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Importance of Performing Radiotherapy and Chemotherapy in the Same Clinic and Bad Prognostic Factors for Small-cell Lung Cancer Patients

Küçük Hücreli Akciğer Kanseri Hastalarında Kemoterapi ve Radyoterapinin Aynı Klinikte Yapılmasının Önemi ve Kötü Prognostik Faktörler

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ABSTRACT

Objective: We evaluated different treatment results reported and showed the effect of treatment at single and multiple clinics for small-cell lung cancer (SCLC). We attempted to show a decreasing impact of chemotherapy (CT) and thoracic radiotherapy (RT) treatment results when implemented at different clinics for SCLC compared to the treatment results at a clinic.

Methods: We conducted a retrospective study on 54 non-metastatic SCLC patients who underwent treatments at various clinics. Patients underwent 1–12 courses of CT before they came to the clinic for thoracic RT. RT was performed at 180–400 cGy dose per fraction for a total of 30–52 Gy doses, and patients were followed for 12–60 months.

Results: When the study was reviewed, the results showed that the median disease-free survival and survival rates were 8 and 9 months and that the 2-, 5-, and 5-year survival rates were 8%, 6.3%, and 1.8%, respectively. The median progression-free survival rates for 2 and 3 years were 4%, and for 5 years, it was 1.8%. Weight loss for disease-free survival (p=0.01) and superior vena cava syndrome for overall survival (p=0.02) were considered as bad prognostic factors. In this study, acceptable toxicity values were found when the results were compared with those from other studies.

Conclusion: We obtained worse results than those from literature data on our SCLC patients who came to our clinic after the progression of their disease. The main causes were identified as insufficient staging and different treatment protocols applied at different clinics. Therefore, we argue that CT and thoracic RT for SCLC must be performed at the same clinic and that the same protocols and staging methods must be used.

Keywords: Small cell lung cancer, chemoradiotherapy, vena cava syndrome

ÖZ

Amaç: Küçük Hücreli Akciğer Kanserinde (KHAK) değişik tedavi metodları ile tek bir klinikte veya farklı kliniklerde yapıldığında tedavi etkinliğini araştırdık. Biz bu çalışmada, kemoterapi (KT) ve radyoterapinin (RT) farklı kliniklerde yapıldığında sonuçları kötü etkilediğini göstermeye çalıştık.

Yöntemler: Tedavileri farklı kliniklerde yapılmış olan 54 metastaz yapmamış KHAK hastası üzerinde retrospektif bir çalışma başlattık. RT için kliniğe gelmeden once hastalara 1-12 kür arası KT uygulanmıştı. 180-400 cGy fraksiyon doz ile total 32-54 Gy RT uygulanmış ve 12-60 ay takipleri yapılmıştır.

Bulgular: Çalışma değerlendirildiğinde medyan hastalıksız yaşam ve yaşam oranlarının 8 ve 9 ay olduğu gösterilmiştir. 2, 3 ve 5 yıllık yaşam oranları sırası ile %8, %6,3 ve %1,8'dir. Hastalıksız yaşam oranları 2 ve 3 yıl için %4 ve 5 yıl için %1,8'dir. Bu çaışmadaki toksisite düzeyleri, diğer çalışmalarla karşılaştırıldığında kabul edilebilir düzeydeydi.

Sonuç: Değişik nedenlerle farklı kliniklerden gönderilmiş olan bu hastalarda, literatürdeki diğer bulgulara göre biraz daha kötü neticeler alınmıştır. Hastalıkları ilerledikten sonra kliniğimize gönderilmiş olan KHAK hastalarımızda yapmış olduğumuz bu çalışmada literatürdeki verlerden daha kötü neticeler elde ettik. Bu sonuçların en önemli sebepleri yetersiz evreleme ve değişik kliniklerde uygulanmış farklı tedavi protokolleridir. Bu yüzden biz KHAK'de KT ve RT'nin aynı klinikte, aynı protokol ve evreleme yöntemleri ile uygulanmasını öneriyoruz.

Anahtar Kelimeler: KHAK, kemoradyoterapi, VCSS

Introduction

Small-cell lung cancer (SCLC) is an aggressive form of lung cancer. Its unique pathological and clinical features were first recognized by Barnard (1). There is a tendency for early dissemination. It has high initial response rates to chemotherapy (CT). An autopsy series on small cell carcinoma patients showed a high frequency of metastases because more than 95% of patients die from the cancer (2).

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The tumor node metastasis staging system is not used because surgical resection is generally not possible. Therefore, the Veterans Administration Lung Study Group system is used as the staging system (3).

A vast majority of patients are symptomatic at presentation. In most cases, they are diagnosed by bronchoscopic biopsy, and usually, additional tissues for immunohistochemical staining are required. Limited-stage disease should be treated with CT concurrently with early thoracic radiotherapy (RT). Prophylactic cranial RT should be considered for all patients to achieve complete remission. Extensive-stage disease should be treated by combination CT administered for 4–6 cycles (4, 5).

In total, 60–70% of patients present with extensive-stage disease. These patients have a median survival and 5-year survival rate of 7–12 and 2%, respectively. However, for limited-stage disease, the median survival is approximately 23 months and the 5-year survival rate is 12–17% (6).

