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Influence of Surgical Resection Prior to Chemotherapy on the Long-Term Results in Small Cell Lung Cancer. A Study of 150 Operable Patients

KELL ØSTERLIND,* MOGENS HANSEN,† HEINE HØI HANSEN,* and PER DOMBERNOWSKY‡

*The Finsen Institute, Department of Oncology II, Strandboulevarden 49, DK-2100 Copenhagen Ø. †Bispebjerg Hospital, Medical Department C, Bispebjerg Bakke, DK-2400 Copenhagen NV. ‡Present address: Department of Oncology, Copenhagen University Hospital, Herlev, DK-2730 Herlev

Abstract—*The effect of surgical resection, prior to chemotherapy, on the long-term results obtained in treatment of operable patients with small cell lung cancer (SCC) was evaluated in a consecutive series of* 874 *patients treated with intensive combination chemotherapy with or without irradiation between* 1973 and 1981. *Evaluation of disease stage and operability was based on broncho-mediastinoscopy, chest X-ray, bone marrow examination, peritoneoscopy with liver biopsy and lung function tests. The same staging procedures were applied for restaging performed after* 18 months *of chemotherapy. The series comprised* 440 *patients with extensive disease and* 437 *with limited disease of whom* 150 *were regarded operable. Fifty-four operable patients received no thoracotomy because the treatment policy of SCC did not include surgery at the hospitals from which they were referred. These patients served as a reference with which data on operated patients were compared. Resections were performed in* 52 *patients while* 44 *were regarded to be irresectable at the thoracotomy. Thirty-six resections were regarded histologically complete while* 16 *patients proved to have microscopic* (9 pts) *or macroscopic* (7 pts) *residual tumor. The number and per cent of* 30 months *disease-free survivors in the various categories of the* 874 *patients were as follows: Completely resected,* 12/36 *patients* (33%); *Resected with residual tumor,* 2/16 (12.5%); *Operable but non-operated,* 7/54 (13%); *Irresectable,* 3/44 (6.8%); *Non-operable patients with limited disease,* 15/284 (5.3%) *and with extensive disease,* 11/440 (2.5%). *The similarity between rates of long-term survival observed in resected patients with residual tumor and operable, non-operated patients suggests that resection,* per se, *has no significant influence on long-term results in SCC. The relatively high rate of long-term survival in completely resected patients may therefore primarily be a result of early stage disease at the initiation of chemotherapy.*

INTRODUCTION

SMALL CELL carcinoma of the lung (SCC) is characterized by early dissemination. Surgery alone is generally always inadequate treatment for SCC, in contrast to the other main histological cell types of lung cancer. In larger series of patients with SCC only about 7% are resectable and very few become long term survivors [1–4]. SCC is sensitive, however, to irradiation and a variety of antineoplastic drugs [5]. The introduction of combination chemotherapy has led to major therapeutic advances [6] and at the same time has produced uncertainty regarding the indications for surgery. In limited-stage SCC surgical resection might be of benefit by reducing the tumor burden and possibly also by eliminating primarily chemo- or radioresistant tumor cells. It has never been clarified, however, whether or not surgical resection really does add to the results obtained in early stages of SCC. A recent study of long-term survival in resected and non-resected patients with SCC supports the view that complete surgical resection of early disease may offer a distinct advantage to the subsequent chemotherapy [7]. The study comprised only 10 completely resected patients, however, and the non-operated control group was derived from the literature. More reliable information on the role of surgery in long-term control of SCC would be obtained from a complete series of patients representing the entire disease spectrum. Accordingly we reviewed the clinical data of a series of 874 consecutive patients, treated with intensive combination chemotherapy.

MATERIAL AND METHODS

From March 1973 to September 1981, 874 patients with SCC were included in trials employing

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Requests for reprints to: Kell Østerlind.

intensive chemotherapy and irradiation at the Finsen Institute and Bispebjerg Hospital, Copenhagen [8–13]. All patients were previously untreated apart from a possible surgical resection. Verification of the histopathological diagnosis (WHO classification) [14] was obtained in all patients by pathologists at the two institutions.

