# Dynamic contrast-enhanced CT compared with positron emission tomography CT to characterise solitary pulmonary nodules: the SPUtNIk diagnostic accuracy study and economic modelling

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# Scientific summary

## SPUtNIk study and economic modelling

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# Scientific summary

## Background

Patients presenting with a solitary pulmonary nodule on diagnostic imaging tests are an important group because if early-stage lung cancer is treated with curative intent with surgical resection, the 5-year survival rate approaches 70%. However, not all solitary pulmonary nodules are due to lung cancer; the accurate characterisation of solitary pulmonary nodules is a diagnostic challenge with significant resource and cost implications. Owing to the association between nodule size and likelihood of malignancy, current management strategies are directed by nodule size. Nodules of < 5 mm require no follow-up, whereas nodules of > 8 mm in diameter require further diagnostic workup with positron emission tomography–computerised tomography or biopsy. However, both approaches are expensive, and positron emission tomography–computerised tomography is not available at all hospitals in the UK. Dynamic contrast-enhanced computerised tomography quantifies the degree of enhancement of pulmonary nodules following the intravenous administration of iodine-based contrast. The degree of enhancement reflects the extent of vascularity of the nodule, which has been shown to be an accurate marker for the diagnosis of solitary pulmonary nodules, with high sensitivity and moderate specificity. Moreover, dynamic contrast-enhanced computerised tomography has been shown to be a more cost-effective approach in the diagnostic workup of nodules than positron emission tomography–computerised tomography. However, the studies underpinning this analysis are weak. They predominantly involved single-centre studies, did not directly compare positron emission tomography with dynamic contrast-enhanced computerised tomography, included pulmonary masses as well as nodules, and incorporated studies using old technology whereby the spatial resolution of positron emission tomography–computerised tomography did not allow for accurate assessment of smaller nodules. Furthermore, these technologies have not been compared for their impact and cost-effectiveness within the NHS structure.

The aim of the current study was to address these gaps in knowledge through the conduct of a large multicentre comparative accuracy trial of dynamic contrast-enhanced computerised tomography with positron emission tomography–computerised tomography in the assessment of solitary pulmonary nodules. Prior to commencing the trial, two systematic reviews were conducted examining diagnostic accuracy studies and economic evaluations of alternative diagnostic imaging techniques (whether individually or in combination) for characterising solitary pulmonary nodules (PROSPERO registration numbers CRD42018112215 and CRD42019124299, respectively). In addition to assessing the different techniques, the systematic reviews provided data relevant to the NHS for decision-analytic modelling.

## Objectives

The primary objectives were to:

- determine, with high precision, the diagnostic performances of dynamic contrast-enhanced computerised tomography and fluorine-18-labelled-fluorodeoxyglucose positron emission tomography–computerised tomography in the NHS for the characterisation of solitary pulmonary nodules
- use decision-analytic modelling to assess the likely costs and health outcomes resulting from incorporation of dynamic contrast-enhanced computerised tomography into management strategies for patients with solitary pulmonary nodules.

The secondary objectives were to:

- assess, in an NHS setting, the incremental value of incorporating the computerised tomography appearances of a solitary pulmonary nodule into the interpretation of integrated positron emission tomography–computerised tomography examinations
- assess whether or not combining dynamic contrast-enhanced computerised tomography with positron emission tomography–computerised tomography is more accurate and/or cost-effective in the characterisation of solitary pulmonary nodules than either test used alone or in series
- document the nature and incidence of incidental extrathoracic findings on positron emission tomography–computerised tomography and dynamic contrast-enhanced computerised tomography undertaken for the characterisation of solitary pulmonary nodules and to model the cost-effectiveness of the two techniques.

