Surgery and Chemotherapy for Small Cell Lung Cancer in Stages I–II with or without Radiotherapy

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Purpose: To analyze the effectiveness of surgery and chemotherapy with or without radiotherapy in the management of limited small cell lung cancer (LSCLC) in stages I and II.
Patients and Methods: 39 patients (median age 62 years) with LSCLC in stages pT1 or pT2 and pN0 or pN1 (stages IA–IIB) who had a tumor resection and systematic lymph node dissection were reviewed retrospectively. The median follow-up period was 29 months. 35 patients (90%) received a median of four cycles of a platinum-containing chemotherapy postoperatively. 16 patients (41%) received an adjuvant thoracic radiotherapy (TRT, median 50 Gy); 21 patients (54%) received a prophylactic cranial irradiation (PCI, median 30 Gy).
Results: The median overall survival for all patients was 47 months, resulting in actuarial 1-, 3-, and 5-year survival rates of 97%, 58%, and 49%, respectively. Distant metastases were found in 13 patients (33%) after a median of 16 months. Patients who received an adjuvant TRT showed a trend toward improved thoracic recurrence-free survival ($p = 0.06$) and improved overall survival ($p = 0.07$) compared to those treated with surgery and chemotherapy only. Brain metastasis-free survival ($p = 0.01$) and overall survival ($p = 0.01$) were improved significantly in patients who received a PCI.
Conclusion: Surgical tumor resection may be considered for carefully selected patients. Adjuvant chemotherapy and PCI are recommended for all patients. Adjuvant TRT is currently used in patients with positive lymph nodes (pN1), because the probability of a subclinical involvement of the mediastinal lymphatic system appears to be increased in these patients.

Key Words: Small cell lung cancer · SCLC · Surgery · Chemotherapy · Radiotherapy

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Operation und Chemotherapie bei kleinzelligen Bronchialkarzinomen der Stadien I–II mit und ohne Bestrahlung

Ziel: Die Effektivität von Operation und anschließender Chemotherapie mit und ohne Strahlentherapie bei der Behandlung von frühen kleinzelligen Bronchialkarzinomen (LSCLC) der Stadien I und II wurde untersucht.
Patienten and Methodik: 39 Patienten (medianes Alter 62 Jahre) mit LSCLC der Stadien pT1 oder pT2 und pN0 oder pN1 (Stadien IA–IIB) wurden nach Tumoroperation mit systematischer Lymphknotendissektion retrospektiv untersucht. Die mediane Nachbeobachtungszeit betrug 29 Monate. 35 Patienten (90%) erhielten postoperativ median vier Zyklen einer platinhaltigen Chemotherapie. 16 Patienten (41%) erhielten eine adjuvante thorakale Bestrahlung (TRT, median 50 Gy); 21 Patienten (54%) erhielten eine prophylaktische Ganzhirnbestrahlung (PCI, median 30 Gy).
Ergebnisse: Das mediane Gesamtüberleben für alle Patienten lag bei 47 Monaten, die 1-, 3- und 5-Jahres-Überlebensraten betrugen 97%, 58% bzw. 49%. Fernmetastasen wurden bei 13 Patienten (33%) nach median 16 Monaten gefunden. Nach adjuvanter TRT wurde ein Trend zugunsten eines verbesserten thorakal-rezidivfreien Überlebens ($p = 0,06$) sowie eines verbesserten Gesamtüberlebens ($p = 0,07$) beobachtet. Durch eine PCI wurden das hirnmetastasenfreie Überleben ($p = 0,01$) und das Gesamtüberleben ($p = 0,01$) signifikant verbessert.
Schlussfolgerung: Eine chirurgische Tumorresektion ist für sorgfältig ausgewählte Patienten sinnvoll. Eine adjuvante Chemotherapie und eine PCI werden für diese Patienten vorgeschlagen. Eine adjuvante TRT wird gegenwärtig bei positivem Lymphknotenstatus (pN1) eingesetzt, da bei diesen Patienten die Wahrscheinlichkeit einer subklinischen Infiltration des mediastinalen lymphatischen Systems höher eingeschätzt wird.