Treatment was given for 18 months when it was discontinued if no residual disease was proven at restaging. Restaging as well as pretreatment staging included physical examination with biopsy or fine needle aspiration from suspected superficial metastatic lesions, chest X-ray, bone marrow examination and peritoneoscopy with liver biopsy.

At the pretreatment staging, spread of disease outside the primary lung and the mediastinum was proven in 467 patients. Records of the residual 407 patients were reviewed in order to select all operable patients. Mediastinal metastases, bronchoscopic signs of irresectability, inadequate respiratory reserve or poor physical condition were regarded to be indications against surgery. The mediastinal lymph node status was based on mediastinoscopy when available and subsidiary radiographic investigations. The operable patients, defined by these means, were separated into those who underwent surgery prior to the chemotherapy and those who did not. The existence of non-operated operable patients was due to differences in the treatment policy of SCC at the various referring departments.

All operated patients were assigned a pathologic (pTNM) stage describing the known extent of disease after examination of peroperative biopsies and the resected specimen and it was also registered whether microscopic or macroscopic residual tumor was left [15].

Seventy-two patients were disease-free at the restaging after 18 months of chemotherapy. A total of 25 systemic recurrences were proven at the subsequent follow-up, now ranging from 3.5 to 11 yr after the start of treatment. The data thus enabled calculation of 18, 30 and 42 months rates of disease-free survival for different categories of the 874 patients. Estimates of long-term survival beyond these benchmarks and estimates of the cumulative risk of late systemic relapse were carried out by use of the life table method [16]. The log rank test was employed to test differences for statistical significance [16] and a test of trend [17] was employed if there was a natural ordering of the groups to be analyzed. The chi square test was used for confidence tests in 2×2 contingence tables [18].

RESULTS

The present series of 874 patients consisted of 434 patients (50%) with limited disease and 440 patients with extensive disease (Table 1). Two-

Table 1. Operability in relation to stage categories of 874 patients with newly diagnosed SCC

Criteria	No. of patients		Stage
Inoperable patients:			
Metastases outsite primary lung and mediastinum	440	440	Extensive
Ipsilateral supraclavicular lymph node metastases	27	284	Limited
Positive mediastinal lymph node biopsies	133		
Mediastinal metastases on chest X-ray	46		
Bronchoscopic signs of irresectability	62		
Poor general or respiratory status	16		
Operable patients:			
Non-operated	54	150	Limited
Resected	52		
Irresectable	44		

hundred-and-eighty-four of the limited stage patients were regarded to be inoperable for the reasons summarized in Table 1, leaving 150 potentially operable patients. Fifty-four of these patients did not undergo thoracotomy. Fifteen of the non-operated patients and 29 of the 96 operated patients were regarded to be operable although no preoperative mediastinoscopy was performed. No significant difference in survival duration was observed between patients with and without mediastinoscopy ($P = 0.92$).

Fifty-two of the 96 operated patients underwent resections while 44 patients were found to be irresectable. Thirty-six resections were complete while microscopic or macroscopic evidence of residual disease was recorded in nine and seven patients, respectively. Based on findings at surgery and examinations of the resected specimens the 36 completely resected patients could be classified as 18 stage I disease, 8 stage II and 10 stage III.

At restaging, performed 18 months after initiation of chemotherapy, disease-free status was proven in 72 (8%) of the 874 patients. The numbers and per cents of patients remaining in complete remission 18, 30 and 42 months after the start of treatment in different categories of patients are summarized in Table 2. Thirty months disease-free

Table 2. Eighteen, 30 *and* 42 months *disease-free survival rates in different categories of* 874 *consecutive patients with SCC*

