Operating on a suspicious lung mass without a preoperative tissue diagnosis: pros and cons†

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Abstract

OBJECTIVES: Patients with a suspicious lung mass sometimes receive surgery with no preoperative tissue diagnosis despite—and sometimes in lieu of—modern medical investigations. The pros and cons of doing so have rarely been studied.

METHODS: Pulmonary surgery was performed in 443 consecutive adult patients with a lung mass confirmed or suspected to be an early stage primary lung cancer. No diagnosis was confirmed preoperatively in 206 (46.5%) patients. Whether to take a core biopsy or wedge excision biopsy for frozen section assessment intraoperatively was decided at the surgeon’s discretion.

RESULTS: Patients without preoperative diagnosis were on average younger than those with a diagnosis (61 vs 66 years, \(P<0.01\)), but were otherwise similar to those who had a preoperative diagnosis confirmed. In all patients operated on without a preoperative diagnosis, there was no mortality or major complication, and the perioperative minor morbidity rate was 9.7%. Among patients ultimately found to have lung cancer and who received a lobectomy, performing a frozen section intraoperatively did not increase mean operation time or morbidity. Among those patients with no preoperative tissue diagnosis, 97 (47.1%) proceeded to surgery without attempts at preoperative diagnosis, and 109 (52.9%), after attempts at preoperative diagnosis failed to yield a positive diagnosis. After surgery, benign disease was found in 16 (7.8%) patients without preoperative diagnosis. A significantly lower proportion of patients without preoperative diagnosis waited an interval of over 28 days between presentation and being accepted for thoracic surgery (42.2 vs 54.9%, \(P<0.01\)). However, they were not more likely to have Stage I disease and did not have better recurrence-free survival rates on survival analysis.

CONCLUSIONS: Proceeding to surgery without preoperative diagnosis in selected patients with a suspicious lung mass is safe and can potentially reduce the interval between presentation and surgical management. However, the shortened workup time is not associated with improved surgical or oncological outcomes.

Keywords: Lung cancer • Lung cancer diagnosis • Lung cancer surgery • Minimally invasive surgery • Solitary pulmonary nodule

INTRODUCTION

There has been an undeniable trend in recent years towards increasing numbers of patients presenting with a lung shadow that is suspected of being lung cancer [1–3]. This is a result of a combination of factors, including: increasing awareness of health issues among the general public; unprecedented accessibility to medical screening and radiological imaging in many regions; advances in radiological imaging (including increasing the use of positron emission tomography, PET) and many others.

This should be good news, in that the chance of disease detection at an early stage should theoretically be increased, leading to a greater chance of surgical cure and better survival. However, the flip side of the coin is that many of these suspicious lung shadows may turn out to be benign [3–6]. There is therefore an increasing burden on diagnostic services—such as bronchoscopy and imaging-guided fine-needle aspiration (FNA)—to investigate these lesions. This may potentially lead to longer waiting times for diagnosis and hence longer intervals between patient presentation and ultimate therapy.

Today, in the age of minimally invasive video-assisted thoracic surgery (VATS), some surgeons have suggested foregoing preoperative diagnosis and proceeding directly to VATS exploration. This would first allow a core biopsy or wedge excision biopsy of the target suspicious lung mass, which can then be sent for frozen section analysis. If the frozen section confirms lung cancer, then the operation can be extended to include curative resection. The potential advantage of this approach is that the interval between the identification of an suspicious lung mass and the surgical resection is minimized, possibly yielding a survival benefit [7–9]. Nevertheless, the worry remains that proceeding to surgery without a preoperative diagnosis may result in an unacceptably high rate of such ‘unnecessary’ operations [3–6].
Thus far, there has been little published data concerning the potential pros and cons of operating on a patient with the suspicious lung mass, but no preoperative tissue diagnosis. The objective of this current study is to address this gap in our knowledge and to help us understand the potential role of such an approach in future management of patients with the suspicious lung mass.