## Methods

### *Systematic review of economic evaluation*

Studies were identified through searches of six electronic databases, from inception to November 2018 [i.e. MEDLINE, EMBASE, Web of Science, Bioscience Information Service (BIOSIS), The Cochrane Library and Science Direct]; through reference lists of relevant studies; and by contacting experts. Cost, cost-effectiveness and cost–utility studies were included that compared strategies involving computerised tomography or positron emission tomography with resection, biopsy and/or clinical follow-up. Studies had to report either costs, cost per case detected or incremental cost per life-year/quality-adjusted life-year gained. Studies were selected through two stages: initially, titles and abstracts were screened, with manuscripts of selected papers then retrieved for full-text screening. At both stages, two reviewers independently screened studies. Data were extracted into a standard template by one reviewer and checked by a second reviewer. Differences at all stages were resolved through discussion. Data were synthesised through narrative review and studies were critically appraised using standard criteria.

### *Multicentre comparative accuracy trial*

The trial was designed in accordance with the guidance for the methods of technology appraisal issued by the National Institute for Health and Care Excellence and adopted by the National Institute for Health and Care Excellence in formulating its guidance for the use of positron emission tomography in the staging of lung cancer.

The trial was designed as a prospective, multicentre observational study to assess the diagnostic performance and incremental value of dynamic contrast-enhanced computerised tomography by addition of this modality to positron emission tomography–computerised tomography in a cohort of 375 patients with solitary pulmonary nodules. Preceding symptoms were collected in a questionnaire at recruitment and at 1 year, and were correlated with the outcome.

### *Settings and participants*

Participants with a solitary pulmonary nodule were recruited from secondary or tertiary outpatient settings at 16 hospitals in the UK.

### *Inclusion criteria*

- A soft-tissue solitary dominant pulmonary nodule of $\geq 8$ mm and $\leq 30$ mm on the axial plane:
    - measured on lung window using conventional computerised tomography
    - no other ancillary evidence strongly indicative of malignancy (e.g. distant metastases or unequivocal local invasion)
    - if clinicians and reporting radiologists believed that the patient was being treated as having a single pulmonary nodule and there were other small lesions of $< 4$ mm that would normally be disregarded, the patient was included in the trial.

- Nodules already under surveillance were included provided that the patient had recently undergone, or had scheduled, positron emission tomography–computerised tomography.
- Aged ≥ 18 years at the time of providing consent.
- Able and willing to consent to the trial.

### *Exclusion criteria*

- Pregnancy.
- History of malignancy in the previous 2 years.
- Confirmed aetiology of the nodule at the time of the qualifying computerised tomography scan; as this was a diagnostic study, if the aetiology of the nodule was confirmed by investigation such as positron emission tomography–computerised tomography or bronchoscopy prior to consent, the patient remained eligible, as the intention to include was made on the analysis of the qualifying computerised tomography scan.
- Biopsy of nodule prior to dynamic contrast-enhanced computerised tomography.
- Contraindication to potential radiotherapy or surgery.
- Contraindication to imaging techniques (assessed by local procedures).

### *Outcomes*

The primary outcome was the diagnostic accuracy of dynamic contrast-enhanced computerised tomography and positron emission tomography–computerised tomography, and their cost-effectiveness in the diagnostic workup of solitary pulmonary nodules.

The secondary outcomes were as follows:

- the accuracy (sensitivity, specificity, overall diagnostic accuracy) of the full spectrum of cut-off points, alone or in combination, of the two tests
- the incremental cost per malignant case treated and the incremental cost per correctly managed case
- the presence of incidental extrathoracic lesions requiring investigation.

The reference standard was histology and/or completion of 2 years of nodule surveillance. For a nodule to be diagnosed as malignant, histological confirmation was required, or an increase in nodule size with multidisciplinary team certainty of malignancy when biopsy/resection was not possible. Benign status was established through either histology or demonstration of stability over 2 years of computerised tomography monitoring. A biopsy of a lesion increasing in size during follow-up was performed if this was considered clinically necessary by the local care team. Lesions showing a < 20% increase in size during the 24-month follow-up were considered benign. The participants' clinical notes were reviewed at 24 months to determine how the patient was managed after imaging. This included investigative procedures received, surgical interventions and associated inpatient stays. This was to confirm that decision-tree models accurately reflected clinical practice (e.g. proportion of patients with imaging positive for malignancy undergoing biopsy or surgical excision), and to inform subsequent economic analyses. Follow-up investigations and outcomes for incidental extrathoracic findings on positron emission tomography–computerised tomography and dynamic contrast-enhanced computerised tomography were also collected.

