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RESEARCH ARTICLE

PET-CT in esophageal cancer management: A cost effectiveness analysis study

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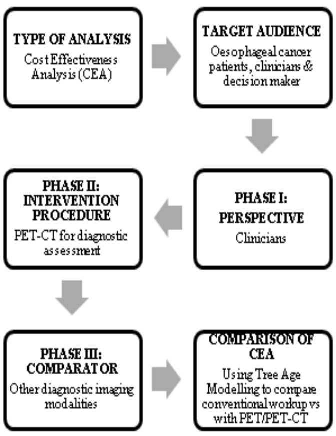
Graphical abstract



Abstract

The present investigation dealt with the assessment of clinicians perceived views on the impact of PET-CT in esophageal cancer management from practicality, clinical efficacy and cost –effectiveness point of views. Reviews on publication and retrospective data to develop and carry out a decision making model-based economic evaluation to investigate the relative cost-effectiveness of PET/CT in esophageal cancer management staging compared with conventional pathway. Clinicians identified from patient medical records were included in the survey. Retrospective analysis of patient data from 2001-2008 was taken from esophageal cancer patient medical records and North West Cancer Intelligence Services (NWCIS) database. A decision tree was developed using TREEAGE software. The results of the cost-effectiveness analysis were presented in terms of the incremental cost-effectiveness ratios (ICERs). PET compared with conventional work-up results for ICER for the strategy estimated at £28,460 per QALY; PET/CT compared with PET for ICER was £ 32,590 per QALY; and the ICER for PET/CT combined with conventional work-up versus PET/CT was £ 44,118. The package became more expensive with each additional diagnostic test added to PET and more effective in terms of QALYs gained. The conventional work-up was the preferred options as probabilistic sensitivity analysis showed at a willingness-to-pay threshold of £ 20,000 per QALY. Result of the current analysis suggested that the use of PET/CT in the diagnosis of esophageal cancer was unlikely to be cost-effective given the current willingness-to-pay thresholds that were accepted in the United Kingdom by decision-making bodies such as the National Institute for Health and Clinical Excellence.

Keywords:PET-CT, esophageal cancer, cost effectiveness analysis, tree age modelling, economic analysis

INTRODUCTION

Cancer is a costly disease to be managed, which consists of diagnosis, investigation and treatment, and is time-consuming, labor intensive and in most cases requires hospital care. Alongside with the urging excitement of new advancement in diagnosis and treatment to improve survival and quality of life, escalation of healthcare cost associated with the new technology also continues to be a major concern and need to be addressed properly. Esophageal cancer, although a malignancy with a relatively low incidence, has a very high mortality due to delayed diagnosis and an inaccurate pre-therapy assessment on the extent of the disease (Dehdashti & Siegel, 2004; Griffin & Wahed, 2011). Evolution of times brings together a continuous rapid advancement in diagnosis and treatment of esophageal cancer that not only can improve chances of survival but also make an early diagnosis, which presents with late onset of symptoms (Eslick, 2009a, 2009b; Findlay *et al*., 2015). Despite this advancement, esophageal cancer continues to be a major health problem worldwide(Kigula-Mugambe & Kavuma, 2015).

As the treatment for esophageal cancer remains in evolution, the fundamental principle of cancer management is patient's evaluation for surgical treatment. The domain prognostic factor for survival is whether the tumour can be completely resected. As esophageal cancer comes with significant morbidity, mortality and cost associated with the surgical treatment, it is important to identify and ~~to~~ exclude patient who will not benefit from the surgical treatment.

Esophageal cancer has high fluorodeoxyglucose (FDG) avidity (Noble *et al*., 2009; Torrance *et al*., 2015; Wong & Chambers, 2008). 18-FDG PET is increasingly used for the staging of esophageal cancer butonly provides limited anatomic information. Hybrid PET-CT imaging can overcome some of these limitations by improving characterization of FDG activity in the vicinity of highly tracer-avid primary tumours before surgery, near organs with high physiological uptake and the presence of postsurgical distorted anatomy. Integrated PET-CT enables optimal anatomic delineation of PET findings and identification of FDG-negative lesions on computed tomography (CT) images and results in improvement in patient management (Bar-Shalom *et al*., 2005; Szyszko, 2016).