METHODS

A retrospective study was conducted on consecutive patients undergoing potentially curative surgery for confirmed or suspected non-small-cell lung cancer (NSCLC) at a university teaching hospital from March 2006 to February 2011 (60 months). All patients received preoperative surgical workup including computed tomography (CT) thorax with contrast and spirometry. Other radiological staging investigations—such as CT brain, bone scanning, abdominal ultrasound/CT—were performed if indicated by the expanded clinical evaluation (as per established international guidelines) [10, 11]. At the time of this study, PET scanning was not offered routinely by the Hong Kong public healthcare system and was only performed as an optional item if the patient paid for it. Mediastinoscopy and/or endobronchial ultrasonography was only performed on those patients in whom nodal metastasis was suggested by the above non-invasive staging modalities. The determination of fitness for surgery conformed to the international guidelines [11]. Patients were included for the study if NSCLC was confirmed by biopsy preoperatively, or if the suspicious lung mass was determined to be sufficiently indicative of NSCLC to warrant early surgery by a multidisciplinary team (MDT) consisting of thoracic surgeons, respiratory physicians, radiologists and oncologists. Patients with previous extrathoracic malignant disease were not excluded provided the MDT felt that the suspicious lung mass in question could potentially be a new primary NSCLC. Patients were excluded if any preoperative investigations discovered nodal or distant metastasis. Patients who received neoadjuvant induction therapy were also excluded.

In patients without a preoperative diagnosis, a VATS exploration was first carried out. The technique is a standard three-port strategy that has been well reported [12, 13]. A core biopsy or a wedge excision biopsy using endoscopic stapler cutters was performed at the discretion of the operating surgeon. When core biopsy was performed, 3–7 cores are usually taken for each suspicious lung mass. For small, deep suspicious lung mass lesions, preoperative localization by CT-guided hook-wire placement was used. The biopsies in all cases were sent for frozen section analysis. If the result showed benign disease or was equivocal, further sublobar or lobar resection was performed at the discretion of the operating surgeon.

In patients with NSCLC confirmed preoperatively or by frozen section, lobectomy with systematic nodal exploration was performed. The choice of an open thoracotomy approach or a complete VATS approach was again at the discretion of the operating surgeon. Our technique of complete VATS lobectomy has been previously reported [12]. In all patients, postoperative management and nursing care followed the same prescribed clinical pathway. This clinical pathway governed all aspects of postoperative recovery, including: analgesic regimen; chest drain management and removal conditions; physiotherapy and mobilization schedules; discharge planning and other aspects. This ensured that all patients received identical, objective postoperative care.

For all patients selected for the study, follow-up data were complete and available through hospital case notes and electronic patient records of the Hong Kong public healthcare system. All data were statistically analysed using MedCalc Version 12 (MedCalc Software, Mariakerke, Belgium) or MS Excel 2007 (Microsoft Corp., Redmond, WA, USA) software. Categorical data were analysed using the Chi-square test and Fisher’s exact test. Continuous variables were analysed using both the unpaired T-test and Mann-Whitney test. Survival analysis was performed using Kaplan–Meier analysis and log-rank testing. Results were considered significant if P-values were <0.05.

RESULTS

All patients

In total, 443 patients met the above selection criteria for inclusion in this study. These included 237 (53.5%) patients with confirmed preoperative tissue diagnosis of NSCLC (the POTD group). There were 206 (46.5%) patients with no POTD (the No POTD group). The key characteristics of the patients in the two study arms are summarized in Table 1. Interestingly, patients in the No POTD group were younger, and there was a trend towards better percentage predicted forced expiratory volume in 1 s (%FEV1) results in the No POTD group. Otherwise, there were no significant differences between the two study arms in terms of demographic and preoperative clinical variables.

In 97 (47.1%) patients of the No POTD group, no preoperative diagnostic investigations had been done, and it had been decided to proceed straight to surgery. In the other 109 (52.9%) patients of the No POTD group, at least one preoperative attempt at obtaining a tissue diagnosis (bronchoscopy, FNA, etc.) had been made, but no positive diagnosis was ultimately obtained by the time of surgery. Overall, in this study, of the 346 patients receiving at least one preoperative attempt at obtaining a tissue diagnosis, a positive diagnosis was not yielded in 31.5%.

