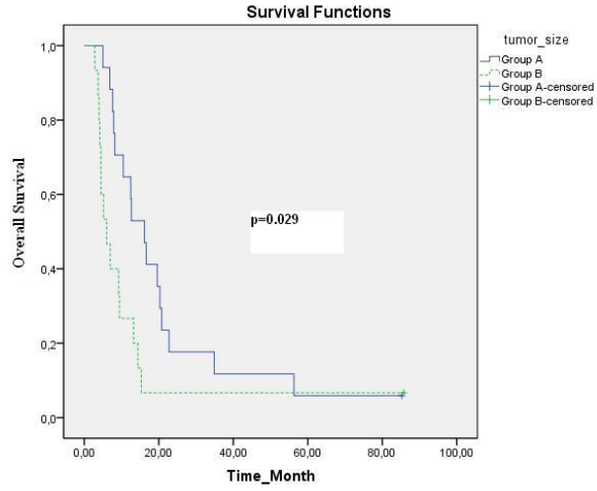

Figure 2. Overall survival according to tm size

Discussion

In our study, we showed that tumor diameter is >4 cm or ≤ 4 cm and the fact that there is lymph node involvement or not had prognostic importance in patients having RT implementation for pancreatic cancer.

Tumors lower than 2 cm are classified as T1 in the TNM classification of the pancreatic cancer. T1 tumors are accepted as small pancreatic cancer in many studies and it is shown that its

prognosis is better [11-13]. However in our study, it is shown that the prognosis is better in patients having a tumor diameter lower than 4 cm. In the study ACOSOG Z05031, in which the adjuvant treatment is evaluated, the patients having a tumor diameter lower and higher than 3 cm are compared and a relationship between survival and tumor diameter is not determined, contrary to our study [14].

The vascular support of the tumor decreases as the tumor diameter increases. Abnormal vascular support in tumors is one of the important mechanisms in the development of hypoxia. Hypoxic cells are more resistant to both radiotherapy and chemotherapy. It is shown that the tumor is completely oxygenated in cases in which the tumor diameter is below 1 mm and that partial hypoxia may occur in bigger tumors [15].

Another reason why the prognosis of patients having small pancreatic cancer is better may be related to the fact that distant metastasis is less seen in these patients. While distant metastasis is identified in only one of the patients having a tumor diameter lower than 4 cm in our study, the primary focus was over 4 cm in other metastatic patients. Similar results were also obtained in studies in which the small pancreatic cancer was 2 cm and lower [11,15].

It is put forward that small pancreatic cancers are better differentiated tumors [16]. On the other hand, no difference is identified when the patients are grouped according to their tumor diameters in our study. The reason for that may be small number of patients and the fact that patients who treated with RT were included to our study. RT is not implemented in metastatic patients except palliative treatment might have caused patient selection bias.

The fact that the tumor grade is an important prognostic factor is shown in many studies [17-19]. However, no relationship is determined between the tumor grade and survival in our study. The reason for that may be the small number of stage IV patients among all the patients who are taken into the study because the prognostic effect of the tumor grade in stage IV patients is significant [20].

It is shown in many studies that lymph node involvement is a poor prognostic factor in pancreatic cancer [21-23]. Slidell et al. showed that; not only the number of lymph node, but also LNR (ratio of metastatic lymph nodes to total number of examined lymph nodes) may be releated with more directive for postoperative survival (24). However, Murakami et al. suggested that the number of metastatic lymph node is more potent prognostic factor than LNR in the 119 patients that pancreatectomy is applied (25). In our country, Büyükkaşık et al. showed that; wide surgical resection of gastric cancer, increased mortality especially over the age of 70, as well as in pancreatic cancer (26).

In another study, in which they examined prognostic factors in pancreatic cancer patients that received chemoradiotherapy, Moghanaki et al. showed that the nodal status and the T stage have prognostic importance [27]. Unlike from our study, they determined that the prognosis is better in patients lower than age of 60.

As a result, the most important limitation of our study is small number of patients; we think that tumor diameter and lymph node involvement should be taken into account as prognostic factors while treatment is considered in patients who are planned to receive radiotherapy because of pancreatic cancer.

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Competing interests

The authors declare that they have no competing interests.

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