Clinical evaluation of systemic inflammatory response syndrome (SIRS) in advanced lung cancer (T3 and T4) with surgical resection

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Abstract

Objectives: The systemic inflammatory response syndrome (SIRS) is well known to occur in patients who have suffered organ damage or trauma, or undergone surgery. SIRS provides useful information in patients with morbidity after surgery. To date, there has been no report of SIRS after surgery in patients with lung cancer. Therefore, based on this new concept of the syndrome, we review here a series of T3 and T4 NSCLC patients who underwent extended resection at our hospital, and attempt to identify the value and correlation of SIRS in predicting the morbidity of such patients. Methods: We retrospectively reviewed the patients with NSCLC treated at our hospital between January 1994 and August 2003. Among these 720 patients, a curative approach was attempted in 444 with advanced stage (T3, 100; T4, 44) cancer. The patients were consequently divided into three groups (G1, negative or less than 3 days in SIRS following surgery; G2, less than 7 days; G3, continued over 7 days). Pre- or peri-operative factors were evaluated, and the 5-year survival rates were analyzed. Post-operative morbidity was also compared between the three groups in association with SIRS. Results: Pre-operative counts of WBC were 8848.28 ± 3879.21/μl in G3 compared with 7383.33 ± 3132.98/μl in G2 and 6778.31 ± 3184.89/μl in G1. Values in G3 were significantly higher than those in the other groups (P <.001). Predicted %FEV1 in G3 was significantly lower than those in the other groups. Duration of SIRS after lung surgery was associated with high levels in WBC and low %FEV1. Post-operative morbidity such as bronchial fistula or ARDS were more frequent in the G3 and G2 groups than in G1. The 1-year survival was as follows; G1, 75.4%; G2, 47.9%; G3, 38.1%. Overall 5-year survival rate for NSCLC with T3 and T4 was 32.2%, and the difference between G3 and the other groups in terms of survival was statistically significant (P <.0001). Conclusions: The concept of SIRS have been associated with post-operative complications and survival in NSCLC. Surgical candidates should be carefully according to the predicting factor of SIRS.

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1. Introduction

Surgical resection remains the only therapeutic modality with a curative potential for patients with non-small cell lung cancer. However, the majority of the patients present a locally advanced stage. Generally, these patients have a poor prognosis. Currently these poor survival rates can be significantly improved by multi-modality treatment using induction chemotherapy or post-operative chemoradiotherapy [1,2]. Surgical resection may continue to offer the best chance of long-term survival in advanced NSCLC. Some subtypes of these patients (i.e. T4 carina or T3 chest wall) showed beneficial outcome in survival [3,4]. And even NSCLC patients who have cancer invasive to the adjacent organ without node involvement have shown a favorable prognosis [5,6]. But the operative mortality rate of extensive surgery for T3 or T4 disease is reported to be high because of the increased risk of peri-operative complication. Recently, the concept of systemic inflammatory response syndrome (SIRS) was proposed by the American College of Chest Physicians/Society of Critical Care Medicine Committee in 1992 [7]. SIRS is defined by ≥ 2 of following abnormal conditions: fever or hypothermia; tachcardia; leukocytosis or leukopenia; tachpnea. Haga and his colleagues reported that SIRS is a useful criterion for the recognition of post-operative complications and end-organ dysfunction following gastrointestinal surgery [8]. It is known that 30-40% of patients with cardiac surgery develop SIRS [9,10]. However, in the field of surgery for lung cancer, SIRS has rarely been reported. Patients undergoing extended resection for lung cancer are thought to be at high risk for the development of post-operative complications, and these complications are associated with high mortality rates. The purpose of this study was to evaluate post-operative complications and survival of patients with T3 or T4 cancer according to the development of SIRS.
2. Patients and methods

From January 1994 to December 2002, 720 patients underwent pulmonary surgical resection for NSCLC at Fukuoka University Hospital. Among these patients, 144 with histologically confirmed NSCLC with T3 and T4, for whom the primary treatment was surgical, were retrospectively selected.

All patients underwent en bloc resection of NSCLC invading the adjacent tissue lobectomy, bi-lobectomy, or pneumonectomy with mediastinal lymphadenectomy. After extubation in the operating room, patients were routinely transferred to the intensive care unit for overnight observation. Antibiotics were administered intravenously for 3 days before and after surgery, respectively. All patients were evaluated by standard pulmonary function tests, arterial blood-gas tests, peripheral venous blood, and patient characteristics. These patients were grouped in terms of SIRS after surgery, and finally separated into three groups (G1, negative or duration of SIRS of less than 3 days; G2, duration of SIRS for less than 7 days; G3, duration of SIRS of over 7 days. Definition of SIRS was in accordance with that set out in the report of a consensus conference [7]. In brief, post-operative clinical assessment was as follows. In the case of each patient, the presence of the following was recorded: temperature (>38 or <36°C), heart rate (>90 beats/min), respiratory rate (>20 beats/min) or PaCO2 (<32 torr), and WBC (>12,000/μl, <4000/μl).

