European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 1998; 2: 137-140

Lung microcytoma: a multidisciplinary therapeutic approach

M. RUGGIERI, F. SCOCCHERA, A. MASCARO, C. HAUGHN*, M. BATORI, M. LAZZARO, M. LEPORE, A. PAOLINI

Institute of General Surgery IV, "La Sapienza" University - Rome (Italy)
**Ohio State University, Columbus, OH (USA)*

Abstract. – **This report is of 26 patients diagnosed with microcytoma of the lung in stages I, II, and IIIa. All patients received surgical treatment as well as postoperative chemoradiotherapy when indicated by stage. Mean survival rates were 16 months for stage I, 10 months for stage II and 6 months for stage IIIa disease.**

For many years surgery was considered contraindicated in the treatment of pulmonary microcytoma. Now a multidisciplinary approach is being used in which surgery has a crucial role. Microcytoma of the lung has a poor prognosis due to its early metastasis and rapid growth. It is crucial to have early diagnosis and accurate, consistent staging as the basis for treatment. A review of literature shows that the use of surgery, chemotherapy and radiotherapy are all important in treatment of microcytoma. Chemotherapy is successfully utilized preoperatively to improve local control, decrease neoplastic mass, induce histological regression and as postoperative adjuvant therapy. Radiotherapy has been shown to be effective preoperatively to reduce local mass and prophylactically for cerebral metastasis. Surgery is crucial to irradicate the neoplastic mass, improve staging accuracy, decrease the possible selection of neoplastic clones resistant to postoperative therapy, decrease local recurrence and allow less aggressive chemoradiotherapy.

We feel the most effective protocol for pulmonary microcytoma includes preoperative chemotherapy and radiotherapy when indicated followed by surgical intervention and finally successive adjuvant therapy.

The limited number of our cases does not consent a statistically significative conclusion. Our data confirm the importance of the surgical procedure in stages I and II, where according also to other authors, the best results are obtained. Surgical indication in stage IIIa is still discussed due to precocius lymphnode dissemination that significantly affects long-term survival.

Key-Words:

Small cell lung cancer, Mycrocitoma, Preoperative chemotherapy, Radiotherapy.

Introduction

For many years small cell carcinoma of the lung has been considered a systemic disease. British medical research conducted in the 1950's and 1960's concluded that surgical treatment added no benefit to radiation therapy alone[1]. Therefore, therapeutic protocol utilizing surgery was widely abandoned and was even considered contraindicated in patients with small cell lung cancer. Results of further research have shown that this is, in fact, not true. We now know that a multidisciplinary approach to treatment is needed, and surgery is assuming an increasingly important role.

Methods

This is the report of data collected from the treatment of twenty six patients diagnosed with microcytoma of the lung. Of these there were 4 patients with stage I, 10 patients with stage II and 12 with stage IIIa disease. Stage IIIa patients were thus distributed: one patient with T3/N1/M0, 3 patients with T2/N2/M0 and 8 patients with T3/N2/M0 belonged to this stage. Treatment strategies were based upon surgical staging. Patients with stage I disease received primary surgery

and postoperative chemotherapy. Patients diagnosed as stage II and IIIa received induction chemotherapy followed by surgery and further chemotherapy. Stage IIIa disease with extensive primary tumor invasion (T3) was treated with initial thoracic irradiation followed by surgery and postoperative chemotherapy. All patients who achieved complete remission received prophylactic cranial irradiation at six months post-op. The surgical procedures utilized included 7 lobectomies (3 with stage I and 4 with stage II disease), 1 bilobectomy of a patient with stage I disease and 18 pneumonectomies (6 with stage II and 12 with stage IIIa disease). The mean survival rates were 16 months ($p > 0.01$) for stage I disease, 10 months for stage II and 6 months ($p > 0.01$) for stage IIIa disease.

In stage IIIa median survival was very short, because this group included 11 patients with T1-3/N2/M0 and only one patient with T3/N1/M0.

Discussion

Pulmonary microcytoma is a malignant neoplasia which is responsible for 25% of all cancers of the lung. It presents an extremely poor prognosis due to its biological aggressiveness by rapid cellular replication and early hematologic metastasis. It has a controversial histogenesis because it is unclear weather it is of neural crest origin, making it part of the APUD system, or if it is of endodermic origin. Regardless the cells undergo a process of specific differentiation caused by unknown factors.

