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Tanı Konulmuş Tek Mediastinal Metastazı (N2) Olan Küçük Hücreli Dışı Akciğer Kanserli Hastalarda Definitif Kemo/Radyoterapi nin Cerrahi ve Sağkalıma Etkisi

The Effect of Definitive Chemo / Radiotherapy on Surgery and Survival in Patients with Non-Small Cell Lung Cancer with A Single Mediastinal Metastasis (N2) Diagnosed

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Öz

GİRİŞ ve AMAÇ: Platin bazlı kemoterapi ve ful doz radyoterapinin kombinasyonu, tek veya çoklu lenf nodu metastazı olan Evre III (N2) KHDAK hastaları için standart tedavi yöntemidir. Bununla birlikte, lenf nodu ve uzak metastazı olmayan hastalarda akciğer rezeksiyonu yapılabilir.
YÖNTEM ve GEREÇLER: Ocak 2010 ile Aralık 2013 arasında patolojik olarak kanıtlanmış, evre IIIA / N2 küçük hücreli dışı akciğer kanserili hastalar kaydedildi. Kemoradyoterapi grubundakiler üç döngü neoadjuvan kemoterapi (AUCx2 karboplatin ve dosetaksel 85 mg / m2 (2) dosetaksel) ve 3 hafta boyunca 34 fraksiyonda 61.2 Gy ile eşzamanlı radyoterapi ve ardından cerrahi rezeksiyon yapıldı. Ayrıca definitif kemoradyoterapi alan bir grup hasta cerrahi grupla karşılaştırıldı. İki gruptaki tüm hastaların kemoradyoterapi sonrası N2 hastalığı olmadığı kanıtlandı.
BULGULAR: Toplam 29 hasta kaydedildi, bunlardan 6'sı definitif kemoradyoterapi, ardından cerrahi rezeksiyon ve 21'i sadece kemoradyoterapi aldı, postoperatif hiçbir hasta ölmedi, iki hastada şiddetli toksisite vardı. Medyan genel sağkalım kemoradyoterapi + cerrahi grubunda 26.66 ± 4.35 ay) ve kemoradyoterapi grubunda 21.75 ± 4.82 ay (4.0-38.6) idi (p = 0, 275).
TARTIŞMA ve SONUÇ: Definitif kemoradyoterapi sonrası pulmoner rezeksiyon güvenlidir ve kemoradyoterapi sonrası cerrahi rezeksiyon, histolojik olarak kanıtlanmış N2 evre IIIA küçük hücreli dışı akciğer kanserinde daha iyi sağkalım sağlayabilir.

Anahtar Kelimeler: definitif kemoterapi, akciğer kanseri, definitif radyoterapi

Abstract

INTRODUCTION: A combination of platinum-based chemotherapy and definitive radiotherapy is the standard of care for Stage III (N2) NSCLC patients who have single or multiple lymph node metastasis. However, lung resection could be performed in patients with residual disease without lymph node metastasis.
METHODS: Between January 2010 and December 2013 eligible patients had pathologically proven, stage IIIA/N2 non-small-cell lung cancer and were prospectively recorded. Those in the chemoradiotherapy group received three cycles of neoadjuvant chemotherapy (AUCx2 carboplatin and docetaxel 85 mg/m (2) docetaxel) and concurrent radiotherapy with 61.2 Gy in 34 fractions over 3 weeks followed by surgical resection. Also, a group of patients who had definitive chemoradiotherapy without chemoradiotherapy was compared with the surgical group. All patients in two groups were proven to have no N2 disease after chemoradiotherapy.
RESULTS: A total of 29 patients were enrolled, of whom 6 received chemoradiotherapy followed by surgical resection and 21 had chemoradiotherapy only. No patient died postoperatively. Two patients had severe toxicity. Median overall survival was 26.66 ± 4.35 and months) in the chemoradiotherapy + surgery group and 21.75 ± 4.82 months (4.0–38.6) in the chemoradiotherapy group (p=0, 275).
DISCUSSION and CONCLUSION: Pulmonary resection after definitive chemoradiotherapy is safe and surgical resection after chemoradiotherapy may provide better survival in histologically proven N2 stage IIIA non-small cell lung cancer.

