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# Benefits of postoperative radiotherapy in multimodality treatment of resected small-cell lung cancer with lymph node metastasis

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## Abstract

*Aim*: The purpose of this study is to evaluate the role of postoperative radiotherapy (PORT) in resected small-cell lung cancer (SCLC).

Methods: This study retrospectively analyzed 143 patients with completely resected SCLC in our institution between 1996 and 2011. The primary endpoint was overall survival (OS). The log-rank test and Cox regression model were used to evaluate the factors influencing local-regional recurrence (LRR) and OS.

*Results*: The median OS for the entire population was 34 months, and the 5-year OS rate was 34.6%. In multivariate analysis, age, surgical procedure, pathology stage, adjuvant chemotherapy and distant relapse were significant factors for survival. For the whole population, PORT had no effect on OS, with a median OS of 40 months in the PORT group versus 27 months in the non-PORT group ($p = 0.260$). However, in patients with N1 disease, the median OS were 40 months in the PORT group versus 14 months in the non-PORT group ($p = 0.032$). The corresponding OS in N2 patients were 35 months versus 17 months, respectively ($p = 0.040$). Similarly, PORT significantly reduced the LRR in patients with positive lymph node. For patients with N1 disease, the 3-year LRR rate was 0.0% in the PORT group versus 14.3% in the non-PORT group ($p = 0.037$). The corresponding LLR rate in N2 patients was 4.2% versus 56.6% ($p < 0.001$).

*Conclusion*: PORT significantly reduced LRR and improved OS in patients with regional metastasis SCLC. We suggest supplementing PORT in the multimodality treatment of resected SCLC with lymph node metastasis.



*Keywords:* Small cell lung cancer; Surgery; Radiotherapy; Adjuvant therapy

## Introduction

Small-cell lung cancer (SCLC) accounts for nearly 15% of all lung cancers[1] and is recognized as a high-grade malignancy with rapid growth of the primary lesion. The disease has a propensity to spread into mediastinal lymph nodes or distant organs.[2] Limited-stage SCLC (LS-SCLC) is found in about 40% of the patients at diagnosis.[3] Combined modality therapy using chemotherapy and thoracic radiation therapy is currently the standard of care for LS-SCLC but overall survival (OS) is still low. Analyses of treatment failures showed that even for patients with an apparent complete treatment response, the primary tumor region and mediastinal lymph nodes are the most frequent sites of recurrence.[4,5]

On the basis of the 2013 National Comprehensive Cancer Network (NCCN) guidelines,[6] surgery is only a recommendation for clinical stage I (T1-2, N0, M0) SCLC patients. However, in daily practice, a small proportion of SCLC patients receive surgical treatment sometimes under the following situations: (1) patients with no definite histopathologic diagnosis after bronchoscopic biopsy and cytologic biopsy, (2) patients with preoperative diagnoses of non-small cell lung cancer (NSCLC).

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Recent studies have reported that multimodality treatment involving surgery achieved a good prognosis in LS-SCLC patients.[7–9] Even with surgical intervention, local-regional recurrence (LRR) rate still ranges from 10% to 22%.[10,11] Most of these studies emphasize the need for chemotherapy as part of a multimodality treatment in LS-SCLC, the value of PORT is unclear. In the literature, only a few studies have separately assessed whether postoperative radiotherapy (PORT) can further reduce LRR and improve OS in resected SCLC patients.[12] To define the efficacy of PORT in resected SCLC patients, we retrospectively investigated the prognosis of LS-SCLC patients with pathologic stage T1a-3, N0-2, and M0 who were treated with complete surgical resection, the results might has a certain guiding significance in clinical therapy.

## Patients and methods

### *Patients*

This retrospective clinical study was approved by our institutional review board. From June 1996 to October 2011, one hundred and forty-three patients were enrolled with pathologic stage T1a-T3, N0-2, M0 SCLC who received complete resection and mediastinal lymph node dissection. None of these patients had proven pathological N3 disease after resection. All specimens were pathologically (postoperative) proven pure SCLC or combined SCLC which contained a NSCLC component by two senior pathologists specialized in lung carcinoma. Pathologic staging was conducted according to the American Joint Committee on Cancer (AJCC) criteria for NSCLC.[13] Complete resection was defined as resection of the primary tumor and mediastinal lymph nodes with negative bronchial residuals.

### *Therapy*

Among the 143 patients, 103 patients underwent lobectomy, 36 patients underwent pneumonectomy and four patients underwent wedge excision. The criteria for patients to receive PORT were according to the surgeon's advice, mainly for patients with positive lymph node, young age and advanced stage. In total, fifty-three patients received PORT, featuring radiation doses between 40 Gy–60 Gy using 1.8 Gy–2 Gy/fraction. The median time interval between radiotherapy and surgery was 3 months. The radiation field covered the bronchial stump, ipsilateral hilum and the mediastinal lymph node regions with confirmed metastasis by preoperative computed tomography scan and/or postoperative pathological evaluation. In fourteen patients, the radiation field also included the supraclavicular area. It should be noted that 54.7% of the patients who received PORT had stage III disease and only 37.8% of the patients who did not receive PORT had stage III disease.

Fifty-eight patients received chemotherapy before surgery and 121 patients received chemotherapy after surgery. Fourteen patients did not receive chemotherapy because of poor clinical condition. All of the chemotherapy regimens were platinum based doublets, with the most commonly used combination being a platinum-based drug combined with either etoposide (81%) or another agents (19%; cyclo-phosphamide, doxorubicin, methotrexate, orifosfamide). The neo-adjuvant chemotherapy was given with a median of two cycles and the adjuvant chemotherapy to a median of four cycles. Only six patients received prophylactic cranial irradiation (PCI).

### *Survival and relapse*

The OS was calculated from the date of surgery to the date of death or censored at the date of the last follow-up (if patient was alive). Time to relapse was calculated from the date of surgery to the date of proven LRR or distant relapse. LRR was defined as recurrence occurring at the surgical site, in the ipsilateral hilum, mediastinum or in the supraclavicular area. Recurrence beyond those areas was considered distant relapse. LRR and distant relapse were diagnosed using either imaging (computed tomography or positron emission tomography/computed tomography) or biopsy.

### *Follow up*

The follow-up schedule started from the time of surgery, and the patients were followed-up every three months for the first year, and every six months thereafter. Development of symptoms led to an immediate examination. The content of each follow-up included chest X-ray or computed tomography scan, and abdomen color Doppler ultrasound. Cranial computed tomography/magnetic resonance imaging was used when necessary. The last follow-up was in December 2012. Fifty-three patients have been followed up for more than 3 years, and 43 patients have been followed up for more than 5 years.

### *Statistical analysis*

Statistical analysis was carried out with SPSS 17.0 software. The OS and LRR rate curve were obtained by the Kaplan–Meier method. The log-rank test was used to compare the differences in OS and LRR between different groups. Multivariate analyses for OS and LRR were conducted with a Cox proportional hazards model using a stepwise variable selection procedure. All tests were two-sided, and statistical significance level was set at $p = 0.05$.

## Results

### *The characteristics of patients*

The median follow-up duration for the surviving patients was 82 months (range: 15–208 months). Altogether, 102 of