By not waiting for a tissue diagnosis before surgery, the interval between the patient first presenting to any physician and being accepted for thoracic surgery was significantly reduced (Table 2).

In the No POTD group, 42% of patients waited over 28 days between first presenting with any suggestion of the suspicious lung mass and being put on the waiting list for surgery—compared

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>POTD (n = 237)</th>
<th>No POTD (n = 206)</th>
<th>P-value</th>
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<tr>
<td>Male (no. of patients)</td>
<td>134 (57%)</td>
<td>120 (58%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>66 (range 40–82)</td>
<td>61 (range 33–84)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking history (no. of patients)</td>
<td>97 (41%)</td>
<td>73 (35%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Preop predicted FEV1 (%)</td>
<td>74 (range 44–119)</td>
<td>76 (range 46–99)</td>
<td>0.08</td>
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FEV1: forced expiratory volume in 1 s; POTD: preoperative tissue diagnosis.
with 55% in the POTD group ($P < 0.01$). There was also a strong trend in favour of the No POTD group when considering the percentage of patients waiting over 14 days from presentation to being accepted for thoracic surgery.

Table 3 shows that overall, patients in the two study arms had similar intra- and postoperative outcomes and safety. The mean operation time in the No POTD appeared shorter, but this was due to 73 patients in that study arm receiving sublobar resections (mostly wedge resections) only. Nevertheless, proceeding to surgery with no POTD did not result in more patient morbidity or harm. Indeed, in the No POTD group, there was no mortality or major complications. Excluding air leakages, 9.7% of patients in the No POTD group experienced minor complications (the most common of which were mild/afebrile pneumonia and minor wound gaping).

**Patients with no POTD only**

The final pathological diagnoses in the 206 patients of the No POTD group are shown in Figure 1. In 64.6% of patients, primary NSCLC was confirmed. In the majority of these patients, the surgery proved to be potentially curative as the disease was still in Stage I. In 27.7% of these patients, the suspicious lung mass turned out to be metastasis from a previous extrathoracic malignancy. Nevertheless, as these patients were found not to have any other metastases on preoperative imaging, their lesions were likely to be solitary lung metastases. Hence, surgery again potentially provided a survival benefit.

Only in 7.8% of patients was benign disease found. In these patients, a diagnosis was obtained from surgery, but otherwise the surgery, strictly speaking, provided no benefit or therapy. In these patients, surgery can be argued to be ‘unnecessary’. However, the surgery did not cause any mortality or significantly morbidity in these patients.

**Patients ultimately receiving lobectomy for lung cancer**

All 237 patients in the POTD group and the 133 patients found to have NSCLC on frozen section in the No POTD group received lobectomy with curative intent. In 13 (5.5%) patients in the POTD group, despite a POTD of primary NSCLC, the final pathology after lobectomy turned out to be something else (benign disease or metastasis from a previous extrathoracic malignancy).

Table 4 shows the outcomes for patients in the two study arms who ultimately received lobectomy for primary NSCLC. Importantly, the need for intraoperative frozen section analysis for diagnosis did not significantly add to the operating time required or to surgical morbidity.

Of patients found to have NSCLC, the eschewing of POTD in the No POTD group did not lead to a higher percentage of patients with Stage I disease compared with patients in the POTD group.

When considering survival outcomes in the patients who received lobectomy for Stage IA NSCLC only, no difference was found between the patients of the two study arms (Fig. 2). If all 357 patients receiving lobectomy for NSCLC of any stage are considered, there was a slight trend towards better survival in the No POTD group, but again, this difference did not reach statistical significance.

**DISCUSSION**

As said above, there are increasing numbers of patients today being found to have small lung masses or ground-glass opacities.
(GGOs) suspected of being pulmonary neoplasms. Although this should be welcome as an opportunity to diagnose and treat the disease at an earlier stage, for some healthcare systems this has serious potential consequences in that greater demands will be put on existing diagnostic resources, resulting in longer waiting times before surgery. In some regions, the waiting times for bronchoscopy and FNA for suspected lung cancer are already significant. The impact of ever-increasing numbers of suspicious lung shadows on waiting times for such investigations can be considerable [1, 7].

