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The value of positron emission tomography in patients with non-small cell lung cancer

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ABSTRACT

Background: Pre-operative assessment of non-small cell lung cancer (NSCLC) is a major application of positron emission tomography (FDG-PET). Despite substantial evidence of diagnostic accuracy, relatively little attention has been paid to its effects on patient outcomes. This paper addresses this by extending an existing decision model to include patient-elicited utilities.

Patients and methods: A decision-tree model of the effect of FDG-PET on pre-operative staging was converted to a Markov model. Utilities for futile and appropriate thoracotomy were elicited from 75 patients undergoing staging investigation for NSCLC. The decision model was then used to estimate the expected value of perfect information (EVPI) associated with three sources of uncertainty—the accuracy of PET, the accuracy of CT and the patient related utility of a futile thoracotomy.

Results: The model confirmed the apparent cost-effectiveness of FDG-PET and indicated that the EVPI associated with the utility of futile thoracotomy considerably exceeds that associated with measures of accuracy.

Conclusion: The study highlights the importance of patient related utilities in assessing the cost-effectiveness of diagnostic technologies. In the specific case of PET for pre-operative staging of NSCLC, future research effort should focus on such elicitation, rather than further refinement of accuracy estimates.

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1. Objectives

The National Cancer Research Institute (NCRI) recently set out a rationale for future research on the use of positron emission tomography (PET) in cancer care [1]. A highlighted theme is the need to ensure that patient outcomes and cost-effectiveness are addressed. In devising its overall strategy, the NCRI was rightly guided by the Fryback and Thornbury framework for technology appraisal [2] that reminds us that technical imaging quality, diagnostic accuracy and ability to change management may count for little if patient outcomes cannot be improved.

FDG-PET is increasingly being used in the management of non-small cell lung cancer (NSCLC). The most comprehensive evidence based report about the use of FDG-PET in NSCLC was produced in 2002 by the Health Technology Board for Scotland (HTBS, now Quality Improvement Scotland, QIS) [3]. There have been subsequent systematic reviews [4,5] but to date there have been only two ran-

domized controlled trials in this area, the Dutch PLUS Study [6] and the Australian trial published by Viney et al. [7]. Both randomized patients to either standard workup with or without FDG-PET. The Dutch trial suggested PET halved the futile thoracotomy rate whereas the Australian trial found no statistically significant difference. This divergent outcome may be partly explained by different definitions used for futile thoracotomy. However, since the publication of these results, PET imaging, particularly using CT-PET with better image quality, is recommended for all patients receiving potentially curative therapy (surgery or radical radiotherapy). With the lack of good randomized trials examining clinical effectiveness decision modeling can be used to investigate the possible implications of the additional information gained from FDG-PET, from the patient's perspective.

The model developed for the HTBS report was a straightforward decision-tree, constructed to reflect the experience of a "typical 62-year old man" with no co-morbidities. The authors of the HTBS report felt that the model could be improved with better data on real clinical outcomes, such as survival rates by stage and treatment, and with utilities for PET-determined health states obtained from patients or the general public. In addition, though thoracotomy can

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carry significant risks of morbidity and mortality (up to 1 in 20 in some centres [8]), no one has yet determined the value that a patient might place on an avoided “futile” thoracotomy. Utility is a measure that reflects the strength of a patient’s preference for an outcome. Taking the value of 1 as being equivalent to full health and zero as a state that is as bad as being dead, other health states can be ranked and valued according to their inherent unpleasantness, to reflect the patient’s preferences for those health states. In fact there have been no empirical studies that have tried to elicit utilities directly for NSCLC patients undergoing PET tests. Those employed by the HTBS model were taken from earlier reports by Berthelot et al. [9] and Marshall et al. [10] using estimates made by oncologists rather than from patients themselves.