Metastases in the central nervous system have been identified in 80–90% of patients (7, 8).

Favorable prognostic factors in SCLC patients are a good performance status, limited-stage disease, female sex, and normal serum lactate dehydrogenase levels. Inconsistently reported prognostic factors are few sites of metastatic disease, age <40 years, absence of pleural effusion, brain metastases, liver metastases, and normal serum sodium and liver function tests (9).

In general, etoposide–cisplatin together with thoracic RT is used for the limited-stage disease. This treatment results in a complete response rate of 80% or higher, a median survival in excess of 17 months, and a 5-year cancer-free survival rate of 12–25% in best series (6, 4, 10, 5).

Topotecan was superior to CAV for providing relief from general symptoms, including anorexia, fatigue, dyspnea, and hoarseness (11). Topotecan is also superior for relapsed SCLC (12).

Hematologic toxicity, cisplatin-induced nephrotoxicity, and paclitaxel-induced neurotoxicity are common toxicities associated with treatment for SCLC. Generally, patients show greater improvements in the quality of life, despite intensive regimens during the first four course of CT. The quality of life declines very quickly when CT is extended to more than four courses (13). Furthermore, survival advantages were not obtained by extending the treatment to beyond 4–6 courses (14, 15).

Many SCLC and lung cancer patients were elderly and had relapsing disease or multiple comorbidities. Therefore, they were unable to tolerate intensive CTs. Many oncologists have also been reluctant to re-treat these relapsing elderly and badly performing patients. Symptom palliation and the quality of life are more important factors in the design of treatment rather than prolonging the survival (16, 17). Single-agent oral or intravenous CT or supportive care may be the best option for elderly or poorly performing patients (18).

Table 1. Patient characteristics

Characters	Number of Patients	%
Gender		
Male	52	96.29
Female	2	3.70
Age		
>50	16	29.62
50–59	8	14.81
60–69	27	50
70–73	3	5.55
Karnofsky score		
<80	9	16.66
60–80	41	75.9
>60	4	7.4
Pre-RT stages		
Disease free	3	5.55
Limited	8	14.81
Extensive	43	79.6
Weight loss		
>10%	8	14.81
5–10%	9	16.66
<5%	3	5.55
Yok	34	62.96

RT: radiotherapy

Treatment for SCLC is often performed in different protocols in different clinics. Different treatment results have been reported in many studies on SCLC. There are various causes for these outcomes. CT is usually performed with distinct course numbers and regimens at different clinics. Further, thoracic RT is performed with various doses and fractionation schedules. Nowadays, the RT volume is controversial (19). We attempted to show a decreasing impact on treatment results of CT and RT when performed at different clinics for treating SCLC.

Methods

We conducted a retrospective study on 54 non-metastatic SCLC patients whose treatments were performed in various clinics between 1980 and 1993. One to twelve course of CT were performed before the patients came to the clinic for thoracic RT. RT was performed at 180–400 cGy dose per fraction for a total of 30–52 Gy doses, and they were followed for 12–60 months. The Veterans Administration Lung Study Group staging system was used as the staging method. Pre-CT stage information of patients and pre-RT stages were confirmed. Forty-three patients had limited-stage disease according to the pre-RT evidence. Patient characteristics are shown in Table 1.

CT was performed for at least 1 and up to 12 courses at the time of pre-RT. The CT regimens are shown in Table 2.

Table 2. Chemotherapy regimens before radiotherapy and response rates

CT Regimens	Number of patients	Complete responders	Partial responders	Minimal responders	Stationer	Progressive
P	16	1	4	1	8	2
A	12	0	2	1	7	2
P+A	46	0	3	0	1	0
Others	6	0	1	0	2	3
Not known	16	2	4	3	6	1
Total	54	3	14	5	24	8

CT: Chemotherapy; P: Cisplatin- containing regimens; A: Adriamycin-containing regimens; P+A: Cisplatin- and adriamycin-containing regimens

Table 3. Radiotherapy planning and treatment characteristics

Radiotherapy	Number of patients	%
Total dose (Gy)		
>44	22	40.74
≤44	32	59.25
Volume		
P+M+Bilat S	14	25.92
P+M+S	20	17.03
P+M	19	35.19
P+M+Aksilla	1	1.85

P: primary tumor; M: mediastinal lymph nodes at risk; Bilat S: bilateral supraclavicular lymph node

Table 4. Response rates of patients at first treatments as pre-RT (outclinic treatment responses)

Pre-RT responses	Number of patients	%
CR	3	5.55
PR	14	25.02
MR	5	9.25
Stationer	24	44.4
Progression	8	14.8

RT: radiotherapy; CR: complete response; PR: partial response; MR: minimal response

Thoracic RT was performed at a median dose of 250 cGy/day and at least 180 cGy/day, up to 400 cGy/day fraction dose for 5 consecutive days a week. LINAC-based therapy was used for 25 patients, whereas others were treated with cobalt-60 teletherapy unit. RT planning was obtained according to pre-RT lung tumor volumes in all patients. Planning was used as 1-cm margin to tumor and additional nodes at risk (Table 3).