Schlüsselwörter: Kleinzelliges Bronchialkarzinom · SCLC · Operation · Chemotherapie · Strahlentherapie

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Introduction

Small cell lung cancer (SCLC) is characterized by rapid tumor growth, early dissemination, and a poor prognosis. Limited-stage disease (LSCLC) is found in only 30% of patients with SCLC at the initial diagnosis [14].

The central role of a platinum-containing chemotherapy regimen in the treatment of lung cancer is well established [25]. The current standard combination is four to six courses of etoposide and cis- or carboplatin, with response rates > 80% [18]. Despite the introduction of new chemotherapeutic agents, survival rates have not improved over the past 10 years [4].

Thoracic radiotherapy (TRT) is an integral component of LSCLC treatment. Several studies showed a significant decrease in thoracic recurrence and demonstrated a 5% advantage in 3-year survival for the use of TRT in addition to chemotherapy [2, 15, 30]. Brain metastases are a common cause of treatment failure. Prophylactic cranial irradiation (PCI) is recommended in patients with LSCLC who achieve a complete response after chemoradiotherapy [3, 16, 19]. However, the median survival after chemoradiotherapy is 20 months, and only 30% of patients with LSCLC survive 2 years after the initial diagnosis [4, 8, 14]. Analyses of treatment failures showed that even for patients with a complete treatment response, the primary tumor region and mediastinal lymph nodes are the most frequent sites of recurrence [2, 15].

There is little data on resected LSCLC for the following reasons. First, early and potentially resectable clinical SCLC stages IA–IIB (TNM stages c2T1–2 c2N0–1 M0) are uncommon at initial diagnosis and for incidental findings [14]. Second, surgery alone is an inadequate therapy for LSCLC. As early as the 1970s, the British Medical Research Council study showed very poor survival rates after surgical treatment alone [7]. In recent years, however, surgery for early LSCLC as a component of a multimodal treatment concept has become the subject of growing interest [1, 5, 29].

In the present study, we reviewed 39 patients with LSCLC in stages I and II (TNM stages pT1–2 pN0–1 M0) who were treated with complete surgical resection. This group comprised only 2.75% of all patients with SCLC treated in our institution during the study period. Long-term results and the roles of adjuvant thoracic and prophylactic cerebral radiotherapies were analyzed.

Patients and Methods

From 1995 to 2006, 39 patients with LSCLC in stages IA–IIB (limited disease, TNM stages pT1–2 pN0–1 M0) who were operated on at the Department of Thoracic Surgery were included in this retrospective analysis. Detailed patient characteristics are provided in Table 1. The median age of patients was 62 years (range 41–78 years). All patients presented in World Health Organization (WHO) performance status 0 or 1. The median follow-up period was 29 months (range 2–110 months).

Tumor operation and systematic lymph node dissection were performed only, if preoperative staging examinations showed a clinical stage I tumor with no signs of mediastinal lymph node involvement (c2N0) or distant metastases (M0). Lobectomy was the most commonly performed surgical intervention (Table 1). All patients had a resection with microscopically tumor-free margins (R0). Histological examinations revealed pure SCLC in 35 patients (90%) and mixed SCLC/NSCLC (non-small cell lung cancer) in four patients (10%).

Adjuvant treatment concepts were not uniform, because patients were referred from different centers and regions. Four patients (10%) were treated with surgery alone, because they refused an adjuvant therapy. 35 patients (90%) received a median of four cycles (minimum two cycles, maximum six cycles) of a platinum-containing chemotherapy postoperatively. The most commonly used combination was cisplatin/etoposide. Depending on the number of postoperative chemotherapy cycles, radiotherapy was started 10–21 weeks after tumor resection.