Therefore, the aims of this study were

- to convert the HTBS decision model for use of FDG-PET in NSCLC into a Markov model and thence assess the impact of variations in the patient’s age and survival experience on the cost-effectiveness of two specific investigation strategies
- to prospectively elicit utilities for PET-determined health states from real patients undergoing investigation for presumed non-small cell lung cancer
- to incorporate these into the decision model in order to evaluate their impact on the cost-effectiveness of the same two investigation strategies
- to explore how uncertainty in patient-derived utility and the possible uncertainty surrounding the accuracy of the technology itself might affect the decision to adopt one or other strategy.

2. Design and methods

The two strategies considered in this report are based on standard investigations for a patient with pathologically confirmed NSCLC (CT scan ± bronchoscopy) referred for surgery.

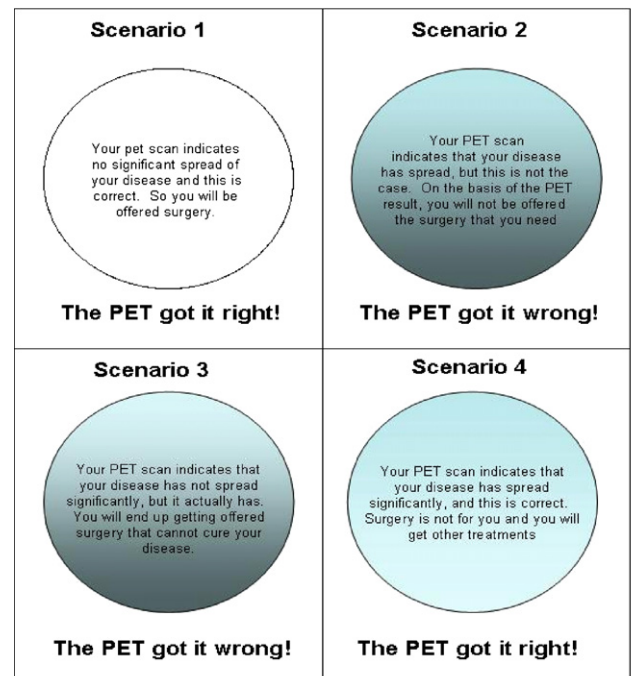
Thereafter either:

- All patients will undergo a mediastinoscopy to biopsy mediastinal lymph nodes. If negative, they will proceed to surgery and if positive, they will be referred for chemo-radiation.
- All patients have an FDG-PET scan. If the scan is negative (no distant or mediastinal node spread) then the patient will undergo surgery. If the PET scan is positive (spread to nodes (N2/3) or distant sites (M1)) the patient is referred for non-surgical management.

Most of the key assumptions and inputs for the decision model as given in the original HTBS report [3] are given in Appendix A. Among the most important inputs – of relevance to patient outcomes – is the patient utility for PET-determined health states.

Seventy-five patients diagnosed with NSCLC were interviewed by a research nurse prior to their PET scan and asked to rate, on a Visual Analogue Scale, each of the following outcomes (actual questionnaire available in the on-line version [Appendix B and Fig. 1]):

- the PET test shows no evidence of regional or distant spread and patient receives potentially curative surgery (true negative);
- the PET investigation shows evidence of loco-regional or more distant spread which rules out the possibility of curative surgery (true positive);
- the PET shows no evidence of regional or more extensive spread but incurable disease is found at thoracotomy or recurrence occurs within six months (“futile thoracotomy” constituting a false negative); and



Please make a mark on the line below indicating the relative desirability of these possible outcomes, using the appropriate colour.



Fig. 1. Assessment of patients valuation of PET determined states.

- the PET falsely indicates some evidence of spread (false positive) and potentially curative surgery is inappropriately abandoned.

Since patients of different ages have different prognoses, the HTBS decision-tree model was converted into a Markov model using the actual survival of a cohort of patients diagnosed with NSCLC in Scotland in 1995 and for whom at least five years of follow-up was available [11]. Four types of patient were represented in the model: (i) patients with N0/1 disease whose primary treatment was thoracotomy; (ii) patients with N2/3 disease who also received surgery (a futile operation); (iii) patients with N2/3 disease whose primary management was chemo-radiation; and (iv) patients with more extensive disease (M1) given palliative treatment. The model was built in TREEAGE [12].