Traditionally, it was mandatory to obtain—or exhaust all preoperative options in attempting to obtain—a POTD. This was because thoracic surgery via a traditional open thoracotomy was widely considered a highly traumatic procedure. Indeed, thoracotomy is well known to be associated with significant postoperative pain and morbidity [14, 15]. It therefore was reasonable to ascertain a definite indication for surgery—lung cancer—before subjecting the patient to such an ordeal.

However, the advent of VATS potentially changes this paradigm. It is well known that VATS significantly reduces pain and morbidity compared with open thoracotomy [16]. VATS is already well established as the approach of choice for most diagnostic and many therapeutic procedures in the chest [12, 13]. With this in mind, some surgeons are now beginning to suggest that VATS exploration could be offered in lieu of preoperatively

Table 4: Surgical outcomes of only those patients receiving lobectomy for NSCLC

<table>
<thead>
<tr>
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<th>POTD (n = 224)</th>
<th>No POTD (n = 133)</th>
<th>P-value</th>
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<tr>
<td>Mean operation time (min)</td>
<td>180 ± 68</td>
<td>176 ± 67</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean blood loss (ml)</td>
<td>124 ± 289</td>
<td>124 ± 249</td>
<td>0.69</td>
</tr>
<tr>
<td>Non-air leakage complications (no. of patients)</td>
<td>25 (11.2%)</td>
<td>16 (12.0%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Stage I disease on histology (no. of patients)</td>
<td>138 (61.6%)</td>
<td>81 (60.9%)</td>
<td>0.89</td>
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Figure 2: Recurrence-free survival after surgery: (a) 219 patients receiving lobectomy for histologically confirmed Stage IA NSCLC only (log-rank test: \( P = 0.601 \)); (b) 357 patients receiving lobectomy for histologically confirmed NSCLC of any stage (log-rank test: \( P = 0.119 \)).
obtained tissue diagnosis in patients whose lesions look sufficiently indicative of malignancy. A core biopsy or wedge excision biopsy of the target suspicious lung mass can be taken using a VATS approach, and this can then be sent for frozen section analysis. If the frozen section confirms lung cancer, then the operation can be extended to include curative resection.

Should the suspicious lung mass turn out to be benign, the patient would only have undergone a minimally invasive VATS procedure as opposed to an open thoracotomy in the past. Theoretically, the chance of significant harm done to the patient even in the event of an ‘unnecessary’ operation for benign disease would be minimal.

The potential advantage of this approach is not only the minimization of presentation-to-treatment times for the affected patient. In addition, it is hoped that a No POTD approach may actually help alleviate waiting times for diagnostic services for other patients who may need them. It is a documented fact that waiting times for cancer surgery have increased significantly since the 1990s [1]. One of the key factors causing this has been the inexorable increase in case loads, which can be explained by the reasons already mentioned above. Besides causing treatment delay by directly affecting surgical waiting lists with increasing patient numbers, there is an indirect impact on treatment delay by the extra burden on diagnostic investigations such as bronchoscopy and FNA. Thus, there is prolongation of the interval from presentation to diagnosis, as well as from diagnosis to surgery [7, 17, 18]. Indeed, one systematic review of 49 studies (mostly from Europe) has already noted that median times to diagnosis and to treatment frequently exceeded published recommendations [17]. An increasing number of diagnostic tests needed to achieve a diagnosis was clearly identified as one of the key factors associated with less timely care in lung cancer patients.

Our study is among the first to specifically quantify the effect of proceeding to surgery without a POTD for patients with suspected lung cancer. In a similar but smaller recent study from Korea, the strategy of surgery with No POTD was described as safe and feasible [19]. Our results here suggest that a significantly lower percentage of patients with the No POTD approach requires an interval of over 28 days from presentation to being accepted for thoracic surgery. Besides shortening the delay to surgical management, this result suggests that the burden on preoperative diagnostic investigations can also be partly relieved.