The diagnostic accuracy of the tests was assessed by sensitivity, specificity and accuracy. For the primary outcome, these used prespecified cut-off points, with further exploratory analyses performed considering the full spectrum of cut-off points and the combination of the two tests. Receiver operating characteristic curves were constructed for these exploratory analyses to compare accuracy. For positron emission tomography–computerised tomography, a test was considered positive if it met one of the following criteria: nodule tracer uptake equal to or greater than that of the mediastinum with irregular/spiculate morphology on computerised tomography, or evidence of distant metastases on positron emission tomography or computerised tomography. For dynamic contrast-enhanced computerised tomography, an enhancement threshold of > 20 Hounsfield units was considered malignant.

The outcome measures used in the economic model-based cost–consequences analysis compared positron emission tomography–computerised tomography, dynamic contrast-enhanced computerised tomography, and dynamic contrast-enhanced computerised tomography plus positron emission tomography–computerised tomography in terms of accuracy, estimated life expectancy and quality-adjusted life-years. Costs were estimated from an NHS and Personal Social Services perspective. The incremental cost per malignant case treated and the incremental cost per correctly managed case were also estimated.

### *Economic evaluation*

The decision-analytic model on which the cost–consequences and cost-effectiveness analyses were based was developed to synthesise evidence and to estimate the expected costs and consequences of each imaging strategy for a cohort of people aged 69 years presenting with a solitary pulmonary nodule (of 8–30 mm) and managed according to the imaging test result. The time horizon of the model was 2 years, but life expectancy and quality-adjusted life-years were extrapolated over the patient lifetime.

Imaging test accuracy and probabilities of following different management pathways were sourced from the trial, the literature and clinical expert opinion. Cost estimates were derived from routine sources (i.e. NHS reference costs, Personal Social Services costs), as well as from the literature, and were inflated, when necessary, to 2018 prices. Further evidence required to estimate life expectancy and health-related quality of life was sourced from the literature.

Parameter uncertainty within the model was addressed using probabilistic sensitivity analysis. Multiple univariate one-way sensitivity analyses were used to identify those parameters to which costs and the proportion of accurately treated cases were most sensitive. Scenario analyses explored the impact of structural assumptions (i.e. exclusion of indeterminate results) on the costs and consequences.

Model validation involved the comparison of results with an independent model, developed to answer the same decision question using different software.

## Results

### *Systematic review of economic evaluation*

Searches identified 664 candidate publications, with nine studies included. These primarily assessed the cost-effectiveness of watchful waiting, computerised tomography, fluorodeoxyglucose-positron emission tomography and surgery, reporting a range of outcomes (i.e. diagnostic accuracy, life-years and quality-adjusted life-years). The studies were judged to be of poor quality when assessed against current methodological guidance for economic evaluations of diagnostic interventions. Although the review provided some evidence of the cost-effectiveness of strategies in relation to the probability of malignancy, it was not possible to make quantitative conclusions because of the heterogeneity among the studies. Given the lack of good-quality evidence on the cost-effectiveness of diagnostic strategies for characterising solitary pulmonary nodules, this systematic review identified the need for a full economic evaluation as part of the trial.

### *Multicentre comparative accuracy trial*

Of the 380 participants recruited, 312 (47% female, median age of 69 years, age range 35–89 years) completed the study with matched dynamic contrast-enhanced computerised tomography and positron emission tomography–computerised tomography examinations. A total of 57% reported being ex-smokers, and 25% reported being current smokers. The median pulmonary nodule diameter on baseline computerised tomography scans was 15 mm (interquartile range 12–20 mm). There was a 61% rate of malignancy at 2 years. These cancers were found to be 76% non-small-cell carcinoma, of which 74% were adenocarcinomas and 21% were squamous cell carcinoma; 6% carcinoids; and 4% small-cell lung cancer.

