Optimising treatment for post-operative lung cancer recurrence

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Surgical treatment offers the best chances for long-term survival in patients with primary nonsmall cell lung cancer (NSCLC). However, long-term survival after surgery remains less than 50%, mostly due to a 30–77% rate of tumour recurrence. Unlike the distant type of recurrence that is treated nonsurgically in the vast majority of patients, local or loco-regional recurrence, which occurs in 4.6–24% of patients after complete resection (~80% of cases in the first 2 years) [1], raises several concerns related to the optimal therapeutic approach.

Unfortunately, literature data are not always helpful in practice. For example, 5-year loco-regional recurrence rates are between 15 and 38.5% [2], and the incidence of local recurrence in early-stage lung cancer of 10–15% [3], or a mean disease-free interval of 14.1–19.8 months, that is similar to distant recurrent disease [4]. Failure to demonstrate the advantage of complete lymphadenectomy over nodal sampling in terms of local recurrence or survival in patients operated for T1–2, N0 or T1–2, N1 disease, makes the clinical approach more complex [5]. Moreover, the impact of intensified follow-up on overall survival or local recurrence detection could not be clearly demonstrated. In ~50–67% of patients, recurrence will appear before a scheduled control because of the onset of symptoms [6].

Finally, switching to seventh edition of the TNM (tumour, node, metastasis) staging system automatically led to the stage migration, reaching 21% in some studies. The only study of the role of computed tomography (CT) in post-operative recurrence detection demonstrated a high negative predictive value of 95%, but a positive predictive value of only 53% (94% sensitivity and 87% specificity) [7]. For positron emission tomography, although it is more sensitive than CT in detecting recurrent tumours (97–100%), variations of the cut-off values for the standardised uptake value (>4.5–>10) make its clinical application difficult, together with its specificity (62–100%) that is lower than for CT.

The role of prognostic factors after surgery is more evidence-based, owing to awareness of the poor 5-year survival of patients in stages IA and IB (73% and 58%, respectively). This also applies to the high recurrence rate in patients with stage I after complete resection (25–50%) [8]. The results of these studies really helped to identify patients who would probably benefit from adjuvant therapy.

Among tumour markers, although increased serum concentrations of carcinoembryonic antigen (CEA) are rare (17%), persistently high post-operative CEA levels were found to be a strong indicator of poor prognosis. In 55–70% of patients with CEA values of 5–10 ng·mL⁻¹, an early recurrence will develop [9].

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The second lung resection is a valuable option for post-operative lung cancer recurrence
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better survival of patients with squamous cell disease stage (stages I and II versus stage III). The evidence indicates 5-year survival rates being 33.3% and operative morbidity up to 62.6% [30], are the consequence of different definitions of complications and inclusion of all types of indications, rather than being strictly procedure-related. Furthermore, reports that the second procedure is better tolerated by the cardiopulmonary system than a one-stage pneumonectomy, combined with a reported 5-year survival approximately 40% in many series, make this operation a reasonable option, provided the patient selection is adequate. There is a broad consensus that pneumonectomy should be performed in dedicated surgical centres. Despite the alleged high complication rate, operative mortality in the majority of series published in the past 15 years is about or slightly above 12% [24–29], operative morbidity is under 40% and the bronchopleural fistula rate is ∼10% (table 1). The wide range of the reported mortality rates, in some series reaching 33.3% and operative morbidity up to 62.6% [30], are the consequence of different definitions of complications and inclusion of all types of indications, rather than being strictly procedure-related. Furthermore, reports that the second procedure is better tolerated by the cardiopulmonary system than a one-stage pneumonectomy, combined with a reported 5-year survival ∼40% in many series, make this operation a reasonable option, provided the patient selection is adequate. There is a broad consensus that bronchial stump protection is of utmost importance, especially in right-sided operations (figure 1).

As for adjuvant radiation therapy, based on earlier data, it is currently only recommended for patients with resected N2 disease [16]. However, these data reflected outdated radiation techniques, which may have contributed to the detrimental outcome. Two recent randomised trials, using modern techniques, support such a statement. The first trial demonstrated lower recurrence rates and better 5-year survival in patients with N0 disease [17], while the second trial confirmed only the lower recurrence rate in patients with post-operative stage T1–3, N0–2, M0 NSCLC [18]. Some data suggest that post-operative irradiation could also be of benefit in patients with resected N1 disease who are at high risk of local relapse [19]. The ongoing LungART trial randomises patients with completely resected N2 disease between those receiving post-operative radiotherapy and those who do not [20].

Concerning the optimal extent of the first lung resection, two ongoing trials are comparing lobectomy versus sublobar resection for peripheral stage IA NSCLC (Cancer and Leukemia Group B 140503 and JCOG 0802 trials) [21]. They will determine more clearly whether sublobar resection is a valid oncological treatment for stage IA NSCLC. The ACOSOG-Z4032 trial investigated the role of sublobar resection with brachytherapy versus sublobar resection alone [22]. Brachytherapy did not reduce the incidence of local recurrence after sublobar resection, underlying the importance of adequate surgical margins of sublobar resections.