16 patients (41%) received an adjuvant TRT, six patients in stage I and ten patients in stage II. 23 patients (59%) were treated without TRT. A median radiation dose of 50 Gy (range 50–60 Gy) was applied with 6- and 23-MV photons in fraction doses of 2 Gy using a linear accelerator (Siemens KD2 linear accelerator, Concord, CA, USA). CT-planned

Table 1. Patient characteristics. PCI: prophylactic cranial irradiation; TRT: thoracic radiotherapy.

Tabelle 1. Patientencharakteristik. PCI: prophylaktische Ganzhirnbestrahlung. TRT: thorakale Bestrahlung.

	Patients	
	n	%
Sex		
Male	31	79
Female	8	21
Localization		
Left lung	23	59
Right lung	16	41
Tumor stage		
T1 N0	9	23
T2 N0	15	38
T1 N1	5	13
T2 N1	10	26
Surgery		
Wedge resection	1	3
Segmental resection	2	5
Lobectomy	30	77
Bilobectomy	2	5
Pneumonectomy	4	10
Radiotherapy		
TRT + PCI	15	38
Only TRT	1	3
Only PCI	6	15
No TRT	23	59
No PCI	18	46
No radiotherapy	17	44

three-dimensional conformal treatment was performed in 14 patients. Treatment planning was based on 10-mm-thickness and -interval CT scans obtained in the treatment position. Tissue heterogeneity correction was applied in the planning process. Radiotherapy targets were defined according to ICRU Reports 50 and 62. Irradiated fields covered the bronchial stump, ipsilateral hilum, and the adjacent mediastinal lymph nodes. A simple anterior-posterior/posterior-anterior (AP/PA) technique was used in two patients; the spinal cord was shielded after 30 Gy in the PA field.

21 patients (54%) received a PCI, eleven patients in stage I and ten patients in stage II. 18 patients (46%) were treated without PCI. A median dose of 30 Gy (range 28–36 Gy) was administered in fraction doses of 2 Gy. All patients were treated with 6 MV and opposing asymmetric fields.

Both TRT and PCI were applied in 15 patients (38%).

Descriptive statistics, Kaplan-Meier estimation analysis, and the log-rank test were applied for statistical analyses. 1-, 3-, and 5-year actuarial rates for overall survival, disease-specific survival, thoracic recurrence-free survival, and brain metastasis-free survival were calculated using the Kaplan-Meier method from the date of radiotherapy by applying STATISTICA version 5.5 software (StatSoft Inc®, Tulsa, OK, USA). Statistical differences in survival rates were tested with the log-rank test. The p-values were two-sided, with $p < 0.05$ considered statistically significant.

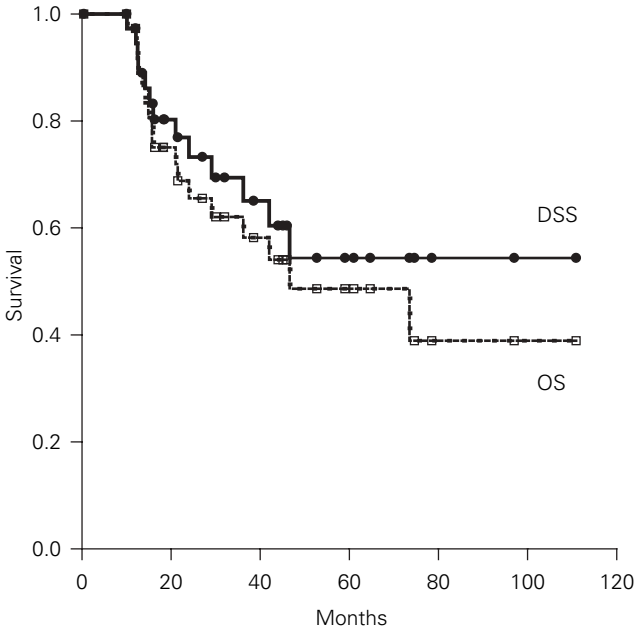

Figure 1. Overall (OS) and disease-specific survival (DSS) for all patients.

Abbildung 1. Gesamtüberleben (OS) und krankheitsspezifisches Überleben (DSS) für alle Patienten.