We calculated the post-operative predicted FEV1 or FVC by using the following equation: pre-operative FEV1×(1−S×0.0526) [11]; pre-operative FVC×(1−S×0.0526).

2.1. Statistical analysis

Data are presented as mean ± standard error of the mean (SEM) unless otherwise specified. Differences between groups were determined using non-repeated measures ANOVA, with P>0.05 considered significant. To compare several groups, Bonferroni test was applied. Pearson’s χ² statistics were used to analyze each factor. A Kaplan-Meier survival curve was generated. Additionally, differences among curves were assessed according to the log rank test.

3. Results

3.1. Patient characteristics

A summary of the 144 patients is shown in Table 1. The mean age of the patients was 70±6.97 years. Of these patients, 100 had pathological p-T3 disease and 44 had p-T4 disease. Factors of T3 were the chest wall (54 cases), the pleura (18 cases), the pericardium (10 cases), the main bronchus (13 cases), and the diaphragm (5 cases). Factors of T4 were judged as the great vessels (21 cases), the atrium (6 cases), the tracea/carina (14 cases), and other (3 cases). Pulmonary resection included lobectomy (100), bilobectomy (4), and pneumonectomy (40). Among the patients, 14 patients required carina-plasty, 5 required replacement of the great vessel, and 23 required bronchoplasty. Of these 144 cases, 20 patients received induction chemotherapy (cisplatin plus docetaxel).

3.2. Variation of respective factors and SIRS

No significant associations were observed between duration of SIRS and gender, age, type of surgery, induction chemotherapy, or N factor. Significant differences were observed in histologic type (P=0.0038), and incidence of squamous cell carcinoma was somewhat higher (67%) in G3. T4 was observed at a somewhat higher rate (67%) than T3 in the G3 groups (P=0.0005). Age (over 65) was not significantly associated with the G3 group (summarized in Table 2). Analysis of pre-operative characteristics is shown in Table 3. The WBC count was 8848.28±3879.21/μl in G3, 7383.33±3132.98/μl in G2, and 6778.31±3184.89/μl in G1. Cases of G3 showed significantly higher levels of WBC than cases of G1 (P=0.0009). Analysis of pre-operative respiratory function data showed the following: %FEV1 was 65.43±10.83 in G3, compared with 76.69±23.32 in G2 and 74.40±15.33 in G1.

Cases of G3 showed significantly lower levels of %FEV1 than cases of G1 (P=0.0297). In terms of change in %FVC, there were no significant differences between the groups. Analysis of pre-operative arterial blood gas levels revealed no significant differences between the groups; the arterial

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>T3</th>
<th>T4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>105</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>78(74%)</td>
<td>10(56%)</td>
<td>12(57%)</td>
</tr>
<tr>
<td>Bil/pneumo</td>
<td>27(26%)</td>
<td>8(44%)</td>
<td>9(43%)</td>
</tr>
<tr>
<td>Induction chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>14(13%)</td>
<td>3(17%)</td>
<td>3(14%)</td>
</tr>
<tr>
<td>–</td>
<td>91(87%)</td>
<td>15(83%)</td>
<td>18(86%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ad</td>
<td>37(36%)</td>
<td>8(44%)</td>
<td>2(9%)</td>
</tr>
<tr>
<td>Sq</td>
<td>57(54%)</td>
<td>4(23%)</td>
<td>14(67%)</td>
</tr>
<tr>
<td>Other</td>
<td>11(10%)</td>
<td>6(33%)</td>
<td>5(24%)</td>
</tr>
<tr>
<td>T factor T3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>54(52%)</td>
<td>8(45%)</td>
<td>10(47%)</td>
</tr>
<tr>
<td>N1</td>
<td>16(15%)</td>
<td>3(16%)</td>
<td>1(6%)</td>
</tr>
<tr>
<td>N2–3</td>
<td>35(33%)</td>
<td>7(39%)</td>
<td>10(47%)</td>
</tr>
</tbody>
</table>

F, female; M, male; Ad, adenocarcinoma; Sq, squamous cell carcinoma; N, node.
PO2 was 82.63 ± 10.33 mmHg in G3, 79.27 ± 12.43 mmHg in G2, and 81.73 ± 9.59 mmHg in G1. Similarly, the arterial pCO2 showed no significant differences between groups. Other factors such as smoking habit (pack-years), body mass index (BMI), and total protein (TP) showed no significant differences between groups. Analysis of ratio of albumin vs. globulin (A/G) data showed the following: A/G was 1.05 ± 0.27 in G3, compared with 1.28 ± 0.16 in G2 and 1.21 ± 0.26 in G1. Cases of G3 showed significantly lower levels of A/G than cases of G2 (P < 0.0011) and G1 (P = 0.0076).