Because small cell carcinoma is a rapidly progressive disease and treatment possibilities are evolving and greatly depend upon the extent of disease it is imperative to utilize a consistent and precise system of staging. There is a common use of the terms “extensive” and “limited” disease throughout current literature. Typically, limited disease corresponds to stages I, II and IIIa and extensive disease to IIIb and IV of the AJCC classification system. Also, some American researchers have introduced the concept of “very limited” disease which includes only stages I and II. However, these terms are not consistent because they are applied to varying stages of disease. Additionally, the use of these terms defeats the purpose of utilizing a reproducible classification system which is vital to the ever-changing knowledge and treatment strategies[2]. The TNM model with AJCC classification fulfills these ideals well for microcytoma of the lung. However, it is clear to many researchers that the prognoses of patients affected by lung microcytoma varies within the stage of disease particularly in relation to lymphnode metastasis[3]. This leaves opportunity for further review of TNM staging in regards to lymphnode metastasis.

It is crucial to emphasize the importance of early diagnosis. Today, this is possible thanks to the sophisticated system of new technology available, particularly fibrobronchoscopy with biopsy sampling.

The treatment of patients affected by microcytoma must be multidisciplinary. Studies conducted in the 1980’s made this evident as the five year survival rate of those affected by lung microcytoma was markedly improved in the patients who were subjected to a combined treatment of surgery and postoperative chemotherapy[4,5]. Survival rates reached up to 51% for patients with stage I disease, 28% with stage II and 19% with stage IIIa[6,7]. Supporting this, other authors have registered five year survival rates which vary from 20-45% in stages II and IIIa[8-11]. In contrast, it is reported that chemotherapy used alone produces poor results, with a five year survival rate of only 5%[12-13].

Our results agree with those of other authors on survival in stages I and II, but are worse in stage IIIa. Probably the lymphnode metastases are the cause of the short survival because these represent signs of early disease diffusion.

The use of primary surgical treatment with an intent to cure in operable lung microcytoma is proving to be important for several reasons. Surgical intervention allows for a histopathological staging which is often more advanced than clinical staging which would imply it to be more accurate. A more accurate staging enhances the ability to choose the most effective form of adjuvant therapy and formulate a more precise prognosis. Surgery also eradicates the neoplastic mass which reduces the number of neoplastic cells to be treated by successive therapy. This improves the results while making it possible to

treat patients with less aggressive therapies which is to the advantage of the whole organism and in particular the hematopoietic system. In addition, by reducing the number of neoplastic cells with surgical excision it diminishes the probability of selection of neoplastic clones resistant to postoperative pharmacological treatment[14-15]. Finally, surgery has been shown to reduce the local recurrence rate when compared to chemoradiotherapy.

Chemotherapy is also maintaining a primary role in treatment of pulmonary microcytoma. Some authors emphasize the importance of preoperative chemotherapy. In addition to improving the local control of disease, it can, in some cases, induce a histological regression of the tumor, transforming it from microcytoma to a form of carcinoma that has a lesser degree of biological aggressiveness and therefore improving the prognoses[16]. Also, oncologic pharmacology is continuously developing more potent molecules which have less toxic effect. We feel that chemotherapy should not be viewed as an alternative to surgical intervention or vice versa in the treatment of pulmonary microcytoma. When used conjunctively surgery greatly enhances the outcome of chemotherapy.

The use of preoperative, local radiotherapy is also assuming an increasing role in the treatment of microcytoma in patients with stage IIIa disease. Several studies have reported very encouraging results[17-18]. Also, some authors suggest that prophylactic cranial irradiation is important in lowering the incidence of cerebral metastasis for patients in complete remission[19].

From this discussion we conclude that it is always necessary to consider surgery in the treatment of pulmonary microcytoma and when this is not possible due to an advanced stage of disease (IIIa), one must consider creating the conditions which make surgery possible with the use of complimentary preoperative therapies. This is done by lowering the stage of the neoplasia through inducing biological regression and a reduction of the overall mass of the tumor.