Results

The median overall survival for all patients was 47 months after the initial diagnosis, resulting in actuarial 1-, 3-, and 5-year survival rates of 97%, 58%, and 49%, respectively (Figure 1). The 1-, 3-, and 5-year disease-specific survival rates were 97%, 65%, and 54%, respectively; the median was not reached. Overall survival did not differ significantly between patients in stages I and II. Distant metastases were found in 13 patients (33%) after a median of 16 months (range 10–47 months). Metastases were located in the liver, central nervous system (CNS), bones, lymph nodes, and adrenal glands. Four patients were treated surgically without subsequent chemo- or radiotherapy. Three of these patients died from distant metastases (liver metastasis, two patients; bone marrow carcinosis, one patient) after 12, 16, and 22 months, respectively. One patient died from an unrelated cause 30 months after initial tumor diagnosis.

Although the current study is a retrospective, nonrandomized analysis, a comparison of the outcome of surgical resection with or without adjuvant TRT or PCI was performed. Patients who received an adjuvant TRT showed a trend toward improved thoracic recurrence-free survival ($p = 0.06$) and improved overall survival ($p = 0.07$) compared to those treated with surgery and chemotherapy only (Figure 2). None of the patients treated with TRT relapsed locally. Four mediastinal recurrences occurred in the group of 23 patients (17%) without TRT after a median of 15 months (range 5–20 months).

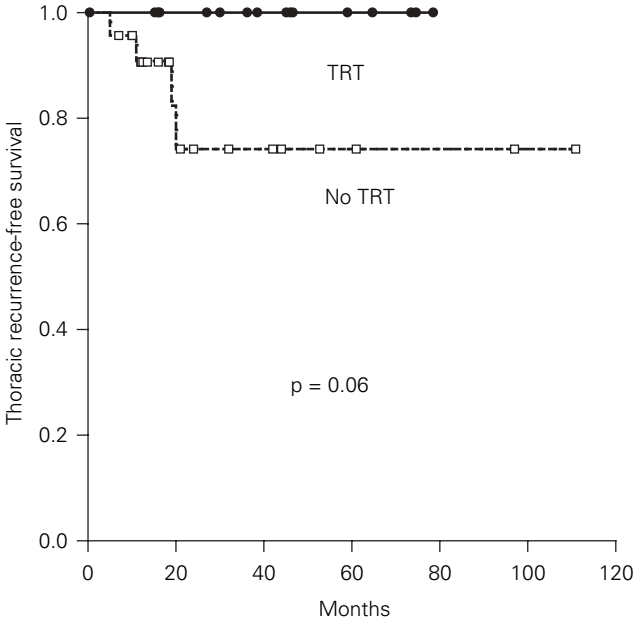

Figure 2. Thoracic recurrence-free survival with and without adjuvant thoracic radiotherapy (TRT). A trend toward improved thoracic recurrence-free survival ($p = 0.06$) was observed with TRT.

Abbildung 2. Thorakal-rezidivfreies Überleben nach Behandlung mit und ohne adjuvante thorakale Bestrahlung (TRT). Ein Trend zu verbessertem thorakal-rezidivfreien Überleben nach TRT wurde beobachtet ($p = 0{,}06$).

Brain metastasis-free survival (p = 0.01) was improved significantly in patients who received a PCI (Figure 3). Four of the 18 patients (22%) in the group without PCI developed brain metastases after a median of 11 months (range 8–27 months), compared to 100% brain metastasis-free survival after PCI. Additionally, overall survival (p = 0.01) was significantly better in patients treated with PCI.

Postoperative complications included pneumonia in six patients (15%), pneumothorax in one patient (3%), prolonged air leak in three patients (8%), wound infection in one patient (3%), and atrial arrhythmias in four patients (10%). None of the patients died of causes related to intra- or postoperative complications (operative mortality, 0%).

Chemotherapy-related neutropenia (WHO grade 2–3) was observed in 23 patients (59%), and mucositis (grade 2–3) was found in seven patients (18%).