The sensitivity and specificity for dynamic contrast-enhanced computerised tomography were 95.3% (95% confidence interval 91.3% to 97.5%) and 29.8% (95% confidence interval 22.3% to 38.4%), respectively; for positron emission tomography–computerised tomography grade, the sensitivity and specificity were 72.8% (95% confidence interval 66.1% to 78.6%) and 81.8% (95% confidence interval 74.0% to 87.7%), respectively. The area under the receiver operating characteristic curve was 0.62 (95% confidence interval 0.58 to 0.67) for dynamic contrast-enhanced computerised tomography and 0.77 (95% confidence interval 0.73 to 0.82) for positron emission tomography–computerised tomography ($p < 0.001$ for difference). Using a quantitative metric of nodule uptake on positron emission tomography–computerised tomography with a maximum standardised uptake value of $\geq 2.5$ as a cut-off point was no more accurate than the combined positron emission tomography–computerised tomography grading (area under the receiver operating characteristic 0.79, 95% confidence interval 0.74 to 0.83; $p = 0.5177$ for difference). Exploratory modelling of the various parameters at different thresholds showed that the maximum standardised uptake value had the best diagnostic accuracy, with an area under the curve of 0.87 (95% confidence interval 0.83 to 0.91), which increased if combined with dynamic contrast-enhanced computerised tomography peak enhancement, with an area under the receiver operating characteristic curve of 0.90 (95% confidence interval 0.86 to 0.93). These exploratory models suggest potential sensitivity and specificity values of 80.5% (95% confidence interval 74.3% to 85.5%) and 78.2% (95% confidence interval 69.9% to 84.6%), respectively, for the maximum standardised uptake value and of 84.7% (95% confidence interval 78.8% to 89.1%) and 77.3% (95% confidence interval 69.0% to 83.9%), respectively, for the combination with peak enhancement.

Dynamic contrast-enhanced computerised tomography was, on average, less costly (£3305, 95% confidence interval £2952 to £3746) than positron emission tomography–computerised tomography (£4013, 95% confidence interval £3673 to £4498) or dynamic contrast-enhanced computerised tomography plus positron emission tomography–computerised tomography (£4058, 95% confidence interval £3702 to £4547). Positron emission tomography–computerised tomography resulted in more correctly managed malignant cases (0.44, 95% confidence interval 0.39 to 0.49) than dynamic contrast-enhanced computerised tomography (0.40, 95% confidence interval 0.35 to 0.45). However, dynamic contrast-enhanced computerised tomography plus positron emission tomography–computerised tomography further improved this proportion to 0.47 (95% confidence interval 0.42 to 0.51). In a sensitivity analysis, the findings of positron emission tomography–computerised tomography being more effective for the correct management of cases and dynamic contrast-enhanced computerised tomography being more cost-effective were robust to varying the model parameters over a range of 50%. In the incremental cost-effectiveness analyses, the cost-effectiveness acceptability curves showed that dynamic contrast-enhanced computerised tomography combined with positron emission tomography–computerised tomography is more likely to be cost-effective at willingness-to-pay thresholds of > £11,395 per malignant case treated and £11,323 per accurately managed case. It was not possible to follow up all incidental findings to determine if these were pathologically confirmed or incidental findings. As a result, a health economic analysis of this was not performed.

Symptom analysis showed that unexpected tiredness first experienced in the previous 3 months and more colds or flu in the previous 12 months were positively associated with lung cancer.