Given the state of current knowledge, our treatment strategy for pulmonary microcytoma includes primary surgical treatment followed by chemotherapy for stage I disease. Stages II and IIIa are treated by preoperative chemotherapy followed by surgical treatment and finally successive adjuvant therapy. In stage IIIa with T3, preoperative thoracic irradiation is utilized followed by surgery and chemotherapy. Prophylactic cranial irradiation is used for patients who are in complete remission.

Our results, eventhough the number of cases is scarse and insufficient to allow a statistically valid conclusion, confirm the findings of other authors on the role of surgery in the multidisciplinary management of SCLC.

References

1) *Fox W, Scadding JG.* Medical research council comparative trial of surgery and radiotherapy for primary treatment of small cell carcinoma of the bronchus, ten year follow-up. Lancet 1973; 2: 63-65.

2) *American Joint Committee on Cancer (AJCC).* Lung, In: Beahrs OH, Hensen DE, Hutter RVP, Myers MH, eds. Manual for Staging of Cancer. 4th Ed. Philadelphia: JB Lippincott, 1992.

3) *Meyer JA, Gullo JJ, Ikins PM et al.* Adverse prognostic effect of N2 disease in treated small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1989; 97: 177-186.

4) *Shields T, Higgins GA, Mathews NJ, Keehn RJ.* Surgical resection in the management of small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1982; 84: 481-488.

5) *Baker RR, Ettinger DS, Ruckdeschel JD et al.* The role of surgery in the management of selected patients with small cell carcinoma of the lung. J Clin Oncol 1987; 5: 697-702.

6) *Shepherd FA, Ginsberg RJ, Patterson GA, Evans WK, Feld R.* A prospective study of adjuvant surgical resection after chemotherapy for limited small cell lung cancer. A University of Toronto lung oncology group study. J Thorac Cardiovasc Surg 1989; 97: 177-186.

7) *Salzer GM, Muller LC, Huber H et al.* Surgery for N2 small cell lung carcinoma. Ann Thorac Surg 1990; 49: 750-762.

8) *Shepherd FA, Evans WK, Feld R et al.* Adjuvant chemotherapy following surgical resection for small cell carcinoma of the lung. J Clin Oncol 1988; 6: 832-838.

9) *Shepherd FA, Ginsberg RJ, Feld R, Evans WK, Johansen E.* Surigical treatment for limited small cell lung cancer. J Thorac Cardiovasc Surg 1991; 101: 385-393.

10) *Karrer K.* Surgery in SCLC as first step of multimodality treatment. Anticanc Res 1994; 14: 327-332.

11) *Wada H, Yokomise H, Tanaka F et al*. Surgical treatment of small cell carcinoma of the lung: advantage of preoperative chemoterapy. Lung Canc 1995; 13: 45-56.

12) *Johnson BE, Grayson J, Makuch RW et al.* Ten year survival of patients with small cell lung cancer treated with combination chemotherapy with or without irradiation. J Clin Oncol 1990; 8: 396-401.

13) *Armstrong J, Shank B, Scher H et al.* Limited small cell lung cancer: do favorable short-term results predicte ultimate autocome? Am J Clin Oncol 1991; 14: 285-290.

14) *Karrer K.* Surgery in SCLC as the first step of multimodality treatment. Anticanc Res 1994; 14: 327-332.

15) *Holmes EC.* The role of surgery in small cell carcinoma of the lung (SCLC). Lung Canc 1995; 3: 17-21.

16) *Karrer K. Shields TW, Denck H et al.* The importance of surgical and multimodality treatment in small cell carcinoma. J Thorac Cardiovasc Surg 1989; 97: 168-176.

17) *Pignon JP, Arriagada R, Ihde DC et al.* Analysis of thoracic radiotherapy for small cell lung cancer. N Engl J Med 1992; 327: 1618-1624.

18) *Warde P, Puyne D.* Does thoracic irradiation improve survival and local control in limited stage small cell carcinoma of the lung? J Clin Oncol 1992; 10: 890-895.

19) *Kristjansen PEG, Hansen HH.* Prophylactic cranial irradiation in small cell lung cancer – an update. Lung Canc 1995; 3: 23-40.