In health management, the demand for health services directly creates desires and preferences for the use of various health technologies. However, there are also certain limitations in terms of resource restriction on time, personnel and money which indicating that the range of health services does not always meet demand. Very rapid technological development in the health care sector also means that there is a gap between what is technically possible and what is economically possible. Newhouse has shown that the greatest contribution to growth in health expenditure came from the use of technology. The gap makes the prioritization of efforts in the form of choices between different health technologies is relevant and inevitable. On a traditional market, demand will be determined by the price at which an article is offered. However, the market for health services does not function that simply, which is why prioritization becomes slightly more complicated (Culyer & Newhouse, 2008; Pauly*et al.*, 2012).

Economic analysis may help to determine how resources find the best possible use in the healthcare sector. The basis for the economic reasoning and analysis is provided by the 'opportunity cost concept', according to which the cost of health technology consists of the gains from other health technologies that have been forgone by committing the resources to the first health technology. However it may also be utility losses elsewhere in society if the health budget is expanded (Rudmik & Drummond, 2013).

There are limited numbers of publications reported on economic evaluations of PET and PET-CT compared with significant number of publications on widespread conventional modalities such as CT, Ultrasound and MRI. Apparently, PET has been conceived as a costly diagnostic test. This leads to significant number of preliminary studies that focusing on cost-effectiveness studies of this modality. In majority of cancers, prospective studies are conducted by the short of evaluation on the cost-effectiveness of PET-CT. In a study by Von Schulthess et al, it was is shown that for diagnostic management of cancer, there wasis a high prospect for PET-CT to be used as one of the cost effective methods(Schulthess, 2007, 2016). In addition to this, there are no explicit clinical conditions for this modality to be cost effectively implemented. In comparison to separate PET and CT studies, slight improvements in term of diagnostic accuracy have been shown in preliminary studies. Consequently, results on studies for PET can be assimilated for PET-CT (Guignard *et al.*, 2014; Krug *et al*., 2010).

The aim of this study was to quantitatively model under what situations PET-CT could play a cost-effective role in the staging of esophageal cancer regarding clinical effectiveness (defined as patient life expectancy) and in avoiding unnecessary surgery and medical expenditure. A decision analysis model was developed that could account for uncertainty involved in some of the relevant variables (e.g.: prevalence, the cost of PET-CT). Optimization of cost-effectiveness as defined by these terms (clinical effectiveness and cost) was chosen to ensure an algorithm in which the cost was minimized without any decrease in patient life expectancy. The cost-effectiveness of this diagnosis strategy takes into account not only the budget costing of the diagnostic test but also the 'downstream' effects the test has on both the cost of medical management and the patients' clinical outcomes. This study was also hoped to be able to demonstrate the application of decision analysis that could be applied to quantitatively determine the role of any diagnostic imaging techniques or another type of interventions in the clinical management.

Introduction of new modality like PET/CT into clinical management is continually assessed in order to ensure continuous improvement and development. A clinicians survey (Phase I) followed by analysis of cancer statistics (Phase II) are considered as an integral phases to highlight the esophageal cancer status in North West in general and specifically at Royal Liverpool & Broadgreen University Hospital Trusts (RLBUHT). Analysis of results from these two phases in combination with PET and PET/CT information from Phase III and cost-effectiveness results from Phase IV are intended to provide a full overview on PET/CT impact in esophageal cancer management.

EXPERIMENTAL

Phase I

This study was divided into four different phases representing two major components for cost-effectiveness analysis (perspective and intervention), according to the conducted studies; Phase I assessing clinicians' perspectives study and Phase II, III and IV covering the PET-CT intervention study.

Phase I was consisted of survey distributed by post to clinicians based at 38 hospitals around North West, UK, and details for this phase was shown in Fig 1. This survey was used as a tool to gather information on the current opinions and perceptions of clinicians involved to determine the impact that it has made to the clinical management of patients. This was the first survey done involving North West clinicians and was the first study done to show the need for ongoing research and co-operative consensus recommendations. Data analysis for this survey used a quantitative technique.

