Does positron emission tomography scanning improve survival in patients undergoing potentially curative lung resections for non-small-cell lung cancer?

Eustace Fontaine, James McShane, Martyn Carr, Michael Shackcloth, Neeraj Mediratta, Richard Page, Michael Poullis*

Liverpool Heart and Chest Hospital, Thomas Drive, Liverpool, England L14 3PE, United Kingdom

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Abstract

Objective: To determine if positron emission tomography (PET) scanning has resulted in an improvement in the short- and long-term survival of patients undergoing potentially curative resections for non-small-cell lung cancer. No publications exist to demonstrate an increased survival of patients with lung cancer due to the use of PET scanning. If PET scanning reduces unnecessary resections, the results from surgery should be improved with its introduction. Methods: A prospective thoracic surgery database was retrospectively analysed. Patients (N = 1999), who had undergone potentially curative resections for non-small-cell lung cancer, and those who had a PET scan pre operatively (N = 934), were compared with patients who had not undergone PET scanning (N = 1065), prior to surgical resection. PET scanning became routine for all patients 4 years ago in our unit. Staging was defined as pathological staging to eliminate bias by ‘better’ preoperative staging due multislice computed tomography (CT) and PET scanning. Propensity matching based on Cox regression analysis was performed for survival analysis at each stage. Results: Propensity matching revealed that the introduction of routine PET scanning did not result in improved survival in the short or long term, for patients undergoing resections for stage Ia (N = 271 in each matched group), p = 0.74, stage Ib (N = 321 in each matched group), p = 0.43 and stage II (N = 164 in each matched group), p = 0.06. PET has however resulted in a significant increased survival for patients undergoing resections for stage III primary lung cancer (N = 68 in each matched group), p = 0.03. Conclusion: We concur with current guidelines for the use of PET scanning for stage III non-small-cell lung cancer. Our results need to be corroborated with other groups as potentially stage-Ia-, Ib-, and stage-II patients may not benefit from PET scanning.

Keywords: PET; Lung cancer; Survival

1. Background

Positron emission tomography (PET) scanning is currently thought to be very accurate in assessing nodal and systemic metastasis, and thus in the prevention of non-curative resections [1]. Despite an extensive literature documenting the sensitivity and specificity of PET scanning, no publications exist to demonstrate an increased survival of patients with lung cancer due to the use of PET scanning [1,2].

As PET scanning reduces unnecessary resections [3], the results from surgery should be improved since its introduction.

We aimed to determine if PET scanning has resulted in an improvement in the short- and long-term survival of patients undergoing potentially curative resections for non-small-cell lung cancer.

2. Materials and methods

A prospective validated thoracic surgery database was analysed for non-small-cell lung cancer stages I–IIIA.

Staging was defined as pathological staging to eliminate bias by ‘better’ pre operative staging due multislice computed tomography (CT) and PET scanning. Routine intra-operative mediastinal lymph node sampling has always been undertaken in our unit. PET scanning became routine for all patients 4 years ago in our unit.

Survival data for all patients are routinely obtained through the National Strategic Tracing Service, as previously described [4].

No patients underwent resection with a preoperative stage N2, or received neo-adjuvant therapy to downstage.
Mediastinoscopy was used in all patients who had mediastinal lymph nodes enlarged by CT criteria, or who had undergone PET scanning and were thought to have positive N2 nodes.

2.1. PET reporting

All PET scans were reported by at least two independent consultant radiologists with accreditation in PET scan reporting. All PET scans were part of a combined PET-CT scan.

2.2. Benchmarking

We benchmarked our long-term outcomes following resection for non-small-cell lung cancer (Fig. 1) against the International Association for the Study of Lung Cancer (IASLC) Lung Cancer Staging Project 7th edition outcome figures [5,6].

2.3. Crude analysis

Kaplan–Meier survival curves were constructed for stages Ia, Ib, II and III (Fig. 2). The number of patients in the stage II group was too small to divide into IIa and IIb.

2.4. Study group characteristics

Possible confounding differences in case-mix between the PET and non-PET groups are shown in Table 1(a), including preoperative characteristics and Table 1(b), including histology and operative characteristics. Differences in categorical variables were evaluated using chi-squared tests, while the Wilcoxon rank sum test was used for continuous variables. The influence on survival of these potentially confounding factors was investigated further. Median follow-up time in the non-PET group was 3.7 years (mean 3.7, range 0–8.1 years), and, in the PET group, 1.5 years (mean 1.7, range 0–5.9).

