A randomized clinical trial of preoperative neoadjuvant chemotherapy followed by surgery in the treatment of stage II non-small cell lung cancer

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Abstract Objective To explore the feasibility and toxicity of preoperative neoadjuvant chemotherapy followed by surgery in the treatment of stage II NSCLC and to evaluate its effects on tumor response, resection rate, tumor downstaging and survival rate. Methods From Jan. 1990 to Jan. 2001, 624 patients were randomly divided into group A preoperative neoadjuvant chemotherapy group and group B control group without neoadjuvant chemotherapy. Group A had 314 patients and group B had 310 cases. The patients in group A were given 2 cycles of neoadjuvant chemotherapy and operations were performed in 4 weeks after finishing the last chemotherapy. Twenty-one patients were given bronchial artery interventional chemotherapy. The other 293 cases were given intravenous chemotherapy. The regimens included MVP in 68 cases, CAP in 36 cases, EP in 67 cases, VIP in 20 cases, Gem + DDP in 30 cases, NVB + DDP in 32 cases, Taxol + NVB in 30 cases and Taxol + DDP in 10 cases. The patients in group B were firstly operated. Thoracic radiation therapy of 50 ~ 55 Gy was given to the patients with N1 and N2 disease both in group A and group B. Results The tumor response to induction chemotherapy was 73.57% in group A and 31.2% in group B. The tumor downstaging was 43.6% in group A and 31.2% in group B. The histological complete response was 15.92% in group A and 0% in group B. The resection rate was 97.69% in group A and 91.94% in group B. No significant differences of blood loss, operative complications and mortality were observed between the group A and group B. The 1-, 3-, 5- and 10-year survival rates were 89.35%, 67.46%, 34.39% and 29.34% in group A and 87.53%, 51.54%, 24.19% and 15.64% in group B respectively. The long-term survival rate in group A was remarkably higher than that in group B. Conclusion The results demonstrate that the preoperative neoadjuvant chemotherapy is safe and effective. It is helpful to decrease the tumor staging to increase the resection rate of the tumor and to improve the long-term survival rate and life qualities of patients with stage II NSCLC.

Key words Lung neoplasms Neoadjuvant chemotherapy Randomized clinical trial Survival rate Tumor downstaging
The treatment of NSCLC lung cancer began in the late 19th century. After many years of clinical research, preoperative neoadjuvant chemotherapy combined with surgical treatment has been shown to have several advantages:

1. By reducing the local tumor and regional lymph node cells, it increases the chance of complete surgical removal and reduces the risk of tumor dissemination during surgery.
2. It may lower the stage of lung cancer.
3. It can eliminate micrometastases that may exist in the patient's body.
4. It helps objectively evaluate the sensitivity of lung cancer to chemotherapy, thus determining effective chemotherapy drugs.

To evaluate the preoperative neoadjuvant chemotherapy plus surgery in the treatment of NSCLC lung cancer, the effectiveness, toxic and adverse reactions, and the long-term survival rate and improvement in the quality of life of patients were reported.

**Material and Methods**

**General Data**

This study included a total of 314 cases of NSCLC lung cancer from 1990 to 2001, of which 264 were enrolled in the preoperative neoadjuvant chemotherapy plus surgery group (experimental group) and 50 in the surgery plus postoperative chemotherapy group (control group). The basic clinical data of the two groups are shown in Table 1.

**Inclusion Criteria**

1. A diagnosis of NSCLC lung cancer by cytology or pathology before surgery;
2. Age < 70 years;
3. A preoperative systemic examination, chest X-ray, head CT, abdominal ultrasound, and bone scan confirmed that the lung cancer was unilateral, with no contralateral mediastinal lymph node metastasis;
4. No prior chemotherapy or radiation therapy;
5. No severe internal disease that precluded surgery;
6. Willing to receive preoperative chemotherapy.

**Exclusion Criteria**

1. No histological or cytological diagnosis;
2. Age > 70 years;
3. Presence of distant metastasis;
4. Small cell lung cancer;
5. Prior chemotherapy or radiation therapy;
6. Severe internal disease that precluded surgery;
7. Unwilling to receive preoperative chemotherapy.

**Preoperative Neoadjuvant Chemotherapy Scheme**

In the experimental group, 264 patients received bronchial artery interventional chemotherapy for 2-5 cycles, while 50 patients received 4-5 cycles of vein chemotherapy. Among them, 17 patients received HUT scheme chemotherapy, 7 patients received KT scheme chemotherapy, 4 patients received VT scheme chemotherapy, 9 patients received UWT scheme chemotherapy, 1 patient received Y ZZT scheme chemotherapy, 2 patients received Y ZZT + CAP scheme chemotherapy, and 1 patient received Y ZZT + Gem scheme chemotherapy.
治疗方法 全部患者均在入组前接受血常规、尿常规、大便常规、肝肾功能检查,胸部X光片,胸部、头部强化扫描,腹部超声检查,全身同位素骨扫描,心电图检查,肺功能测定。凡符合入选标准者按随机数字表随机分入试验组或对照组。试验组患者均接受个周期的静脉化疗,天为一周期。对有度降低者,则适当给予治疗。每周期化疗结束均行一次胸部X线拍片,最后一周期化疗结束后周复查胸部、头部强化扫描,腹部超声或/和全身同位素骨扫描。对病灶缩小、病情稳定的患者,则于化疗结束第周行外科手术治疗,对病情进展者,则改作胸部放疗和其它方案化疗治疗。凡进入对照组的患者,则先行外科手术治疗。两组患者均在术后根据分期和组织学类型结果,给予术后周期化疗或/和一疗程的胸部放疗治疗。