It is reasonable to hope that such a reduction in waiting times may be reflected in more No POTD patients being found to have Stage I disease and better survival. However, this was not found to be the case in our series. In reality, the time-saving with the No POTD approach is in terms of a few weeks or less, and this amount of time is perhaps too brief for most lung cancers to have progressed. The scope of our study did not extend to looking at how many patients progressed from a potential operable stage to an inoperable one while awaiting the obtaining of a POTD.

Paradoxically, a couple of studies seem to suggest that shorter presentation-to-treatment intervals were associated with poorer survival [20, 21]. However, this peculiar observation has been explained by the fact that patients with more severe signs and symptoms—and hence more advanced disease—were likelier to have received prompt treatment. It has since been further argued that even if survival benefit is not confirmed by reducing treatment delay, it remains important to strive for such reductions for a number of reasons. These include: alleviating the enormous psychological stress on lung cancer patients and their families awaiting treatment; maximizing the surgical resection rate and the chance of curative surgery and increasing the likelihood of radically treating disease at the earliest possible stage [7, 9].

Regardless of whether any survival benefit is gained, the No POTD approach nevertheless achieves reduction in waiting times for diagnosis and surgery at very little cost to the patient. Our results show that, with modern VATS and perioperative care, the approach is generally safe and the rate of postoperative morbidity is acceptably low. Admittedly, the apparent safety is partly explained by the fact that the No POTD group included many more patients who received sublobar resections only. Patients in this group were also younger and tended to have better lung function preoperatively. However, this precisely highlights the point of using the No POTD approach. In young, medically fit patients who are strongly suspected to have lung cancer, the risks of surgery are quite low nowadays—and sublobar resection can be performed if primary NSCLC is excluded. One is therefore compelled to ask: why not proceed to surgery if the patient accepts those operative risks over the risk of delayed management?

Even if one looks only at patients who had a lobectomy done, the average operating time in the No POTD group was no longer than in the POTD group, suggesting that taking an intraoperative biopsy for frozen section did not significantly prolong the operation. In practise, while awaiting the frozen section result, the release of pleural adhesions and preliminary dissection of the hilar structures in preparation for a lobectomy can be started, saving considerable time.

Besides any risk to the individual patient, the other concern over proceeding to surgery without a preoperative tissue diagnosis must be whether a large number of ‘unnecessary’ operations (mainly for benign disease) are being performed. This will have implications for both medical ethics and usage of medical resources. In this study, we found that close to two-thirds of patients with the suspicious lung mass in the No POTD actually had lung cancer—which was then resected. Around a quarter of patients had solitary lung metastasis from a previous extrathoracic malignancy, and surgery provided potentially curative resection. Only in less than 8% of patients was benign disease found. This suggests that adapting a No POTD approach does not necessarily result in an excessive burden of ‘unnecessary’ operations. For comparison, previous studies investigating surgery for suspicious lung masses found that rates of benign disease ranged from 9 to 86%—probably reflecting how selective different centres may be in determining whether the suspicious lung mass is worrisome enough to warrant surgery [3–6]. There is a growing consensus that a benign resection rate of around 10% may be ‘reasonable’ when managing suspicious lung masses [3], and our results would conform with this view.

In particular, it should be noted that preoperative diagnostic investigations themselves do not always yield positive diagnoses [4]. A significant proportion of those 8% of patients with benign lesions in our study would still have ultimately received surgery had an array of preoperative diagnostic investigations failed to confirm benign disease. It is therefore not entirely accurate or fair to dismiss these 8% of patients as having had ‘unnecessary’ surgery.