Keywords: lung cancer, definitive chemotherapy, definitive radiotherapy

INTRODUCTION

Lung cancer, as the most common and the deadliest form of cancer around the world (1), still needs major improvements on the treatment of particularly advanced stages. Of all non-small cell lung cancer (NSCLC) cases, locally advanced disease (i.e., stage IIIA) constitutes approximately

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30% (2). The main problem to define an optimal treatment in this group of patients, is high heterogeneity, from those with minimal disease and a single station ipsilateral mediastinal lymph node, to those with bulky lymph nodes in multiple stations. Outcomes of treatment are unfavorable when patients with NSCLC have ipsilateral mediastinal nodal metastases (N2) (3). The low survival rate of N2 disease is attributable to the possibility of undetected systemic metastasis although N2 disease, by definition, is a localized disease (4). NSCLC with ipsilateral mediastinal lymph node metastasis is very difficult to cure implementing only a local treatment modality such as radiation therapy or surgery alone (5,6).

Definitive concurrent chemoradiotherapy or induction chemo/radiotherapy followed by surgery in select patients are recommended options (7-9). However, the role of surgery in the treatment of stage IIIA-N2 non-small cell lung cancer is still unclear. In a randomized phase III trial, surgery following chemoradiotherapy was found superior to chemoradiotherapy alone in local control but overall survival was not improved, probably because of the high mortality of patients who underwent pneumonectomy (8). Albain and colleagues reported that, NSCLC patients with stage IIIA(N2) disease can benefit chemoradiotherapy followed by surgery if the mediastinal lymph node became non-metastatic and if the performed surgery is lobectomy (8).

In this study, we aimed to investigate the role of surgery if previously stage IIIA-NSCLC patients received definitive chemoradiotherapy followed by surgery if the tumor is downstaged.

METHODS

We retrospectively evaluated a series of 29 patients with initial clinical Stage III N2 non-small cell lung cancer (NSCLC) who were found have single-station N2 disease by mediastinoscopy/video-assisted mediastinoscopic lymphadenctomy or endobronchial ultrasonography-transbronchial needle aspiration (EBUS-TBNA) first treated with definitive chemoradiation therapy followed by lung resection from January 2010 to December 2013. Patients included in this study met the following criteria: (i) prior treatment of lung cancer with curative-intent radiotherapy (61.2-64.0 Gy in 34 fractions over 3 weeks chemotherapy (Carboplatin AUCx2, docetaxel 85 mg/m2) for a total of 4 times; (ii) no a priori plan for induction multimodality therapies incorporating surgical resection;(iv) pretherapeutic histological or cytological results showing NSCLC and (v) Stage III (T1-3 single station N2) disease prior to chemoradiotherapy. The disease stage was determined in accordance with the seventh edition of the TNM Classification for Lung and Pleural Tumors (9). The patients with multiple station N2 or N3 or T4 disease were excluded from the study.

All patients received weekly platinum-based chemotherapy concurrently with definitive radiotherapy. Radiotherapy was based on 3-dimensional computed tomography planning tailored to minimize toxicity to nearby structures for all patients and was administered to the primary tumor and mediastinum with curative intent.

The preoperative workup included routine blood tests, posteroanterior and lateral chest radiographs, bronchoscopy, pulmonary function tests, with diffusion capacity of lung for carbon monoxide and ventilation-perfusion lung scan in select patients, and blood gas analysis. Computed tomographic scans of the thorax, and cranial magnetic resonance imaging, and positron emission tomography–computed tomography analysis was performed in patients. The patient characteristics are shown in Table 1.

Mediastinal lymph node sampling through cervical mediastinoscopy at stations 2, 4 (both left and right), and 7 was performed in almost all

patients. Preoperative mediastinal exploration was supplemented by left anterior mediastinotomy (n=1) or extended mediastinoscopy (n=2) in patients whose tumor lay in the left upper lobe or left main bronchus.

Table 1. Clinical Characteristics of the Patients.