2.5. Univariate analyses

Univariate analysis of all variables in Table 1 was performed first – supplemental files – with the objective of identifying significant factors for inclusion in a multivariate Cox regression model. Categorical variables were assessed using the log-rank test. For each of the continuous variables, a univariate Cox regression was performed.

2.6. Multivariate Cox regression

A Cox regression model (Table 2) to predict survival for all stages and then for each stage (I, II and III) was developed individually. Significant predictors of survival (and those approaching significance ($p < 0.1$)) were used to propensity match patients from the PET and no-PET groups. Survival in the matched groups was then plotted using the Kaplan–Meier
method and differences evaluated using a log-rank test. Therefore, any differences between the curves are solely due to the impact of PET scanning.

3. Results

Between 1998 and 2010, 1999 patients underwent a lung resection for proven or suspected non-small-cell lung cancer. Total survival follow-up of all patients in our study population was achieved. Patients with small-cell cancer were excluded.

3.1. Benchmarking

Benchmarking (Fig. 1) revealed no significant differences in our long-term outcomes compared with the IASLC Lung Cancer Staging Project 7th edition outcomes [7].

3.2. Crude analysis

The Kaplan–Meier survival curves in Fig. 2 demonstrate the crude survival for patients undergoing potentially curative resections with or without PET scanning. PET scanning did not result in an increased survival.

3.3. Study group characteristics

It can be seen from Table 1 that the PET group and the non-PET group had a number of significantly different characteristics (age, body mass index (BMI), diabetes, New York Heart Association (NYHA), forced expiratory volume in 1 s (FEV1) and peripheral vascular disease), indicating that a direct comparison between the two groups may result in incorrect conclusions being drawn.

3.4. Multivariate Cox regression

Table 2(a)–(d) demonstrates the results of the Cox regression analysis for the whole group and each stage that were used for the separate propensity matches to construct the Kaplan–Meier survival curves.

3.5. Propensity-matched survival

The Kaplan–Meier survival curves for the study cohort and each stage are shown in Fig. 3. PET scanning was associated with a significantly improved overall 5-year survival (61 ± 0.02% vs 53 ± 0.03%), p = 0.04, and for stage-III patients (41 ± 0.09% vs 20 ± 0.05%), p = 0.03, only (standard error shown in brackets).
4. Discussion

Patients with stage III non-small-cell lung cancer should undergo PET scanning prior to surgical resection. In our study population, PET scanning makes no difference to survival in patients with stage Ia, Ib, or stage II disease. We are unsure if our result for stage II is a type II error due to inadequate power.

Our data confirm a recent much smaller randomised study, which failed to demonstrate any survival benefit of PET scanning [2]. We were unable to find any studies in lung cancer that demonstrated that PET scanning has resulted in an improved survival.

Propensity matching confirmed that, despite the group mismatch on univariate analysis, significant advantage of PET scanning in stage III still existed.

We are unable to explain why the patient risk factors have altered over the last 10 years of surgical practice, resulting in the PET and non-PET groups having different risk profiles. However, the statistical methodology used (Cox multiple regression analysis guided propensity matching) has taken this into account.

PET scanning is thought to be highly sensitive, but not specific with regard to the detection of N2 and metastatic disease [1]. This high sensitivity should result in improved survival, as 'hopeless' cases will be prevented from having an operation. As the survival has not changed potentially, we may be inappropriately labelling patients falsely as having inoperable disease based on PET scanning, when they do not.

Adjuvant chemotherapy could potentially be a confounding factor. None of our stage-Ia- and Ib-and very few of our stage-II patients would have had adjuvant therapy as part of their curative treatment, but this was not recorded on our database. We recognise that adjuvant therapy for the stage-IIa patient maybe a confounding factor, as it is in the current IALSC data set. If this is so, then PET scanning may not have a role in stage IIIa disease either.

We are unable to explain our finding of a survival advantage for wedge resections with PET scanning. This may be due to patients not fit enough for a lobectomy being turned down for wedge resections, if the PET reported possible N1 disease, as these would not be curative resections.

We concur with current guidelines for the use of PET scanning for stage III non-small-cell lung cancer. Our results need to be corroborated with other groups as potentially stage-Ia-, Ib- and stage-II patients may not benefit from PET scanning.

4.1. Limitations

The median follow-up time in the PET group was only 1.5 years (mean 1.7). The majority of 'missed' metastasis in lung cancer present as recurrent disease in the first 18 months post surgery; hence, our result is still clinically significant. Combined PET-CT scanners, as was routine in this cohort, is too new a technique to have a median follow-up time of 5 years.