After TRT, acute mucosal and skin reactions (WHO grade 1–2) were observed. Three patients (19%) developed pneumonitis (grade 2) with moderate breathing problems and a dry cough. They had complete symptom relief after treatment with steroids and antibiotic medication. No serious early or late complications were associated with PCI.

Discussion

The prognosis for patients with LSCLC is poor. The 5-year overall survival after chemoradiotherapy even for LSCLC in stages I and II is approximately 15%, and ~20–30% of patients relapse locally [4, 13, 14]. Currently, the role of surgery in very early LSCLC is not strictly defined, and only a few series exist that address a bi- or trimodal treatment approach including chemotherapy and/or radiotherapy. In the 1980s, the series by Meyer et al. reported prolonged survival in patients treated with surgery and subsequent chemotherapy [20]. In the 1990s, a prospective randomized trial showed no advantage for surgery in the treatment of SCLC, but the authors discussed the fact that the statistical power was too low for different tumor stages [17]. A recent population-based study compared standard radiochemotherapy with surgery plus adjuvant therapy for stage I patients, revealing a significantly prolonged 5-year survival (11% vs. 45%) for the surgically treated patients [23]. However, these results must be interpreted carefully and cannot define a treatment standard due to the small number of resected patients (n = 38) and the retrospective study design with data collection from reports provided to the Norway Cancer Registry by clinical and pathologic departments.

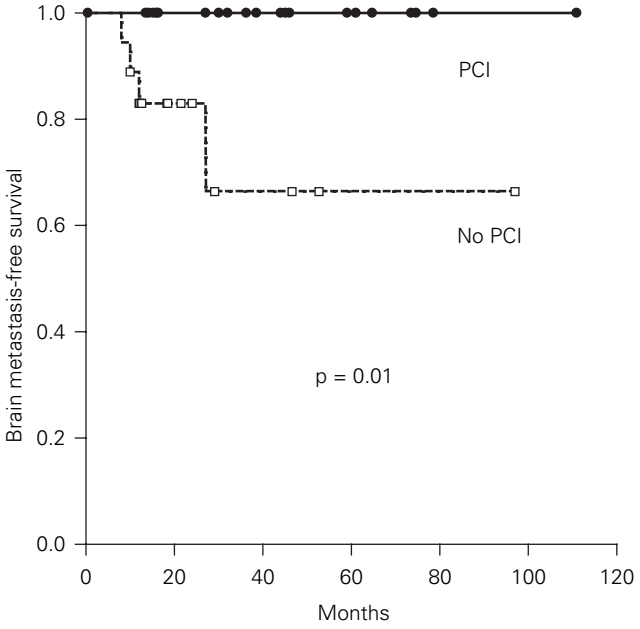

Figure 3. Brain metastasis-free survival with and without prophylactic cranial irradiation (PCI). Brain metastasis-free survival was significantly improved with PCI (p = 0.01).

Abbildung 3. Hirnmetastasenfreies Überleben nach Behandlung mit und ohne prophylaktische Ganzhirnbestrahlung (PCI). Das hirnmetastasenfreie Überleben war nach PCI signifikant verbessert (p = 0,01).

In the current study, surgical resection of LSCLC in stages I and II followed by adjuvant treatment resulted in a 5-year overall survival rate of 49%. These results are comparable to those obtained by Granetzky et al. who showed a 5-year survival of 42% for patients with LSCLC stages I and II after operation, chemotherapy, TRT, and PCI [10]. Rea et al. reported a 5-year survival of 52% for patients with stage I SCLC and of 30% for patients with stage II disease after trimodal treatment [22]. Other authors published 5-year survival rates ranging from 13% to 43%, depending on postoperative treatment concepts and tumor stages [1, 23, 29]. By comparison, several large trials report 5-year overall survival rates of ≤ 26% for LSCLC patients treated with a combination of chemo- and radiotherapy without surgery [24, 27, 28]. Interestingly, survival rates in our series were not significantly different for stages I and II. This may be due to the fact that the adjuvant treatment was not uniform, and more patients in stage II received an adjuvant radiotherapy in our series. PCI was given to 67% of patients in stage II but to only 46% of patients in stage I. 67% of patients in stage II were treated with an adjuvant TRT, whereas only 25% of patients in stage I received a TRT.