	Min –Max	Avg +/- SD
Age	41-70	58.3 ± 6.87
Smoking	20-60	39.1 ± 13.9
FEV_1 (mL)	1200-3690	2399 ± 681

Patients were re-evaluated radiologically after definitive therapy. The CONSORT flow diagram of the study is shown in Figure 1. Response to definitive chemoradiotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) using CT or PET-CT (11). Histological re-assessment of the mediastinal nodes was performed EBUS, or mediastinoscopy (Figure 1). Patients were deemed to be operable provided that there was no progression after chemoradiotherapy and no mediastinal lymph node involvement proven by EBUS or VAMLA (Figure 1). Six patients (22.2%) who were proven to have no mediastinal lymph node positivity after definitive chemoradiotherapy patients underwent surgery after definitive therapy. The time elapsed between completion of chemoradiotherapy and surgery was 6-9 weeks.

For restaging mediastinal lymph node in 6 (25%) patients who underwent surgical resection after definitive therapy. We included the patients who had 'no-progression' on PET-CT according to RECIST criteria (11).

Eight patients (29.6%) who showed progression after definitive treatment were excluded from the study.

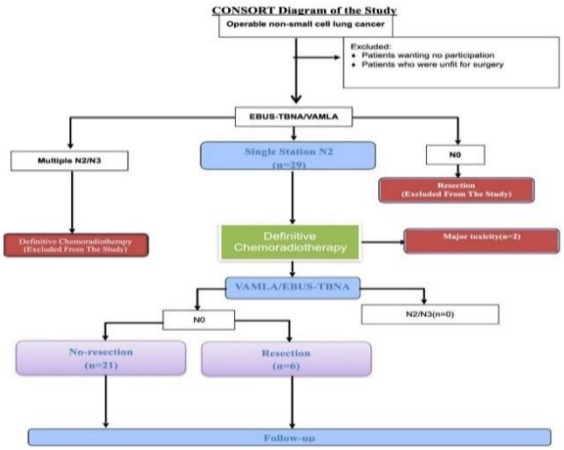

Figure 1. The CONSORT diagram of the study

Restaging of the patients who underwent surgery was performed through radiological imaging only in 2 (33.3%) patients, EBUS-TBNA on 3 (50%) patients, and VAMLA on 1 (16.6%) patient. Two patients (7.4%) could not complete the treatment because of chemoradiotherapy related toxicity and 2 patients (7.4%) died due to (radiation hypersensitivity in 1 case and chemotherapy-related hematoxicity in 1 case). Surgical resection was performed after it was pathologically proved that mediastinal lymph node involvement was not observed. All patients underwent an anterior thoracotomy. All patients who received definitive chemoradiotherapy underwent a lobectomy. Lymph nodes 2, 4, 7, 8, 9, 10, 11 on the right side and 5, 6, 7, 8, 9, 10, 11 on the left side were dissected. Bronchial stump was closed with parietal pleura or pericardial adipose tissue in all patients.

A systematic mediastinal lymphadenectomy was performed in every patient, in addition to anatomic lung resection (i.e, all patients underwent uniform staging to determine a final surgical-pathologic stage, based on information obtained through thoracotomy and pathology examination)The final surgical-pathologic stage of the patients who underwent resection before 2009 was reconstructed according to a recent staging system(10).Complete resection was defined as the removal of all detectable disease by the surgeon and histologic confirmation of tumor-free resection margins. The mean number

of resected N2 lymph nodes was 4.8 (between 4 and 12) and the mean number of resected N1 lymph nodes was 15.3 (between 6 and 43)

Complications were evaluated in two groups as major and minor complications. Major complications were identified as those requiring the patient to be treated in the intensive care unit or requiring revision (such as bleeding, prolonged air leak, fistula, pneumonia, ARDS). Minor complications were the postoperative adverse events which do not require intensive care, such as temporary atrial arrhythmias, atelectasis, and minimal air leak.

There were 21 patients who had definitive chemoradiotherapy who did not undergo surgical resection (Table 2).

The need for Institutional Review Board Approval was waived according to our country's law because the study is a retrospective cohort study.

Recorded clinical variables were age, gender, presence of comorbid factor, smoking, FEV1 values, location of computed tomography, type of resection, clinical stage before and after treatment, pathological stage after surgery, histological type, clinical and pathological response, recurrence, presence of complication, duration of hospital stay, duration of clinical follow-up.