References


Appendix A. Conference discussion

Dr E. Rendina (Rome, Italy): Unfortunately in this case I was not able to read the manuscript in advance, and since there are some differences between what was reported in the abstract and the actual data which was presented here, I’m a little embarrassed. The question of whether preoperative staging by PET would increase survival is a very important one. Unfortunately, to answer this question conclusively, we would need a prospective randomised study, which probably will never be done.

My question is the following. You have demonstrated that there is a survival advantage for PET when wedge resection is performed. Can you comment on your indications for wedge resection versus lobectomy for stage I disease?

Dr Fontaine: I think this is probably a reflection of patients with poor pulmonary reserve and just a lack of fitness, and we felt the nonanatomical resection would probably be more favourable to conserve lung, and these probably may have been slightly smaller tumours as well, but I do not have all the data to clarify that properly. I suspect it is a combination of these two factors.

Dr Rendina: So it’s only a matter of functional reserve?

Dr Fontaine: I think the significant difference when we just had a wedge as well is that possibly the PET scanning, once it was introduced, was staging that group of patients slightly more accurately, such that prior to the introduction of PET, they were just going to have a wedge resection and they may have had more extensive disease which was not recognised. It’s a combination of all these things.

Dr R. Cerfolio (Birmingham, USA): I want to make sure I get your conclusion right, that patients with stage IIA are the ones who benefit from PET and not the other ones?

Dr Fontaine: Yes.

Dr Cerfolio: Would you agree that a PET scan is more sensitive at finding mediastinal N2 lymph nodes?

Dr Fontaine: It would appear so, yes.

Dr Cerfolio: So then how do you know who has stage IIA unless you do the PET?

Dr Fontaine: I think it would be very difficult to not do a PET in everyone, but what I think it reflects is that if you’ve got a smaller tumour, you are probably less likely to have mediastinal metastasis compared to a big central tumour. So on the CT scan it would suggest that if you have a very small tumour with no nodes, what we were doing before, with not having a PET scan and these people going on to have lung resections, probably –

Dr Cerfolio: But you would agree that some of those people, 10% or 15%, have microscopic N2 disease that the PET would miss, but sometimes it might find it.

Dr Fontaine: It might find it.

Dr Cerfolio: And your conclusion was on clinical stage IIA or pathologic stage IIA?

Dr Fontaine: Pathological.

Dr Cerfolio: That’s very different than what we’re seeing in the clinic. When I’m ordering a PET, it’s based on their clinical stage. I think you need to go back and really carefully think about that. If I know they are pathologically I-II, I don’t need any tests. I’ve already operated on them and all the nodes have been removed.

Dr Fontaine: Well, the reason why we chose pathologic stage was to eliminate the bias of better selection due to preoperative PET staging.

Dr Cerfolio: I understand, but you need to be very careful about making your recommendation on pathologic stage for a test that is done when there is only clinical stage available.

Dr Fontaine: Absolutely.

Dr P. Van Schil (Antwerp, Belgium): Continuing on the same line, when you perform routine PET scanning, patients with clinical early stage lung cancer will have distant metastases in approximately 10% to 15% of cases. So your conclusions are not right as you only looked at pathologic staging and selected those patients without metastases beforehand.

Dr Fontaine: Sorry?

Dr Van Schil: You did do a routine PET scan, and when you only look at pathologic stage, you already selected those patients with clinical early stage disease without distant metastases.

Dr Fontaine: Yes. We looked at the pathologic stage, because if we staged them by PET, we would have created a bit of bias.

Dr M. Poullis (Liverpool, United Kingdom): I’m one of the authors. You are right. One of the things in the paper, we think you’re turning down people you shouldn’t be turning down, which is actually the conclusion of a previous paper. That’s why you’re not finding an increased survival. We agree that it’s very sensitive at picking up mediastinal disease, so we should be seeing an increased survival but we’re not, so we must be turning people down. That also partly correlates with our paper yesterday about having microscopic N2 disease. Some of them do as well as stage II, depending on other factors that are going on.

So I think we haven’t really sorted this PET story and staging business out yet, to be honest. I’m sorry about the manuscript. It is in the manuscript, but we submitted it late, and that’s the problem.

Dr M. Dusmet (London, United Kingdom): Do you have any data on stage migration? That’s what you expect to see with PET. How many patients were preoperatively staged I and became stage II or III, and how does that impact on survival in clinical stage I versus pathologic stage II? Do you have any data on stage migration?

Dr Fontaine: Not at present, but I’m sure we would probably be able to try and extract that.

Dr Dusmet: Well, that’s really the key element that’s missing, if you’ll forgive me for saying so.