Category	No. of patients	Disease-free at: 18 mths (%)	30 mths (%)	42 mths (%)	Deaths in systemic CR
Resected:					
Stage I	18	10 (56%)	7 (39%)	4 (22%)	2
Stage II + III	18	5 (28%)	5 (28%)	5 (28%)	0
Residual tumor	16	3 (19%)	2 (13%)	2 (13%)	0
Non-resected:					
Operable	54	9 (17%)	7 (13%)	3 (5.6%)	1
Irresectable	44	3 (6.8%)	3 (6.8%)	1 (2.3%)	2
Non-operable					
Limited stage	284	30 (11%)	16 (5.6%)	8 (2.8%)	11
Extensive stage	440	12 (2.7%)	9 (2.0%)	8 (1.8%)	0
	874	72 (8.2%)	49 (5.6%)	31 (3.5%)	16*

* Including three deaths from isolated brain recurrence.

survival was recorded in 17 (18%) of the 96 patients who received a thoracotomy, which was not significantly superior to the 7/54 (13%) observed in non-operated operable patients ($P = 0.45$). The total of 24 (16%) 30 months survivors recorded in the 150 operable patients was significantly more than the 7% observed in the 284 non-operable limited stage patients ($P < 0.005$).

A total of 25 systemic relapses occurred between the 18th and the 42nd month after the initiation of treatment. Sixteen patients died without evidence of recurrent systemic disease. Post-mortem examinations were obtained in 63% of the patients [19].

Life table estimates were undertaken of the disease-free survival and of the cumulative risk of systemic recurrence in the period from restaging to 5 yr after the start of treatment (Figs. 1 and 2). The seven patient categories in Table 2 were reduced to the following four: 1, all 15 completely resected 18 months survivors; 2, the three incompletely resected plus the nine operable patients; and 3, the three irresectable patients plus the 30 non-operable patients with limited disease. The 12 extensive stage long-term survivors constituted the fourth group. Relatively more deaths occurred in the 30 irresectable plus three non-operable 18 months' survivors compared to any of the other three groups but none of the differences were significant. Eleven of the 22 deaths recorded during months 18–42 were not associated with systemic recurrences, however, while most deaths in the other three groups were caused by recurrent SCC (Table 2).

The cumulative risk of late systemic relapse did not differ significantly between the four categories

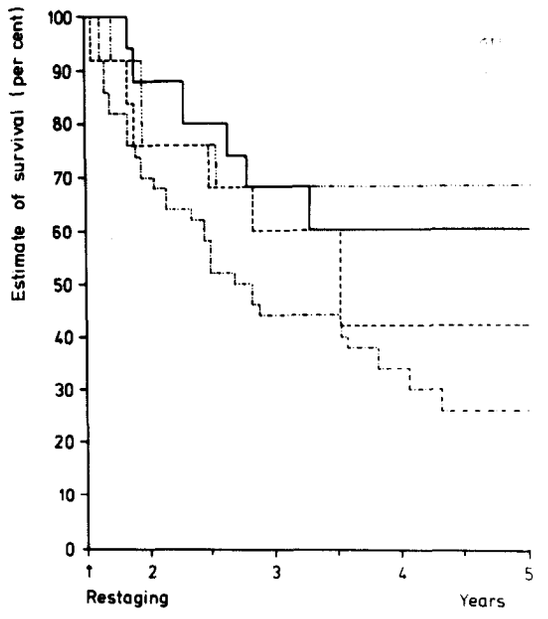

Fig. 1. *Estimated disease-free survival in four categories of patients with SCC, disease-free after* 18 months *of chemotherapy*: ——: 15 *completely resected patients*. ----: *three incompletely resected patients* + 9 *operable non-operated patients*, -.-.-: *three irresectable* + 30 *non-operable limited disease patients, and* –···–···: 12 *extensive disease patients.*

(Fig. 2). Recurrences tended to occur earlier in the non-operable limited stage 18 months' survivors compared to operable patients and earlier in operable patients compared to completely resected patients but the trend was not significant ($P = 0.35$).