However, survival for surgically treated patients with LSCLC and N2 lymph nodes (stage III) is reduced significantly compared with stages I and II [10, 12, 22]. Therefore, careful patient selection and complete preoperative staging examinations including mediastinoscopy, endobronchial ultrasound, and, if possible, PET (positron emission tomography) scan are warranted to determine treatment groups and to avoid understaging in patients with SCLC or NSCLC [6, 9, 11, 21].

The mediastinal lymph nodes and primary tumor bed are the most common sites of first tumor recurrence after standard chemoradiotherapy, even for patients who had a complete response [15, 29, 30]. The importance of an adjuvant TRT for prevention of local relapse after complete surgical excision of small LSCLC remains unclear. The number of pa-

tients treated with an adjuvant TRT varies in most of the published studies [1, 22, 23]. In our series, treatment with surgery followed by chemotherapy and TRT resulted in excellent locoregional control without major toxicities. Locoregional control was achieved in all patients who were treated with TRT, whereas 17% of patients treated with surgery and chemotherapy only developed a mediastinal relapse. This difference was not significant. However, due to the small number of patients, significance could only result, if survival curves showed a difference of ~30%. The superiority of surgery, chemotherapy, and adjuvant TRT over surgery and chemotherapy alone is supported by the findings of other groups, especially in lymph node-positive patients, but prospective randomized data do not exist due to the low numbers of surgically treated patients in stages I and II [1, 10, 29].

The incidence of brain metastasis in SCLC increases with prolonged survival after an initial response to multimodal treatment. Approximately half of patients will develop brain metastases at some point during the course of disease. If cases from autopsy series are included, CNS metastases can be as high as 80% at 2 years [3, 4, 16]. PCI improves overall survival by ~5% at 3 years and decreases the cumulative incidence of brain metastasis to 50% among patients in complete remission [3, 19]. Positive impacts on quality of life and cost-effectiveness have also been shown [26]. In our series, brain metastasis-free survival was 100% in patients treated with PCI compared to 78% in the group treated without PCI. Surgically treated patients with LSCLC stages I and II are in complete remission; therefore, PCI should be suggested after chemotherapy.

Conclusion

The standard treatment approach for LSCLC consists of chemo- and radiotherapy. Surgical tumor resection may be considered for carefully selected patients. Four cycles of a platinum-containing chemotherapy regimen are suggested for all patients. Currently, we use an adjuvant TRT in patients with positive lymph nodes (pN1), because the probability of a subclinical involvement of the lymphatic system and the resulting estimated risk of a mediastinal recurrence appear to be increased in these patients. All LSCLC patients at our institute receive a PCI to minimize the risk of brain metastasis. However, due to the small number of patients in this retrospective study, general recommendations for radiotherapy cannot be given.