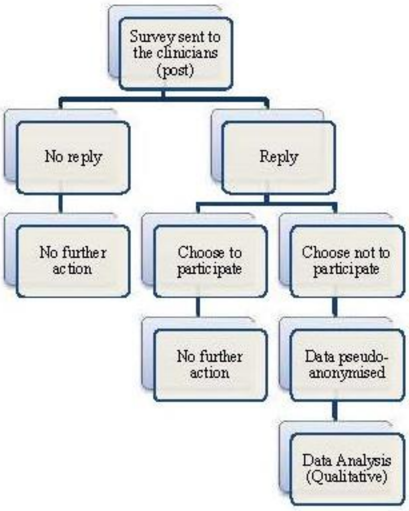


Fig.1 Procedure Flow Chart for Phase I.

Phase II & III

The starting point for Phase II was an audit of esophageal cancer from North West Cancer Intelligence Services (NWCIS) database. It gave a brief overview to determine the current cancer incidence, prevalence and crude survival rates in North West Regions for comparison between pre and post PET era. In Phase (III), a more detail analysis focusing on patient from Royal Liverpool and Broadgreen University Hospital registry was done. Key point taken from analysis in this phase provided baseline information for more comprehensive data analysis in later phase of this study (Phase III) which would provide information on the implementation of PET and PET-CT in esophageal cancer management. In order to develop a model on which to test the impact of PET or PET-CT, it was necessary to understand the stages of patients at presentation and the range of diagnostic modalities used for patientsthat were currently referred for PET- based investigation. Information from Phase II and III were then used for further cost-effectiveness modelling in the final Phase IV of this research.

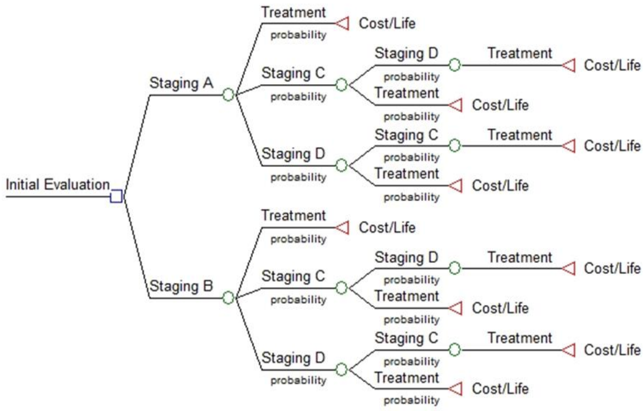


Fig.2 Basic decision tree.

Phase IV

The study design for Phase IV was consisted of 3 main processes: developing decision tree structure models, extraction of data to be populated in the models from Phase II and III and also based on data taken from publication, and the selection of outcomes measurement from the models chosen to best present the models. Basic decision tree modelling used for data analysis was shown in Fig 2. Total number of patients included was 35 patients' data for the modelling using Tree Age software. A cost-effectiveness analysis was performed using PET-CT alone as the reference strategy. Comparison was done based on incremental effectiveness and cost between strategies that included (as either first or second diagnostic choice) or excluded PET-CT in the management. Incremental effectiveness was measured based on the difference in expected average life expectancy between the PET-CT + other strategy and the reference strategy. Incremental costs were evaluated using similar reference strategy.

The cost- effectiveness analysis was based on an incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs by the incremental effects of 2 strategies according to the following formula with T for test strategy and REF as reference strategy:

$$\text{ICER} = \frac{\text{(COST (T) – COST REF)}}{\text{(LIFE EXPECTANCY (T) – LIFE EXPECTANCY REF)}}$$

The most cost-effectiveness strategy was defined as the lowest ICER. Sensitivity analysis was performed on all key variables (such as the cost of an FDG PET study or the specificity of a CT study) to analyse sensitivity of the cost savings, baseline value and life expectancy to variation of the variables.

RESULTS AND DISCUSSION

Cost effectiveness analysis perspectives study: Phase I

Results from Phase I showed that the clinicians perceived views of the various issues on practicality, clinical efficacy and cost-effectiveness of PET-CT introduction in esophageal cancer management was compared with reference to the participants' field of speciality. Most of the questions included in this survey werepositive based questions. Based on the analysis done, the majority of the participants showed a tendency of agreement towards positive trends (agree or strongly agree) in 9 out of 15 questions included in this survey ranging from 31.5% up to 49.3%. In 10 out of 15 questions, a negative trend of opinion (disagree or strongly disagree) could be seen from the data analysis which summing up the questions with lowest percentage of feedback ranging from 1.4% to 4.1%. Comparative details of the trend rate analysis finding from this survey were shown in Figure 3.