Post-operative calculated %FEV1 showed a significant correlation to the grade of SIRS, and the G3 group demonstrated lower post-operative predicted %FEV1 than the G1 group (P = 0.0141). The blood loss was significantly higher in the G3 group (P = 0.028) (Fig. 1). Blood transfusion results were similar.

3.3. Assessment of post-operative morbidity

Post-operative mortality occurred in 7 cases (4.86%). Post-operative morbidity was mainly observed in the G3 and G2 groups (Table 4). Incidence of bronchial fistula and adult respiratory distress syndrome (ARDS) was observed in G3 and G2, whereas neither of these major complications was observed in G1.

3.4. Survival analysis

Overall 5-year survival rate for NSCLC with T3 and T4 was 32.3%. Regarding the relationship between group and prognosis, Fig. 2 shows the Kaplan-Meier survival plots generated on the basis of curves stratified by SIRS. The 1-year survival was as follows: G1, 75.4%; G2, 47.9%; G3, 38.1%. The 5-year survival rate was 39.9% for patients who had G1, 37.7% for G2, and 0% for G3 at 5 years. There was no significant difference in survival rate between G1 and G2. However, G3 showed a remarkable disadvantage for survival, and the difference in survival rate between G3 and the other two groups was statistically significant (P < 0.0001).

4. Discussion

Post-operative degree of SIRS after surgery correlated well with morbidity and mortality [8]. In the field of cardiothoracic surgery, it is well known that SIRS occurs after cardiac surgery. The mechanisms that lead to SIRS in patients who are operated on under cardiopulmonary bypass (CPB) are considered to involve several factors, including ischemia, hypothermia, reperfusion injury, blood contact with foreign material, and excess shear stress. SIRS after lung surgery has rarely been reported. Our study indicated that SIRS can also play an important role after surgery in T3 or T4 advanced lung cancer. Subgroups in T4 (great vessels or atrium) are thought to endure stress similar to that of cardiac surgery. In particular, lung resection combined with great vessels has a tendency to develop SIRS. As shown in
Table 1, of the 21 cases that underwent resection great vessels, 5 cases involved replacement of these vessels. Three patients (60%) of these 5 showed prolongation of SIRS. Patients were divided into three groups according to the classification of duration of SIRS. As shown in Table 2, there were significant differences in T status (T4 vs. T3) relative to the three groups. Frequency rate and duration of SIRS were greater in T4. This may be reflective of wide surgical manipulation or cancer spread in the lung. Recently, Kolsuz et al. reported that in serum and BAL from the involved lung, IL-6 concentrations were higher in the systemic inflammatory response syndrome (SIRS) group than in the non-SIRS group, whereas CRP, TNF-alpha, IL-1beta, and IL-8 concentrations showed no difference between SIRS and non-SIRS [12]. Cigarette smoking is known to contribute to inflammatory diseases of the respiratory tract by promoting recruitment of inflammatory-immune cells such as neutrophils. We hypothesized that smoking habits (pack-years) or nutrition degree (BMI) may demonstrate differences among our three groups. Unexpectedly, there were no significant differences in pack-years or BMI among the three groups.

We also analyzed the relationship between WBC count and each of the three groups. G3 showed a significantly higher WBC than those of the other two groups. This finding suggested that WBC already rises before extended lung surgery and primes the patient for SIRS; in these patients, SIRS is easily triggered, and they progress to prolongation of SIRS after lung surgery. Pre-activation of peripheral blood leukocytes can result in activation of inflammatory cells, which may be an intermediate step to the progression of SIRS. Chronic obstructive pulmonary disease (COPD) is characterized by a chronic inflammation in the pulmonary tissue. Oudijk et al. reported that chronic inflammation in the pulmonary tissue is also associated with systemic effects that result from cytokine-induced priming of peripheral leukocytes [13]. As shown in Table 3, G3 was shown to have a significantly lower predicted %FEV1 (65.43 ± 10.83), which characterized COPD. An increased risk of pulmonary complications in general surgery has been found to be associated with a predicted FEV1 or FVC of less than 70% [14]. Major pulmonary resection compared to general surgery, also increases the risk for the development of post-operative complication. As shown in Table 2, post-operative %FEV1 was significantly decreased in G3 compared to values in the other groups. This may indicate the possibility that, as far as SIRS is concerned, pre- and post-pulmonary function is important. The existence of some stress with low pulmonary function may lead to SIRS. Interestingly, Friedlander et al. reported that counts per second, a parameter used as an index of RBCD, may lead to SIRS if there is a blood transfusion. Further, transfusion-related acute lung injury (TRALI) is well known to occur, and patients’ plasma has demonstrated increases in interleukin 6 [17]. TRALI, like ARDS, may play additional roles in SIRS after lung surgery.