One might imagine that further non-surgical investigations would be beneficial in terms of monetary and human costs by reducing the rates of surgery for benign lesions. However, this turns out to not necessarily be the case. One recent study, for
example, looked at the use of PET scanning in managing patients with suspicious lung masses [22]. Among patients ultimately found to have a benign nodule, 22.8% had a false-positive PET scan. These patients had a greater cost of treatment (US$33783 vs $19115, P < 0.01), more surgeries and biopsies, and 3.8 times the mortality risk (95% confidence interval 1.6–9.2) compared with true negatives. Overall, over one-half (54.5%) of individuals with positive PET scans received surgery anyway. In another study looking at the use of bronchoscopy for the investigation of suspected lung cancer, the ultimate interval between presentation and a decision-to-treat was delayed by over 3 weeks on average in patients for whom bronchoscopy was tried but failed to yield a positive diagnosis [18]. In patients for whom bronchoscopy was tried but failed to yield a positive diagnosis, the ultimate interval between presentation and a decision-to-treat was delayed by over 3 weeks on average. For patients with suspicious lung mass, it therefore appears that an extensive array of diagnostic investigations may not always be more cost-effective or beneficial than simply proceeding to surgery with No POTD.

Following from the above points, in this study, 109 patients in the No POTD indeed proceeded to surgery after attempts at preoperative diagnosis failed to yield a positive diagnosis. In other words, of a total of 346 patients receiving at least one preoperative attempt at obtaining a tissue diagnosis in this study, no positive diagnosis was obtained in almost one-third. Indeed, even with a preoperative tissue diagnosis of primary NSCLC, the final pathology after lobectomy turned out to be something else in 5.5% of patients. To put this into context, a recent study of the use of FNA for diagnosis in 1182 suspicious lung mass lesions found that no positive diagnosis was found in 406 (34.3%) cases [23]. Even among the 474 (40.1%) cases where FNA cytology showed NSCLC, a specific histotype could not be identified in 15%, and the false-positive rate was 8% for adenocarcinoma and 18% for squamous cell carcinoma. This matches closely with our own findings and further suggests that the extratime spent waiting for diagnostic investigations may lead to disappointing outcomes in a proportion of patients. The question that looms again is: is it really worthwhile waiting for these preoperative diagnostic investigations when they fail to give a diagnosis in a third of patients, and when proceeding to surgery with No POTD actually entails reasonably low risk?

The counter-argument is, of course, that our study has its limitations. It remains a retrospective study, and in lieu of a randomized, controlled trial, it is difficult to definitively prove the costs and cons of the No POTD approach. The failure to find a survival benefit in the No POTD group could still be a consequence of an insufficient number of patients or events. As noted above, we also have no information concerning patients who may have had disease progression while awaiting a POTD. There is also the likelihood of selection bias in favour of the No POTD approach. However, this latter weakness actually reflects a clinically relevant insight. That is, the No POTD approach can only succeed precisely because there has been careful patient selection by an experienced MDT. Our results show that if the MDT panel concurs that the suspicious lung mass is sufficiently indicative of lung cancer and that the patient is fit enough to undergo surgery, the No POTD can yield safe surgical management with reasonably low rates of ‘unnecessary’ operations. We acknowledge that there may be medical-legal implications in some countries if the operation is conducted with No POTD and the pathology turns out to be benign. Further experience is therefore warranted before a broad recommendation on the use of a No POTD approach can be advocated in all countries.

In summary, we can therefore conclude from this study that in patients carefully selected by an MDT, proceeding to surgery without preoperative diagnosis in those with the suspicious lung mass involves little risk of significant added harm to the patient, or increased rates of ‘unnecessary’ surgery. Although it was not associated with improved oncological outcomes, the No POTD approach may potentially reduce the interval between presentation and surgical management and alleviate the burden on preoperative diagnostic investigations in the face of ever-increasing numbers of patients presenting with suspicious lung masses.

Conflict of interest: none declared.

REFERENCES

APPENDIX. CONFERENCE DISCUSSION

Dr R. Rami-Porta (Terrassa, Spain): This is a topic not frequently found in our sessions. Your numbers are easy to break down. From the whole population, around 50% had a diagnosis of malignancy, and 50% did not. In about half of those without diagnosis, at least one attempt had been made to diagnose the lesion; in the others there was no attempt and they went directly to surgery. You have shown in your results that there are no major differences between the two groups.