Number	Ratings / Questions	0 No Answer	1–2 Strongly Disagree / Disagree	3 Neutral / No opinion	4–5 Agree / Strongly Agree
Practicality					
Q1	PET-CT studies are easily available to be included in any stage of patient management whenever needed.	1.4%	42.4%	12.3%	43.8%
Q2	PET-CT studies enable the physician to avoid any tests or procedures that are usually will be included as part of the management?	4.1%	35.6%	20.5%	39.7%
Q3	If PET-CT were not available, would you have done some type of alternative assessment in most of the cases?	1.4%	26%	28.8%	43.8%
Clinical Efficacy					
Q4	PET-CT is useful for clinical studies for the detection, staging in clinical management of oesophageal cancer.	1.4%	5.4%	9.6%	83.5%
Q5	PET-CT is useful for clinical studies for follow up on disease progression in clinical management of oesophageal cancer.	1.4%	17.8%	32.9%	47.9%
Q6	PET-CT studies altered the initial course of clinical management for oesophageal cancer.	1.4%	9.5%	12.3%	76.7%
Cost Effectiveness& Service Delivery					
Q7	PET-CT is cost-effective because the modality is precise for staging disease, improve treatment plans and avoid unnecessary treatments for oesophageal cancer	1.4%	9.5%	26%	63.1%
The only drawback to include PET-CT study in patient management is the limitation to its availability due to: (Tick one or more):					
Q8a	Financial Issues	5.5%	23.2%	17.8%	53.4%
Q8b	Availability of Isotopes	4.1%	28.7%	13.7%	53.4%
Q8c	Access to Equipment	8.2%	28.8%	43.8%	19.1%
(Q9a-Q9e)	Shortage of Staff				
Q9a	• PET-CT Technician	8.2%	21.9%	57.5%	12.3%
Q9b	• Reporting Staff (Radiologist, Nuclear Medicine Specialist,etc)	6.8%	30.1%	39.7%	23.3%
Q9c	• End-user staff (Oncologist, Surgeon, etc)	8.2%	34.2%	46.6%	11%
Q9d	Training for staff	8.2%	28.8%	45.2%	17.8%
Q9e	Bureaucracy (e.g.: Long waiting list)	9.6%	24.6%	41.1%	24.6%

Fig.3 Trend rates survey analysis shows positive agreements for practicality (min = 39.7%) and clinical efficacy (min = 47.9%) and neutral opinion for cost effectiveness (min = 39.7%)

Analysis done on practicality topic showed a mirror compatibility of findings with topics covering clinical efficacy of this modality in clinical practice. In both topics, the majority of respondents showed tendency towards positive agreement with the statement (agree or strongly agree) and lowest percentage trends could be seen from respondents who did not answer the survey ranging from 1.4% to 4.1%. Positive trends of agreement could be seen in the majority of respondents on practicality topic and might be associated with the fact that despite of an increase in demand of PET-CT scans for patients in North West, the practicality for application in clinical practice was still restricted due to the limited availability of this modality in North West. Thus they have to use their good clinical judgement to use other alternative modalities or procedures available locally to deliver the best services for their patients.

Trend rate analyses for topics covering cost-effectiveness have found an uncommon finding in comparison to other topics. Interestingly, the majority of feedback related to limiting factor associated with the availability of PET-CT showed that the majority of feedback (6 out of 9 question) was skewed towards neutral or no opinion at all (39.7% - 57.5%) in contrast to other questions in other topics as in practicality and clinical efficacy. Also, the lowest percentage of respondent for this topic was came from respondents who strongly agreed with the statement (0% -2.7%), which showed a strong contrast to findings in comparison to other topics results. This might be due to these topics were not something within the respondents' responsibilities or expertise as their speciality was more devoted towards assessment on clinical application and practicality of this procedure in medical practice.

