Institutional report - Thoracic general

Preoperative TNM evaluation of peripheral clinical stage I small cell lung cancer treated by initial lobectomy with adjuvant chemotherapy

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Abstract

Surgery with chemotherapy has been the accepted procedure for treating pathological stage I small cell lung cancer. However, there is a question of whether all clinical stage I patients should undergo surgery or not because of discrepancies between clinical and pathological staging. We conducted a retrospective analysis of TNM evaluation and postoperative survival on 10 clinical stage IA (T1N0M0) and 6 stage IB (T2N0M0) patients who had undergone initial lobectomy followed by chemotherapy. Clinical stage IB showed a high incidence of hilar or mediastinal lymph node involvement than stage IA (P=0.04). The accuracy of the T-factor did not differ between both stages. The pathological mean dimension of primary tumors with lymph node metastasis (33.4 mm) was significantly larger than that without metastasis (22.1 mm) (P=0.04). The difference in survival between clinical stage IA (7 of 10) and stage IB (2 of 6) was large but not significant (P=0.07). Four patients in each clinical stage died of cancer relapses. When indicating surgery for clinical stage I small cell lung cancer, it should be taken into account that primary tumors of more than 30 mm in diameter may suggest the possibility of stages more advanced than pathological stage II because of a high incidence of lymph node metastasis.

Keywords: Small cell lung cancer; Preoperative diagnosis; TNM staging; Lymph nodes metastasis

1. Introduction

Small cell lung cancer (SCLC) is characterized by high grade malignancy with rapid growth and early distant metastasis as compared with non-small cell lung cancer [1]. Systemic combination chemotherapy and thoracic radiotherapy play important roles in treatment strategies for SCLC [2–4]. However, local recurrence and distant metastasis after therapy have been frequently found even after complete remission. To improve local control and survival in very early stage SCLC, surgery with combined chemotherapy has recently become accepted [5]. Although the five-year survival rate in pathological stage (p-stage) IA (T1N0M0) having undergone this bimodal therapy appears to be higher than in p-stage IB (T2N0M0) [6–9], clinical stage (c-stage) I SCLC frequently shows more advanced diseases because of the underestimation of preoperative TNM evaluations [6,9,10]. To create a profile of patients in c-stage I SCLC who could benefit from surgery, it is necessary to analyze the characteristics of c-stage I SCLC patients which could indicate more advanced diseases. We retrospectively compared the clinicopathological differences between c-stage IA and c-stage IB SCLC patients who had undergone initial surgery followed by chemotherapy.

2. Materials and methods

Between January 1984 and December 1998, 30 surgical resections for SCLC were performed at the Tsukuba University Hospital. Twenty of them were c-stage I patients. We excluded patients who had undergone limited surgical resection consisting of segmentectomy, wedge resection and cases treated with initial chemotherapy and/or radiotherapy before surgery. We carried out a retrospective review of 16 c-stage I patients (IA 10, IB 6) who had undergone lobectomy and systematic mediastinal lymph node dissection followed by chemotherapy. The characteristics of these patients are summarized in Table 1. We estimated the accuracy of preoperative TNM evaluation by comparing clinical factors and pathological factors in each c-stage and p-stage. The disease stages were based on the TNM classifications of the International Union Against Cancer [11]. Primary lung tumors and nodal status were evaluated using 7–10 mm thick contiguous sections of thoracic computed tomography (CT). Diagnostic radiologists evaluated preoperative T-factor based on maximal tumor dimension and N-factor based on CT findings of mediastinal or...
hilar lymph nodes 10 mm or larger in their short axis diameter as metastasized nodes. All patients underwent magnetic resonance imaging or CT of the brain, ultrasonography of the abdomen, and radionuclide scanning of the bone to evaluate distant metastasis. Preoperative histologic or cytologic examination was performed using the specimens obtained by transbronchial lung biopsy or sputum cytology. Neither mediastinoscopy nor mediastinotomy was performed prior to the surgical resection of main tumors. All resected specimens were evaluated microscopically by plural pathologists. Pathological review confirmed that cases of large cell neuroendocrine carcinoma were not included in the analysis. A total of 198 dissected lymph nodes revealed that 13.2% were metastasized in 76 hilar lymph node metastasis of 33.4 mm was significantly larger than that without metastasis of 22.1 mm (P=0.04) (Fig. 2).