I have two concerns and two questions. The first one is about staging. Many diagnostic tests are at the same time staging procedures, like bronchoscopy. You may find contralateral occult lesions at bronchoscopy, you may find ipsilateral ones, you may define the TNM by the endobronchial location of the lesion, and so on. There are other lesions that are small, peripheral, but if you know that they are adenocarcinoma and the CEA level is very high, for example, I would perform mediastinoscopy irrespective of how CT scan or PET was regarding the mediastinum. So I think that you may lose the capacity to stage the tumour properly if you do not perform certain procedures. This may not be shown in the long-term survival of the whole cohort of patients but may affect individual patients that we treat one by one. We do not treat masses of patients at the same time but individual patients. That's my first concern.

The second concern is that your sublobar resection rate is quite high at 25%. There are three ongoing trials that are not completed trying to define the role of sublobar resection for peripheral small lesions, so the standard of care today should be lobectomy for tumours or for lesions which you suspect are tumours. So this is the question: What is your policy on sublobar resection?

Finally, I would like to know what you are going to do. What would be your policy according to the results that you have now?

Dr Sihoe: Those are very insightful questions from Dr Rami-Porta and went, really to the heart of the matter. Let me address each of them. First of all, staging. It is true that there is room for improvement in terms of our staging; as you saw, some of our patients did actually end up with more than stage 1 disease. In terms of bronchoscopy, we do do bronchoscopy, actually on-table. It is true that we don't do it preoperatively on all patients, but we do always have a final-look bronchoscopy after the patient is intubated on the table. Anecdotally, in those 400-odd patients, I can't remember a single case where we actually found significant contralateral disease. In terms of the CEA and mediastinoscopy, unfortunately in Hong Kong we don't actually use such an aggressive approach. We don't check CEA routinely in all of our patients. So we haven't actually factored that into our staging algorithms. As I say, there is certainly room for improvement, and this is one aspect where we could actually improve. In terms of whether or not we should do, for example, PET scanning in all patients, again, during the time period of this study in Hong Kong, unfortunately PET scan was not routinely available as a free investigation for all patients, especially those in whom lung cancer had not yet been determined. On the other hand, though, despite these limitations in our staging algorithms, what we found is that the incidence of stage 1A disease, stage 1 disease, was actually similar in the two groups. Because we used the same staging algorithms in both arms of the study, we weren't actually missing out on staging within the 'no preoperative tissue diagnosis' group, and I think that was reflected in the results: Having said that, if we routinely do PET scans in all patients, for example, with GGOs, as we just saw, I think the jury is still out on whether or not PET scan is useful in all cases of GGOs, which contribute to quite a large portion of the patients in this study. So in answer to your question, at the moment, yes, we could do better for staging, but in the context of this particular study, I don't think it really was a significant factor towards survival.

Now, in terms of the sublobar resections, actually in this study, if we looked at the sublobar resections we did in the 'no preoperative diagnosis' group, that actually corresponded almost exactly to the number of patients who had solitary metastasis from extrathoracic sources, and I think that was the reason why we had quite a high sublobar resection rate, when the frozen section said it was an extrathoracic malignancy. For the primary lung cancers within our study, the lobectomy rates were actually quite similar within the two study arms. That is certainly something that we will be looking into in the future, because, as we see, there is a trend around the world nowadays for sublobar resections for the AISs and the MIAs, and I think certainly as time goes on, we'll probably see increasing sublobar resection rates in both study arms in the future.

Now, how does this all tie into our practice in Hong Kong? At the moment, it hasn't really changed too much. As you see, there is no significant improvement in the oncological outcomes. However, from a practical standpoint, because, as I said, there is increasing bottle-necking at the diagnostic stage, I think now that we have proven that at least there is no inferiority with using the 'no preoperative tissue diagnosis' approach, we are actually more prepared to go on with that. I think not only does this benefit the individual patient with shorter waiting times, but from the overall population point of view, it actually relieves the burden on the diagnostic services, so even for the patients who do require a preoperative tissue diagnosis, the waiting times for those diagnostic investigations should hopefully come down as well.