Follow-up:

After discharge, patients were called for follow-ups on the 10th day, in the 1st month, and thereafter in 6-month intervals. The follow-ups were generally performed via computed tomography. Further examinations were requested in case of additional symptoms. The mean follow-up period was 15.3 months (4-40 months)

Statistical Methods:

Characteristics of patients according were compared with Fisher exact test for categorical variables. Length of survival was defined from the date of surgery to the date of last contact or death. Survival curves were plotted using the Kaplan-Meier method and log-rank test was used to assess differences in survival between groups. Multivariate Cox proportional hazard test was used to assess the if any parameter is independently associated with survival.

RESULTS

The mean age of the patients receiving definitive therapy was 58.3 ± 6.87 (between 41 and 70). 26 patients (96.3%) were male and 1 patient (3.7%) was female. No postoperative mortality was observed.

It was found that 1 patient (3.7%) did not have history of smoking and the mean smoked cigarette was 39.1 ± 13.9 package. Year (between 60 and 20). Ten patients (37.0%) did not have additional disease, whereas 17 patients had at least one additional comorbidity (63.0%) The mean duration of hospital stay was 4 ± 1.54 (between 3 and 7) days. When histological types in the patients receiving definitive therapy are examined, it is found out that 5 (18.5%) patients had squamous cell carcinoma, 5(18.5%) patients had adenocarcinoma, and 17(63%) patients had NSCLC.

Surgical procedures performed on the patients were: right lower lobectomy, right upper lobectomy, right middle lobectomy, right middle-lower bilobectomy, left upper lobectomy and eft lower lobectomy in 1 (16.6%) patient each.

Of the patients who received definitive therapy, 5 (83.3%) patients had N0 and 1 (16.7%) had N1 lymph node. R0 resection was performed on all of the patients who received definitive therapy.

Causes of Not Performing Surgery on the Patients Receiving Definitive Therapy

A total of 17 patients could not undergo surgical resection for various reasons. It was observed

that 2 patients (7.4%) had died during treatment and 8 patients (29.6%) had had distant metastasis after treatment. Two patients (7.4%) developed RT/CT-related toxicity, 3 patients (11.1%) did not want to be operated, 2 patients (7.4%) were considered as inoperable for respiratory causes.

Postoperative Pathology

In the examination of surgical specimen after definitive therapy (ypTNM), it was found that 2 patients (33.3%) were stage 0(ypT0N0M0), 3 patients (50%) were stage IB, and 1 patient (16.7%) was IIA.

When the pathological stages of patients who underwent lung resection after definitive treatment were compared with their clinical stages before definitive therapy, complete response was achieved in 2 patients (33.3%) and partial response in 4 patients (66.7%).

Survival in Operated and Non-operated Patients after Definitive Chemoradiotherapy

The mean survival time in patients who underwent resectional surgery and the one who did not have surgery were 26.66 ± 4.35 and 21.75 ± 4.82 months respectively (p=0.275; Figure 2, Table 2).

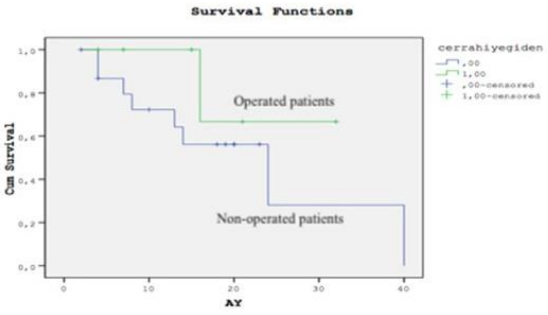

Figure 2. Survival Graph of the Patients Who Were and Were Not Operated (p=0.275)

Table 2. Survival Analysis of the Patients Who Were and Were Not Operated

Surgical status	N	Exitus	Alive	Mean Survival (Month)
Operated	6	1	5	26.66 ± 4.35
Not Operated	21	8	13	21.75 ± 4.82