Cost Effectiveness Analysis Intervention Study: Phase II, III & IV

Data from Phase II and III was used as modelling analysis baseline data in Phase IV. The presentation of base deterministic results from the modelling analysis in Phase IV weere for all of the strategies included in the studies that based on the QALYs outcomes, avoidance of diagnostic errors and case of esophageal cancer appropriately diagnosed and treated were presented as shown in Table 1. The results were presented in terms of cost per QALYs. The least costly diagnostic strategy provided the lowest numbers of QALYs was the conventional work up. PET in comparison with conventional work up has a mean cost of £ 11474.00 and was £ 2180.00 more costly. The incremental QALY gained was 0.0766 with total effectiveness of 4.8394 compared with conventional work up. These diagnostic strategies have an estimated ICER of £ 28460.00 per QALY. This indicated that there was an incremental cost of £ 28460.00 for every additional QALY from PET.

Table 1 Base-case results from the analysis cost per QALY

Strategy	Mean cost/ strategy (£)	Difference in costs (£)	Effectiveness (QALY)	Incremental QALYs	ICER(£)
Conventional work-up	9094	-	4.7628	-	-
PET	11474	2180	4.8394	0.0766	28460
PET/CT	12380	906	4.8672	0.0278	32590
PET/CT + conventional work-up	13730	1350	4.8978	0.0306	44118

PET/CT resulted in £ 906.00 higher but has an incremental QALY gained of 0.0278 in comparison with PET alone. The estimated ICER between PET /CT and PET was approximately £ 32590.00. The final comparison between the diagnostic strategy showed that PET/CT combined with conventional work up has a mean cost of £ 13730.00 and cost approximately £ 1350.00 more than PET/CT with total effectiveness of 4.8978 QALYs, which was an incremental gain of 0.0306 compared with PET/CT. PET/CT in adjunct with conventional work up has an ICER of £ 44118.00 per QALY.

The ICER for the strategy of PET compared with conventional work-up was estimated at £28,460 per QALY; the ICER for PET/CT compared with PET was £ 32,590 per QALY; and the ICER for PET/CT combined with conventional work-up versus PET/CT was £ 44,118. Clearly, for each additional diagnostic test that was added to PET, not only the more expensive the package became, but also the more effective it became in terms of QALYs gained. The probabilistic sensitivity analysis showed that at a willingness-to-pay threshold of £ 20,000 per QALY, conventional work-up was the preferred option.

CONCLUSION

This project was one of the very few researches that assessing cost effectiveness of PET-CT introduction in the management of patients with esophageal cancer, giving a brief overview on the economic values of PET-CT. A major strength of this research was the cost-effectiveness analysis using Tree-Age modelling software alongside a survey on clinicians' perceived views on this modality practicality, clinical efficacy, cost effectiveness and service delivery, a study design that iswas scarcely covered in other research published to date. Furthermore, a full health care sector perspective was used rather than estimation of prices, increased the level of findings reliability to estimate the real economic values of PET-CT in esophageal cancer management.

This study has limited follow up information and relatively short to provide enough information on the quality of life for patients with esophageal cancer. In addition to this, therewas also limited information on types and length of treatment for individual patients, thus added a significant bias to the economic modelling analysis in this study.

In a world where financial resources were limited, a decision to introduce any diagnostic procedures or interventions required an economic evaluation that conducted further than clinical effectiveness measurement using a combination of cost and outcome of the distinctive diagnostic procedures or intervention.

Imaging roles for patient management needed to be in parallel with current clinical practice and kept up to date with new findings in research. From the initial steps of diagnosis, imaging played a pivotal task in the assessment of the extent and distribution of disease, thus providing the best accurate information to be used in multi-disciplinary team decision for the best outcome of treatment. Based on the current model and the limitations given that were apparent in terms of limited availability of data, the result of the current analysis suggested that the use of PET/CT in the diagnosis of esophageal cancerwas unlikely to be cost-effective, given the current willingness-to-pay thresholds that wereaccepted in the UK by decision-making bodies such as the National Institute for Health and Clinical Excellence.

The economic modelling suggested that conventional work-up could be the most cost-effective diagnostic strategy based on given current data. Future studies needed to secure robust cost data that could be verified from more than one source for the diagnostic tests involved in PET and PET/CT. Reliable and verifiable data on quality of life associated with this clinical condition were also crucial.