Pre-RT staging was performed, and the response rates of primary treatment are shown in Table 4.

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method. The ratios between the groups were analyzed by the qi-square test.



Figure 1. Survival curve for SCLC in this study

Results

Weight loss was shown to be the most prominent bad prognostic factor for disease-free survival (p=0.01) and superior vena cava syndrome or overall survival (p=0.02), which were assessed with the chi-square test (nonparametric statistic test, İn USA, 1934). No factor was determined for local control except the CT and RT responses.

The median survival was 9 months, and the 2-, 3-, and the 5-year survival rates were 8%, 6.3%, and 1.8%, respectively, which were assessed by the Kaplan–Meier method ("Non-parametric estimation from incomplete observations", in USA, 1958).

As shown in Figure 1, the median disease-free survival rate was 9 months, and the 2-, 3-, and 5-year disease-free survival rates were 4%, 4%, and 1.8%, respectively. The complete response rate increased to 20.37% post RT, while it was 5.55% pre RT. The partial response rate increased to 53.7% post RT, while it was 25.92% pre RT.

The grade I eusophagit was 66.6%, grade II was 14.8%, and grade III was 3.6%. Grade I hematologic toxicity was 66.6%, grade II was 27.7%, and grade III was 14.8%. The grade I radiation pneumonia was shown 27.7%, grade II was 14.8%, and grade III was 3.6%.

Discussion

SCLC accounts for approximately 18% of the lung cancers (20). The 5-year survival rates with limited ranges from 5% to 10%. In total, 60–70% of patients present extensive-stage disease. These patients have a median survival and 5-year survival rate of 7–12 and 2%, respectively. The median survival for extensive-stage SCLC patients is approximately 8 months (21, 22, 23). However, in the limited-stage disease, the median survival is approximately 14–23 months and the 5-year survival rate is 12–17% (4, 5, 6, 15).

A bad performance status, number and location of metastases, disease-free interval, and unsuccessful first-line CT are very important bad prognostic factors. Survival was clearly improved in patients who responded to first-line treatment. The progression-free interval was under 3 months following first-line treatment for chemoresistant patients. The median survival is generally comparable or slightly superior to the best supportive care cases (i.e., 16–21 weeks) (24, 25). The prognosis is generally unfavorable in relapsed patients, with an unsatisfactory proportion of patients surviving for more than 1 year.

The median survival was 8–9 months in relapsed SCLC associated with currently existing therapies (26).

The survival of recurring and/or progressive advanced SCLC is 1.5–4 months for the best supportive care. There have been no large randomized trials to compare the survival among patients who had CT compared with those who had the best supportive care. The largest randomized study conducted to date for relapsed SCLC patients shows that the survival could be significantly improved for patients receiving short-term treatment (4 courses) compared with those receiving symptomatic treatment (median survival: 20 vs. 11 weeks, respectively; $p<0.001$) (27). Other studies on active intervention with CT in relapsed patients have reported median survivals ranging from 6 to 8 months (28, 29, 11, 24, 25).

In SCLC, most patients relapse and have a poor prognosis. Treatment options include RT, CT, or combined modalities for relapsed patients. Potential barriers to further treatment include toxicity, patient comorbidities, and performance status. However, numerous clinical trials have demonstrated that some patients benefit from different treatment regimens (30).

The complete response rate increased to 20.37% post RT, while it was 5.55% pre RT in this study. The partial response rate increased to 53.7% post RT, while it was 25.92% pre RT. These results suggest that RT is effective for the patients who do not shown a good response to CT despite the different reported results in the literature (5, 31). The response rates to CT for SCLC were 60–95% in many studies (6, 4, 10, 5). However, the total response rate to CT was 45% in our study because these patients were sent from other clinics after disease progression or bad results of CT.

In this study, acceptable toxicity values were found when the results were compared with those from other studies (10, 13).

The CT responses are very significant during the first 6 weeks of treatment (19). The clinical tendency to send patients who do not show a good response to different clinics is a very important factor that reduces the effectiveness of treatments. Because of the lack of good communication among doctors, other staff and the patient, valuable time is lost when patient transfer takes place. Some clinics may not readily accept patients whose treatment might have started at other clinics. After the transfer, required diagnostic tests may not be performed to not disturb the patient response and to control the overall treatment cost. As a result, the actual staging may not be properly updated and the treatment history applied at other clinics may not be understood.

When the study reviewed, the results showed that the median disease-free survival and survival were 8 and 9 months and that the 2-, 3-, and 5-year survival rates were 8%, 6.3%, and 1.8%, respectively. The 2-, 3-, and 5-year progression-free survival rates were 4%, 4%, and 1.8%, respectively. Weight loss for disease-free survival ($p=0.01$) and superior vena cava syndrome for overall survival ($p=0.02$) were considered as bad prognostic factors.

The wrong staging, different treatment protocols, and disease progression contributed to the relatively negative treatment results of patients sent from other clinics for various reasons according to other studies. Therefore, we argue that CT and RT for SCLC must be performed in the same clinic that uses the same protocols and staging methods.

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