3.3. Five-year survival

The overall 5-year survival was 9 of 16 cases. As for c-stage, the survival was 7 of 10 cases for c-stage IA and 2 of 6 cases for c-stage IB, though this difference was not significant (P=0.07) (Fig. 3A). As for p-stage, the survival difference between p-stage IA and p-stage IB was not significant because there was only 1 case in p-stage IB. The survival in p-stage I was significantly higher than that in more than p-stage II disease (P<0.01) (Fig. 3B).
3.4. Recurrent diseases

All 7 patients who died within 5 years of surgery suffered cancer relapses (Table 3). In the 9 patients who remained well for more than 5 years, 1 patient in c-stage IA died from distant metastasis at 73 months. There are no surviving patients with SCLC.

4. Discussion

We have shown that the number of instances of metastasis in dissected lymph nodes of less than 10 mm in diameter is small. However, we also showed that c-stage IB SCLC in initial surgery cases had a high possibility of hilar or mediastinal lymph node metastasis as compared with c-stage IA. Our pathological review revealed that the mean tumor dimension with lymph node metastasis was significantly larger than that without metastasis. However, as shown in a previous study [9], no survival differences between clinical stages could be demonstrated.

TNM staging for non-small cell lung cancer could also define prognostic subgroups for patients undergoing surgery for SCLC [5,6]. In our preoperative TNM evaluation, the accuracy of T-factor measurement was acceptable. On the other hand, the accuracy of N-factor evaluation was not acceptable in either c-stage IA or c-stage IB. Especially, the accuracy of N-factor evaluation in c-stage IB was significantly lower than that in c-stage IA. Although we determined the N-factor based on mediastinal or hilar lymph nodes of 10 mm or larger in their short axis diameter as metastasized nodes, this criterion was assumed to be unsuitable for clinical staging for SCLC. Previous studies [6,9,10,12] have also shown that 19–42% of clinical N0 patients had more advanced stages according to more precise pathological TNM staging or at operation.

Because of this low sensitivity of N-factor evaluation using CT, new methods such as fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) have been introduced into the staging of lung cancer to provide more accurate evaluation [13]. FDG-PET appears to be valuable for initial
staging of limited-stage SCLC, because FDG-PET can identify primary or nodal SCLC masses that are suspected in CT with high sensitivity and can detect distant nodal and bone metastasis that are not suspected in CT [14]. However, tumor size is one of the potential limitations of FDG-PET. Small metastatic lesions, of approximately 4–8 mm, cannot be detected because of the limited resolution of the current PET equipment [13]. Because all macroscopic dimensions of our resected lymph nodes were less than 10 mm, they may not be detectable by FDG-PET.

Shields [7] suggested that mediastinoscopy or mediastinal lymph node metastasis when a diagnosis of SCLC has been established preoperatively. According to our pathological review, the number of occurrences of N2 metastasis was small, only approximately 2.5% in both c-stage IA and c-stage IB. Because the number of instances of N2 metastasis is small in the case of c-stage I SCLC, mediastinal lymph node metastasis can be missed even if mediastinal exploration is performed. Our results also showed that the mean dimension of primary tumors accompanying lymph node metastasis was significantly larger than those not accompanying metastasis.

Therefore, when indicating surgery for treating c-stage I SCLC, it should considered that a maximal primary tumor dimension of more than 30 mm may suggest the possibility of higher than p-stage II as compared with those of less than 30 mm.