References

1. Anraku M, Waddell TK. Surgery for small-cell lung cancer. Semin Thorac Cardiovasc Surg 2006;18:211–6.
2. Arriagada R, Pignon JP, Ihde DC, et al. Effect of thoracic radiotherapy on mortality in limited small cell lung cancer. A meta-analysis of 13 randomized trials among 2,140 patients. Anticancer Res 1994;14:333–5.
3. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999; 341:476–84.
4. Cooper S, Spiro SG. Small cell lung cancer: treatment review. Respirology 2006;11:241–8.
5. De Antonio DG, Alfageme F, Gamez P. Results of surgery in small cell carcinoma of the lung. Lung Cancer 2006;52:299–304.
6. Ernst-Stecken A, Lambrecht U, Mueller R, et al. Hypofractionated stereotactic radiotherapy for primary and secondary intrapulmonary tumors. First results of a phase I/II study. Strahlenther Onkol 2006;182:696–702.
7. Fox W, Scadding JC. Medical Research Council comparative trial of surgery and radiotherapy for primary treatment of small-celled or oat-celled carcinoma of bronchus. Ten-year follow-up. Lancet 1973;2:63–5.
8. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4837–45.
9. Gagel B, Piroth M, Pinkawa M, et al. Gemcitabine concurrent with thoracic radiotherapy after induction chemotherapy with gemcitabine/vinorelbine in locally advanced non-small cell lung cancer. A phase I study. Strahlenther Onkol 2006;182:263–9.
10. Granetzky A, Boseila A, Wagner W, et al. Surgery in the tri-modality treatment of small cell lung cancer. Stage-dependent survival. Eur J Cardiothorac Surg 2006;30:212–6.
11. Grosu AL, Piert M, Weber WA, et al. Positron emission tomography for radiation treatment planning. Strahlenther Onkol 2005;181:483–99.
12. Herrmann T, Baumann M. Prolongation of latency or overall treatment time by unplanned radiation pauses. The clinical importance of compensation. Strahlenther Onkol 2005;181:65–76.
13. Imamura F, Ueno K, Kusunoki Y, et al. High-dose-rate brachytherapy for small-sized peripherally located lung cancer. Strahlenther Onkol 2006; 182:703–7.
14. Jemal A, Ward E, Hao Y, et al. Cancer statistics, 2006. CA Cancer J Clin 2006; 56:106–30.
15. Kies MS, Mira JG, Crowley JJ, et al. Multimodal therapy for limited small-cell lung cancer: a randomized study of induction combination chemotherapy with or without thoracic radiation in complete responders; and with wide-field versus reduced-field radiation in partial responders: a Southwest Oncology Group Study. J Clin Oncol 1987;5:592–600.
16. Kotalik J, Yu E, Markman BR, et al. Practice guideline on prophylactic cranial irradiation in small-cell lung cancer. Int J Radiat Oncol Biol Phys 2001;50:309–16.
17. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994;106:320–6.
18. Mascaux C, Paesmans M, Berghmanns T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer 2000; 30:23–36.
19. Mehta MP. Models support prophylactic cranial irradiation. J Clin Oncol 2006;24:3524–6.
20. Meyer JA, Comis RL, Gottlieb AJ, et al. Phase II trial of extended indications for resection in small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1982;83:12–9.
21. Paulsen F, Scheiderbauer J, Eschmann SM, et al. First experiences of radiation treatment planning with PET/CT. Strahlenther Onkol 2006;182:369–75.
22. Rea F, Callegaro D, Favaretto A, et al. Long term results of surgery and chemotherapy in small cell lung cancer. Eur J Cardiothorac Surg 1998;14:398–402.
23. Rostad H, Naalsund A, Jacobsen R, et al. Small cell lung cancer in Norway. Should more patients have been offered surgical therapy? Eur J Cardiothorac Surg 2004;26:782–6.
24. Ruysscher D, Pijls-Johannesma M, Vansteenkiste J, et al. Systematic review and meta-analysis of randomised, controlled trials of the timing of chest radiotherapy in patients with limited-stage, small cell lung cancer. Ann Oncol 2006;17:543–52.
25. Semrau S, Bier A, Thierbach U, et al. 6-year experience of concurrent radiochemotherapy with vinorelbine plus a platinum compound in multimorbid or aged patients with inoperable non-small cell lung cancer. Strahlenther Onkol 2007;183:30–5.
26. Tai TH, Yu E, Dickof P, et al. Prophylactic cranial irradiation revisited: cost-effectiveness and quality of life in small-cell lung cancer. Int J Radiat Oncol Biol Phys 2002;52:68–74.

27. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054–60.
28. Turrisi AT, Kyungmann K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265–71.
29. Waddel TK, Shepherd FA. Should aggressive surgery ever be part of the management of small cell lung cancer? Thorac Surg Clin 2004;14:271–81.
30. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992;10:890–5.

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