In the management of esophageal cancer or any other terminal diseases, aims of treatment were to achieve long term survival benefits that in clinical practice have always been balanced by the significant toxicity and costing expenses of chosen treatments. Economic burden of disease management, with choice of treatments as the main cost driver made it essential to perform a thorough imaging evaluation to find the best treatment paradigm for each patient. Hybrid imaging, as in this study was focused on PET-CT costing impact on esophageal cancer management using population based approach which played a role in patient's decision making process.

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REFERENCES

Bar-Shalom, R., Guralnik, L., Tsalic, M., Leiderman, M., Frenkel, A., Gaitini, D.,Israel, O. (2005). The additional value of PET/CT over PET in FDG imaging of esophageal cancer. *European journal of nuclear medicine and molecular imaging, 32*(8), 918-924.

Culyer, A. J., & Newhouse, J. P. (2008). *Handbook of health economics Vol. 1A Vol. 1A*. Amsterdam [u.a.: Elsevier.

Dehdashti, F., & Siegel, B. A. (2004). Neoplasms of the esophagus and stomach. *Semin Nucl Med, 34*(3), 198-208.

Eslick, G. D. (2009a). Epidemiology of esophageal cancer. *Gastroenterol Clin North Am, 38*(1), 17-25, vii. doi:10.1016/j.gtc.2009.01.008

Eslick, G. D. (2009b). Esophageal cancer: a historical perspective. *Gastroenterol Clin North Am, 38*(1), 1-15, vii. doi:10.1016/j.gtc.2009.01.003

Findlay, J. M., Bradley, K. M., Maile, E. J., Braden, B., Maw, J., Phillips-Hughes, J., . . . Middleton, M. R. (2015). Pragmatic staging of esophageal cancer using decision theory involving selective endoscopic ultrasonography, PET and laparoscopy. *BJS British Journal of Surgery, 102*(12), 1488-1499.

Griffin, S. M., & Wahed, S. (2011). Esophageal cancer. *MPSUR Surgery (Oxford), 29*(11), 557-562.

Guignard, R., Ouvrier, M. J., Krug, B., Otte, A., Darcourt, J., & Dierckx, R. A. J. O. (2014). ¹⁸F-Fluorodeoxyglucose PET Procedures: Health Economic Aspects in Neurology.

Kigula-Mugambe, J. B., & Kavuma, A. (2015). Cancer of the Oesophagus.

Krug, B., Crott, R., Roch, I., Lonneux, M., Beguin, C., Baurain, J.-F., . . . Borght, T. V. (2010). Cost-effectiveness analysis of FDG PET-CT in the management of pulmonary metastases from malignant melanoma. *SONC Acta Oncologica, 49*(2), 192-200.

Noble, F., Bailey, D., Panel, S. U. G. T., Tung, K., & Byrne, J. P. (2009). Impact of integrated PET/CT in the staging of esophageal cancer: a UK population-based cohort study. *Clin Radiol, 64*(7), 699-705. doi:10.1016/j.crad.2009.03.003

Pauly, M. V., McGuire, T. G., & Barros, P. P. (2012). *Handbook of health economics. volume 2 volume 2*. Amsterdam: Elsevier, North Holland.

Rudmik, L., & Drummond, M. (2013). Health economic evaluation: Important principles and methodology. *LARY The Laryngoscope, 123*(6), 1341-1347.

Schulthess, G. K. v. (2007). *Molecular anatomic imaging : PET-CT and SPECT-CT integrated modality imaging*. Philadelphia, PA: Lippincott Williams & Wilkins.

Schulthess, G. K. v. (2016). *Molecular anatomic imaging : PET/CT, PET/MR, and SPECT/CT*.

Szyszko, T. A. (2016). PET/CT in esophageal and gastric cancer.

Torrance, A. D. W., Almond, L. M., Fry, J., Wadley, M. S., & Lyburn, I. D. (2015). Has integrated 18F FDG PET/CT improved staging, reduced early recurrence or increased survival in esophageal cancer? *SURGE The Surgeon, 13*(1), 19-33.

Wong, W. L., & Chambers, R. J. (2008). Role of PET/PET CT in the staging and restaging of thoracic esophageal cancer and gastro-esophageal cancer: a literature review. *Abdom Imaging, 33*(2), 183-190. doi:10.1007/s00261-007-9241-1