2.3 统计学处理 试验数据在四川大学华西医学中心统计教研室用美国Statview 5.0统计软件处理,以65.68为有显著性差异,65.69为有非常显著差异。本研究采用的统计方法有:检验、检验、检验、秩和检验、对数秩和检验和生存曲线。

结果
2.1 随机试验组与随机对照组治疗前一般资料比较 随机试验组和随机对照组治疗前两组患者病例数、性别、年龄、组织学类型、原发肿瘤大小、淋巴结转移状态,以及临床分期比较,均无显著性差异(65.68),表明两组患者具有较好的可比性(表1)。

表1 术前新辅助化疗的主要并发症

<table>
<thead>
<tr>
<th>主要并发症</th>
<th>试验组</th>
<th>对照组</th>
</tr>
</thead>
<tbody>
<tr>
<td>发热</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>白细胞减少</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>贫血</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>肝功能损害</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>肾功能损害</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>肺部感染</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

2.2 随机试验组化疗后不良反应 术前新辅助化疗的主要并发症为发热、白细胞减少、贫血,轻度肝功能损害,轻度肾功能损害和肺部感染。有3例患者因度和白细胞减少,给予治疗。D例患者因化疗后肺部感染给予抗生素治疗。肝、肾功能损害均为度,均未作特殊治疗,化疗结束后均能自行恢复,不影响外科手术治疗(表2)。

表2 手术失血量

<table>
<thead>
<tr>
<th>手术失血量</th>
<th>试验组</th>
<th>对照组</th>
</tr>
</thead>
<tbody>
<tr>
<td>平均</td>
<td>350ml</td>
<td>300ml</td>
</tr>
</tbody>
</table>

2.5 随机试验组新辅助化疗后病期下调率和组织学完全缓解率 随机试验组例患者经术前新辅助化疗后,有例患者病期下降,病期下降率为35.2%。术后病理组织学检查例患者的组织标本中找不到残留癌组织,组织学完全缓解率为28.5%。

2.6 随机试验组手术并发症 随机试验组接受手术治疗的例患者中,发生各种并发症共38例次,并发症发生率为50.8%。随机对照组例患者中发生各种并发症36例次,并发症发生率为45.2%。试验组除切口感染发生率(65.69)明显高于对照组(65.68)外,其余手术并发症发生率,两组间比较均无显著性差异(65.68)。
### Tab 3  Comparison of the operative types in the patients between the randomized trial group and control group

<table>
<thead>
<tr>
<th>Operative types</th>
<th>Trial group( n = 303)</th>
<th>Control group( n = 310)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy</td>
<td>235</td>
<td>221</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Bronchusangioplasty</td>
<td>22</td>
<td>20</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Sleeve lobectomy</td>
<td>14</td>
<td>25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Sleeve lobectomy + SVC reconstruction</td>
<td>15</td>
<td>9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Lobectomy + PRA +</td>
<td>10</td>
<td>10</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Exploratory thoracotomy</td>
<td>7</td>
<td>25</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Resection rate %( % )</td>
<td>97.69</td>
<td>91.94</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* PRA = Partial resection of left atrium

### Tab 4  Comparison of the operative complication between the randomized trial group and control group

<table>
<thead>
<tr>
<th>Operative complications</th>
<th>Trial group( n = 303)</th>
<th>%</th>
<th>Control group( n = 310)</th>
<th>%</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision infection</td>
<td>13</td>
<td>4.29</td>
<td>2</td>
<td>0.65</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>9</td>
<td>2.97</td>
<td>10</td>
<td>3.23</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>5</td>
<td>1.65</td>
<td>6</td>
<td>1.94</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Emphyema</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.65</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2</td>
<td>0.66</td>
<td>3</td>
<td>0.97</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>6</td>
<td>1.98</td>
<td>7</td>
<td>2.26</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>11.55</td>
<td>30</td>
<td>9.68</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

\[ P < 0.01 \]

### 3

#### 3.1

**95.83%** 598/624 4.17% 26/624

- **2.10**
  - 89.35% 3
  - 87.53% 3
  - 21.64% Kaplan-Meier **P < 0.01**

### 4

- NSCLC 20 80 80
- SCLC 20 80
- **136** I A NSCLC 20 80
- MVP 2 80
- 77% 136
- 65%
- 21%
- 17%
- Saito 51
- 51 NSCLC MVP
- 10 DDP
- 40%
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P-N2。两组(术前行179例、176例)B P < 0.01

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