DISCUSSION

Management of stage III non-small cell lung cancer presents a significant treatment challenge. Chemotherapy-based multimodality treatment including radiotherapy is the standard of care (7), but ideal local therapy is yet to be identified. It is still a controversial issue to perform surgical resection after definitive chemoradiotherapy therapy or to determine the patients who will benefit from this application (2,4,5,6). Some studies indicate that the clinical response after induction treatment and the fact that the disease can be eradicated through operation is sufficient in terms of surgical outcome (2). We set out to analyze the perioperative safety and efficacy of salvage lung resection following definitive chemoradiation therapy for Stage IIIA disease with single mediastinal lymph node metastasis in NSCLC patients. Resection following definitive chemoradiotherapy is called salvage lung resection but has encompassed a large variety of situations using prior treatments, high-dose radiation, targeted therapies such as epidermal growth factor receptor tyrosine kinase inhibitors and stereo-tactic ablative radiotherapy (12-14, 15-17). As definition, salvage lung resection is intended to eradicate all remaining or recurrent tumours when applied modalities have failed. Shimada and colleagues reported that, carefully selected Stage IIIA NSCLC patients, salvage surgery was safely performed and may provide satisfactory long-term survival after curative-intent chemoradiathrepy (18). Albain and colleagues emphasized in Intergroup 0139 study that (8), there was no significant survival advantage to surgery following chemoradiotherapy, despite improved progression free survival. However, they showed improved overall survival for patients who underwent lobectomy (8).

In our study, we implemented definitive chemoradiotherapy in 27 patients with single station mediastinal lymph node metastasis (Stage

IIIA). In our series, metastatic spread is observed in 55% of the patients with lung cancer and 25% of the patients have regional lymph node metastasis. On the other hand, only 15% of the patients have limited disease and can undergo surgical resection. Similarly to previous studies (8,16), we did not find any statistically significantly different overall survival between the patients who underwent surgery and patients who were followed up after surgery. It has been suggested that in advanced stage patients preoperative chemo-/radiotherapy reduces primary tumor volume, thereby increasing resectability, decreasing early micrometastases and contributing to the average life expectancy (3). Histologic identification of mediastinal metastatic lymph nodes according to different clinical criteria affects the results (19). Luke et al. disclosed N2 or N3 disease in 296 patients after performing mediastinoscopy in 1000 patients who were evaluated to have negative mediastinal lymph node through CT (19). They indicated the necessity of routine mediastinoscopy in almost all patients.

Both the possibility of reduction of tumor size and the decrease of mediastinal lymph node involvement after definitive chemoradiotherapy confirm that such treatments increase the possibility of resection (5,6,8). In our study, a downstaging in mediastinal lymph nodes was observed in all of the patients who underwent surgery after definitive chemoradiotherapy, only 1 patient (16.7%) had pathologic Considering the studies having been conducted before, we concluded that mediastinal re-staging should be performed and mediastinal lymph node dissection preoperatively if possible, and thus it provides a correct mediastinal lymph node staging and survival advantage. Turna et al showed that, bilateral mediastinal lymph node dissection performed via videomediastinoscopy might increase survival in patients undergoing resectional surgery for NSCLC (20).

It is thought that the addition of preoperative radiotherapy to chemotherapy provides a better outcome and more aggressive locoregional control than neoadjuvant chemotherapy alone (6).

In our study, the mean survival was 26.66 months in the patients operated after definitive therapy and 21.75 months in the patients who did not undergo surgery. The 5-month difference was not found to be statistically significant although the difference could not be underestimated. The lack of statistical significance may be due to insufficient number or short follow-up period.

There is a consensus on performing surgery in patients with N2 if down staging is observed after neoadjuvant chemo/radiotherapy (7,8). The role of surgical resection is controversial if downstaging is not observed in patients and surgery should be avoided due to the high risk of mortality in patients requiring pneumonectomy (8). Chemoradiotherapy is the appropriate treatment for the patients with multiple-station N2 (9).

In our study, no surgical mortality was observed in the patients operated after definitive therapy. The fact that hospital mortality was not observed may be due to the low number of patients.

There are limitations of our study that must be addressed. Our series include patients from one center. Some of the patients developed toxicity precluding surgical resection despite their tumors responded to chemoradiotherapy. Also, the number of all patients as well as the number of patients who underwent surgical resection was relatively low.

In conclusion, we recommend surgical resection after definitive therapy since the surgical morbidity is low and we believe that it prolongs the average life expectancy although the difference was not statistically significant. Furthermore, by giving definitive chemoradiotherapy, the stage IIIA patients were given recommended definitive

chemoradiotherapy. However, further studies are needed to clearly identify the role of surgical resection in Stage IIIA(N2) NSCLC patients who were administered definitive chemoradiotherapy.

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