Approximately 33% of cases of SCLC were pathologically diagnosed as SCLC for the first time at or after operation [6,10]. In these cases, our treatment consisted of initial lobectomy followed by postoperative chemotherapy. Previous studies have reported that the 5-year survival rate of c-stage I SCLC undergoing initial surgery followed by chemotherapy was approximately from 30% to 65% [6,10]. When comparing the 5-year survival rates between p-stage IA and p-stage IB, the survival rate in p-stage IA (56–65%) appears to be higher than that in p-stage IB (27.9–43%) [6–8]. Unfortunately, a comparison could not be made between p-stage IA and p-stage IB. P-stage I cases in the present study had small mean tumor dimensions of less than 20 mm, and this may be the reason why survival in p-stage I in this study was better than those in previous studies. The survival rate after surgery in p-stage II and p-stage III in this study was low, and was almost the same as that as after chemoradiotherapy [1–3]. The role of surgery in these cases is controversial.

As for first relapses, surgery has proved effective in decreasing local recurrence in both c-stage IA and c-stage IB. The incidence of distant metastasis in p-stage I was 44% as found in other previous studies [9,10]. Because SCLC tends to relapse to distant metastasis, systemic chemotherapy has been incorporated for stage I SCLC [15]. However, a chemotherapy protocol has not been standardized. Previous retrospective studies have shown that less than 4 courses or a single drug protocol was insufficient for adjuvant chemotherapy [6,9]. Although our adjuvant chemotherapy protocols were not uniform and were performed in 2 courses, the incidence of distant metastasis was not inferior to previous studies. However, this does not mean that 2 courses of chemotherapy are sufficient after surgery, because we had distant metastasis in 44% of the cases in c-stage I SCLC.

In summary, a retrospective analysis of c-stage I SCLC having undergone initial surgery followed by chemotherapy suggests that a diagnosis of clinical T2 may have the possibility of being p-stage II or p-stage III in which surgical indication may be questionable. Because the incidence of metastasis in dissected lymph nodes of less than 10 mm in diameter was small, it may be difficult to evaluate the N-factor accurately even if using FDG-PET or mediastinal exploration.

References

Appendix A. ICVTS on-line discussion

Author: Francesco Petrella (Bologna University, Italy)

eComment: I read with interest the article of Sakai and colleagues dealing with the role of lobectomy and adjuvant chemotherapy for peripheral state I SCLC. I have three questions: (1) Did you stop this approach in 1998 or are you still continuing? (2) Regarding lymphnodes metastases, which kind of metastasis did you find? (micrometastasis, intracapsular, perilymphonodal - extracapsular); (3) Have you ever performed lobectomy after induction chemotherapy followed by response? If yes, have you ever found complete pathological response (yp T0 N0)?

Author: Mitsuaki Sakai (University of Tsukuba, Japan)

eResponse: Thank you for your comments. I would like to respond to your questions as follows:

(1) We are still continuing the same approach with the clinical stage (c-stage) I SCLC patients, but we have had no cases after 1998.

(2) The macroscopic sizes of all observed lymph nodes were less than 10 mm in diameter. We could detect the micrometastasis and intracapsular metastasis microscopically. There was no perilymphonodal or extracapsular metastasis.

(3) We performed lobectomies after induction chemotherapy on 3 SCLC patients in the 1980s. Clinical stages were IIIA (T2N2M0) in 2 patients and IB (T2N0M0) in 1 patient. We performed 2 courses in each pre- and postoperative chemotherapy of carboplatin, etoposide, and ifosfamide. Postoperative pathological examination showed that 2 c-stage IIIA and 1 c-stage IB patients had down-staging induced to yp-stage IB and yp-stage IA (T1N0M0), respectively. However, we could not find a pathological complete response.

The difference in the benefit regarding survival between pre- and postoperative chemotherapy is controversial. Preoperative chemotherapy may help to realize good prognoses in c-stage I SCLC patients, but we have had no cases after 1998.

In these cases, treatment consisted of initial lobectomy and postoperative chemotherapy. Because c-stage I SCLC is a very rare disease, it may be difficult to compare the benefits of pre- and postoperative chemotherapy cases.

References