## Discussion

In this trial, we have found that positron emission tomography–computerised tomography is the more accurate technique for the diagnosis of solitary pulmonary nodules. However, despite its slightly poorer performance, dynamic contrast-enhanced computerised tomography is a more cost-effective strategy. When the willingness-to-pay threshold per correctly treated malignancy was < £9000, dynamic contrast-enhanced computerised tomography was always the preferable strategy. However, when society's willingness to pay for one more correctly treated malignancy increased to £16,000, the strategy that combines dynamic contrast-enhanced computerised tomography with positron emission tomography–computerised tomography becomes the strategy most likely to be considered cost-effective, with a probability equal to 1.

These findings have significant implications for the NHS, especially in the light of the introduction of computerised tomography-based lung cancer screening. The availability of positron emission tomography–computerised tomography is limited to relatively few centres and is constrained by the national positron emission tomography contract. The fluorodeoxyglucose radiotracer is produced off-site and supply can be unreliable, resulting in delayed or postponed examinations. In comparison, computerised tomography machines are widely available and relatively inexpensive, and a contrast examination is quick to perform. This raises the possibility of same-day progression from initial nodule detection to subsequent workup with dynamic contrast-enhanced computerised tomography. Case selection could be achieved with artificial intelligence algorithms incorporated into routine screening workstreams.

In this study, the radiation dose to the patient from dynamic contrast-enhanced computerised tomography was higher, at 30 mSv, than a standard positron emission tomography–computerised tomography dose of 14.1 mSv. The protocol was designed 9 years ago and the high radiation dose ensured a minimum signal-to-noise ratio on all scanners, irrespective of manufacturer. However, dual-energy scanning is a routine feature of newer computerised tomography scanners, as is iterative reconstruction, which significantly reduces radiation dose without loss of image quality. A second, and more significant, limitation of dynamic contrast-enhanced computerised tomography in the current study is poor specificity, compared with that expected from the meta-analysis of the current literature. The examinations were not always read by dedicated thoracic radiologists, which is the recommendation for the computerised tomography lung screening programme.

The clinical predictors of unexpected tiredness first experienced in the previous 3 months and more colds or flu in the previous 12 months, which were positively associated with lung cancer, is highly novel, but it is emphasised that these are exploratory findings and of little value until demonstrated in a prospective study of a different data set.

The NHS England lung health check recommendation is that all solitary pulmonary nodules of $> 5$ mm or $> 80$ mm$^3$ on lung settings should be classified indeterminate. Our study used a threshold of 8 mm and was designed well before this lower size threshold was introduced.

## Conclusion

Although positron emission tomography–computerised tomography is the more accurate technique, the low cost of dynamic contrast-enhanced computerised tomography means that dynamic contrast-enhanced computerised tomography alone, or as a gate keeper to positron emission tomography–computerised tomography, is the most cost-effective approach to the diagnosis of solitary pulmonary nodules, albeit with an increased radiation dose. A combination of maximum standardised uptake value and peak enhancement had the highest accuracy, with a small increase in costs. A combined positron emission tomography–computerised tomography and dynamic contrast-enhanced computerised tomography approach with a slightly higher willingness-to-pay threshold to avoid missing small cancers or avoid a watch-and-wait policy should be considered.

The research recommendations are as follows:

- Explore the integration of the dynamic contrast-enhanced component into the positron emission tomography–computerised tomography examination for the characterisation of solitary pulmonary nodules.
- Explore the feasibility of two-stage computerised tomography lung screening with dynamic contrast-enhanced computerised tomography at the same visit if a suspicious nodule is found.

- Undertake analysis of positron emission tomography–computerised tomography and dynamic contrast-enhanced computerised tomography by tumour type, grade and size, using different standardised uptake values and enhancement thresholds to improve accuracy.
- Develop a new protocol for dynamic contrast-enhanced computerised tomography with a lower radiation dose suitable for the newer computerised tomography machines.

## Study registration

This study is registered as PROSPERO CRD42018112215 and CRD42019124299, and the trial is registered as ISRCTN30784948 and ClinicalTrials.gov NCT02013063.

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