Surgery for post-operative loco-regional recurrence or metachronous tumours is possible in up to 4% of patients [23]. They usually undergo a "completion pneumonectomy", meaning removal of the remaining lung after the first lung resection. The reason is that the great majority of patients requiring this type of surgery previously underwent lobectomy or bilobectomy, and rarely a sublobar resection.

In patients with positive bronchial margins after lobectomy, metachronous bronchogenic cancer or with metastases after surgery for primary cancer, a completion pneumonectomy is also an option. In contrast, patient selection in the case of local recurrence is more challenging and insufficiently evidence-based. Only a few series exceed 50 patients, dealing mostly with the appropriateness of this operation in the light of quite a high operative morbidity and mortality, switching the focus from the disease stage towards the operative risk assessment. Based on the literature and our experience, patients older than 65–70 years, with unfit general condition, renal insufficiency or other major cardiological or combined cardiopulmonary comorbidities, are not suitable candidates for this kind of surgery. Intrapерicardial dissection is usually necessary even without direct pericardial involvement of the recurrent tumour. Equally, completion pneumonectomy should be performed in dedicated surgical centres.

As presented in table 1, both earlier and recent survival data are consistent throughout the literature, with 5-year survival rates being ∼40% in many series. The worse survival rates reported, for example 23% in one series, are counterweighted by the high proportion (>65%) of stage III patients. The evidence indicates better survival of patients with squamous cell versus adenocarcinoma [2] and a significant influence of disease stage (stages I and II versus stage III).
Chemotherapy is the third available treatment option. In patients with the metastatic type of recurrence, chemotherapy is the treatment of choice. The exception is mono/oligo-metastatic recurrences that can be treated either with local therapy (surgery and/or radiotherapy) alone or combined with chemotherapy. As the risk of relapse is higher in more advanced stages, most of these patients have previously undergone adjuvant or neoadjuvant therapy with a third generation platinum-based drug combination. It is still questionable whether these patients should receive, in case of recurrence, a second-line or a first-line protocol (monotherapy) or a new/re-challenge with a platinum doublet combination, because literature data are limited. In fact, in some studies, patients with post-operative recurrence underwent both the first- and second-line protocols after previous neoadjuvant/adjuvant chemotherapy, so that no separate analysis is available. Most experts argue that patients relapsing after surgery (including those with adjuvant/neoadjuvant chemotherapy) should be considered as chemotherapy naïve and treated with the first-line protocol. However, the influence of other clinical factors relevant for this choice is unknown. To the best of our knowledge, there is only one trial dealing with chemotherapy in patients relapsing after surgery:

<table>
<thead>
<tr>
<th>First author [ref.]</th>
<th>Year</th>
<th>Patients n</th>
<th>30-day post-operative mortality</th>
<th>Operative morbidity</th>
<th>Bronchopleural fistula</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MASSARD [24]</td>
<td>1995</td>
<td>37</td>
<td>10.8</td>
<td></td>
<td></td>
<td>44.5</td>
</tr>
<tr>
<td>TRONC [25]</td>
<td>1999</td>
<td>77</td>
<td>10.5</td>
<td></td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>MILLER [30]</td>
<td>2002</td>
<td>115</td>
<td>17.6</td>
<td>62.6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>TERRI [26]</td>
<td>2002</td>
<td>59</td>
<td>3.4</td>
<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>GUGNONE [23]</td>
<td>2004</td>
<td>55</td>
<td>11.9</td>
<td>58.2</td>
<td>12.7</td>
<td>44</td>
</tr>
<tr>
<td>JUNGRAITHMAYR [27]</td>
<td>2004</td>
<td>26</td>
<td>33.3</td>
<td>29.3</td>
<td></td>
<td>23</td>
</tr>
<tr>
<td>CHATAIGNER [28]</td>
<td>2007</td>
<td>69</td>
<td>12.7</td>
<td>40.6</td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>CARDILLE [29]</td>
<td>2012</td>
<td>152</td>
<td>10.5</td>
<td>55.1</td>
<td>7.9</td>
<td>48.9%/23.9%</td>
</tr>
</tbody>
</table>

Data are presented as %, unless otherwise stated. \*: squamous cell; \*: adenocarcinoma.

![FIGURE 1 Techniques for bronchial stump protection. Upper row: transposition of the omentum; a) vascularised omental flap harvested, ready for transposition; b) omental flap transposed into the thorax (arrow: sutured bronchus); c) omental flap sutured to the bronchus and surrounding structures. Lower row: d) intercostal muscle flap; e) diaphragm flap (arrow: flap; 1: pericardium; 2: diaphragm); f) pericardial fat (1: vascularised fat sutured to the bronchus; 2: diaphragm; 3: pericardium). DOi: 10.1183/13993003.01490-2015](image)
chemotherapy [31]. This trial tends to support this attitude and showed a nonsignificant increase in progression-free survival and overall survival with doublet chemotherapy. There was a more favourable outcome for epidermoid tumours and those relapsing after 12 months of previous therapy. However, major recruiting difficulties made this trial severely underpowered.

To summarise, the choice of the optimal treatment for post-operative lung cancer recurrence is not sufficiently evidence-based. Repeat surgery is a valuable option, but the selection of patients remains a major challenge. Due to the limited literature, the choice of the appropriate drug combination for this type of recurrence relies upon local practice and case by case discussion in a multidisciplinary team.

References