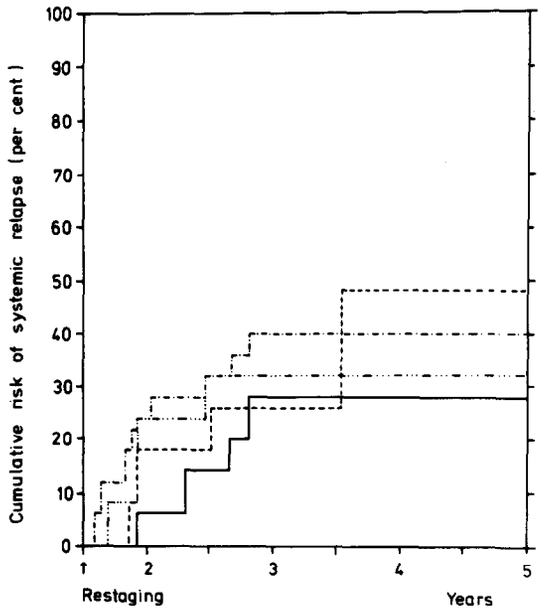

Fig. 2. Cumulative risks of late systemic relapse in —: 15 *completely resected patients,* ----: *three incompletely resected* + *nine operable non-operated patients,* -·-·-: *three irresectable* + 30 *non-operable limited disease patients, and* –···–···: 12 *extensive disease patients.*

DISCUSSION

The survival data for patients with SCC undergoing surgical resection prior to chemotherapy are generally substantially superior to those observed in almost any series of non-resected patients [7, 20, 21]. Such observations suggest that surgical resection of tumor prior to chemotherapy increases the likelihood of cure by subsequent systemic therapy. Attempts to assess how much resection of the primary tumor influences the prognosis in SCC are lacking, however, presumably because it is difficult to establish an adequate control group of unresected patients. Optimally this question should be evaluated by prospective randomisation of patients to resection or not. Such a controlled trial may meet obstacles, however, because several centers must participate if enough patients shall be included within a reasonable amount of time and because many would feel it conflicting to omit surgery in otherwise operable patients with SCC.

Retrospective studies are hampered by difficulties in matching non operated patients with the very selected group of completely resected patients. Control patients should at least be operable although this requirement does not preclude that a considerable proportion would be irresectable if surgery was performed. Many resected patients undergo an explorative thoracotomy because the primary tumor is too small or otherwise inaccessible for biopsy [7]. In the present series 47% of the completely resected patients underwent diagnostic thoracotomies. This category presumably comprises the very earliest stages of the disease, associated with an especially favourable prognosis [22].

The present study confirms previous experience of a better prognosis in completely resected patients as compared to other categories of SCC [7, 20, 21] but the observed 30 months' survival rates were not in accordance with those mentioned in a recent report based on data compiled from different centers [7]. The present data may, however, give a more reliable impression of the difference in long-term results between resected and non resected patients, because the patients were consecutively accrued and all received current, intensive combination chemotherapy. The similarity between the survival rates observed in incompletely resected and operable, non-operated patients suggests that resection, per se, has only minor influence on the probability of long survival. The better outlook of completely resected patients accordingly may be a result of early stage disease at the start of chemotherapy. Our data do not preclude a possible advantage of surgical resection but if a beneficial effect exists it appears to be more modest than suggested by Meyer's data [7].

The cumulative risk of relapse recorded in the different categories of the 18 months disease-free survivors did not differ significantly. Late relapses tended to occur later in completely resected patients, however, compared to the other subsets perhaps indicating that tumors with long doubling times preponderate in patients with early stage disease at diagnosis. It has recently been shown that the pretreatment size of the primary tumor has prognostic impact beyond the earliest stages of the disease [23]. Accordingly it would seem reasonable to TNM stage limited SCC, as suggested by Meyer [7]. There is no simple correlation, however, between the clinical T-categories and the tumor volume, because the definitions of the T-categories primarily reflect the potential resectability of the tumor rather than the tumor volume [15]. A more direct assessment of the tumor volume using one of the new imaging techniques [23, 24] may therefore be more useful in pretreatment staging of SCC.

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