In the patients with T3 and T4 lung cancer, morbidity appeared to correlate with SIRS grade. More specifically, frequency rate of bronchial fistula, ARDS, and severe pneumonia were increased in G2 and G3. But in the G1 (negative or less than post-operative 3 days of SIRS) group, no post-operative complications occurred. Operative techniques with protection of the bronchial stump or anastomosis can contribute to reduce the occurrence of bronchial fistula in patients who show pre-operatively high WBC and low pulmonary function. Of the 144 patients with advanced lung cancer who underwent surgery, 39 (27.1%) who had post-operative SIRS for more than 3 days, and 58.9% of these combined groups (G2 and G3) demonstrated post-operative morbidity. Duration of SIRS is an important predictor for complication following surgery in T3 or T4 lung cancer. SIRS is well known to be a state of hypercytokinemia and if such a condition persists, it might be progression for the post-operative complications. Leukocyte activity which represents host immune defense is suppressed following surgery in patients with G2 and G3 and it might be related to complications. Recently, newer chemo-therapeutic agents (gemcitabine, paclitaxel) have been introduced, and they hold great promise for cases of advanced lung cancer. These new drug and cisplatin-based combinations have been shown to improve the outcome of surgery and the chance of favorable results even in advanced cases [18]. Stamatis et al. reported that of 350 patients who underwent thoracotomy for locally advanced lung cancer with pre-operative chemotherapy, 154 patients (44%) developed early or late complications; the hospital mortality rate was 4.9% (17 patients) [19]. In our series, 20 patients who also received induction chemotherapy did not show increased morbidity but some cases, though not a significant number, progressed to SIRS. The clinical importance of SIRS has not been previously presented in extended lung surgery in spite of many other reports regarding other types of surgery, including cardiac, liver, gastrointestinal surgery [20,21]. One reason for the difficulty in the field of lung surgery is that SIRS was defined by a respiratory rate of more than 20 beats/min or a PaCO2 of less than 32 mmHg. Based on the SIRS definition, SIRS after open lung surgery is thought to be underestimated compared to that after other surgeries. As shown in Fig. 2, there was a statistical difference in survival among the 3 groups relative to SIRS duration. These results showed that long duration of SIRS has a worse prognosis than short duration does. Patients with relatively long duration SIRS suffered many complications, and SIRS may lead to mortality in the early post-operative stage. SIRS might represent a prognostic indicator independent of tumor spread. In pre-operative patients with T3 and T4 lung cancer, both blood sample (high WBC) and pulmonary function (low FEV1) might induce SIRS, and some
consideration might be given to prepping them with combined multi-therapy. Drugs for reducing inflammation or de-activating cells and cleaning the lung or pre-operative rehabilitation may prevent SIRS and improve the survival rate in advanced cases.

The molecular events that initiate SIRS are currently unknown. Recent studies are now proving that various factors are associated with SIRS. Recently, Johnson showed that an endogenous pathway to a SIRS-like reaction is related to a Toll-like receptor in a mouse model [22]. Activated polymorphonuclear leukocytes in SIRS patients showed increased HGF in their granules and demonstrated enhanced degranulation of HGF [23]. Survival in patients with T3 and T4 lung cancer appears to have a favorable outcome after surgery when patients remain free from SIRS. Our study was a small retrospective study, though it is the first, to our knowledge, to investigate the effect of pulmonary resection on SIRS.

4.1. Conclusion

Patients with T3 and T4 lung cancer presented SIRS following surgery. Duration of SIRS was significantly associated with post-operative complications. Pre-operative factors, including high WBC levels and low pulmonary function, showed a correlation to duration of SIRS. Further, volume of blood loss and blood transfusion were also associated with SIRS status. Survival rates of these patients following lung surgery were affected by SIRS status.

References