Required transition probabilities (the probabilities of surviving each month over an 84-month follow-up period) were estimated from Weibull models fitted to the Scottish data using STATA [13]. An example showing the syntax, model fit and estimated probabilities is available from the authors and in the on-line supplementary material (Appendix C). The four tables of transition probabilities were then imported into TREEAGE.

A Monte Carlo sensitivity analysis was conducted to assess sensitivity to the major sources of uncertainty as described by the HTBS report: patient utility for futile thoracotomy and the true positive rates (TPR) of PET and CT. The distributions for PET and CT TPR are estimated from the results in Gould et al. [14]. PET TPR was assumed to follow a Beta (42, 9) distribution in CT-negative patients and a Beta (32, 5) distribution in CT-positive patients. CT TPR follows a Beta (111, 77) distribution.

The distribution used for the utility of futile thoracotomy was obtained from the patient survey which was used to derive a

Table 1
Incremental cost effectiveness of diagnostic strategies for suspected NSCLS with and without PET.

Strategy	Cost	Incr Cost	Eff	Incr Eff	C/E	Incr C/E (ICER)
For a 50-year old						
Without PET	£4,827		2.3129 qaly		£2,087	
With PET	£4,994	£166	2.3377 qaly	0.0248 qaly	£2,136	£6,704
For a 60-year old						
Without PET	£4,827		2.0450 qaly		£2,361	
With PET	£4,994	£166	2.0648 qaly	0.0198 qaly	£2,418	£8,385
For a 70-year old						
Without PET	£4,827		1.7450 qaly		£2,766	
With PET	£4,994	£166	1.7607 qaly	0.0156 qaly	£2,836	£10,636
For an 80-year old						
Without PET	£4,827		1.4267 qaly		£3,384	
With PET	£4,994	£166	1.4388 qaly	0.0121 qaly	£3,471	£13,785

weighting of the utilities used in the HTBS model. The results of the VAS scoring (Appendix D) of the four possible PET outcomes were used as follows: on a per-patient basis the ratio of the VAS scores for the false negative (FN) to the true negative (TN) states was calculated (FN_{VAS}/TN_{VAS}) to give an indication of the dis-utility of futile surgery. This was used as a weighting to be applied to the utility values for the futile thoracotomy state.

Heterogeneity is accounted for by deriving incremental cost-effectiveness ratios (ICERs) separately for patients in different age groups.

The Monte Carlo sensitivity analysis was used to generate two outcomes. First, a summary estimate of the probability that the PET-containing strategy is the more cost-effective, at any given value of willingness to pay (often shown graphically in a cost-effectiveness acceptability curve, or CEAC [15]; second, an estimate for each of the three uncertain quantities of the expected value of perfect information (EVPI) [16]. The EVPI is an estimate of the maximum amount we might wish to pay for perfect information on a particular variable (i.e. in order to minimize the uncertainty surrounding the variable) and can be a useful way to characterize the importance of uncertainty in a particular variable for the decision at hand.

One thousand iterations were initially employed in the Monte Carlo simulation to derive CEACs for patient utility, CT accuracy and PET accuracy separately. The simulation was then allowed to run for 5000 iterations when the three variables were permitted to vary simultaneously. In each case, the EVPI was derived using standard syntax in the TREEAGE package.

The study received approval from the local Medical Ethics Committee.

3. Results

Using only the base-case values for the HTBS model, updated to include a weighting factor for patient-derived utility (the average over the 75 patients interviewed) and the updated values for sensitivity for PET from Gould et al. [14], Table 1 summarizes the comparison of “without PET” and the “with PET” strategies in a Markov version of the HTBS model. The figures shown are averages, across all iterations for separate age groups.

Thus the incremental cost-effectiveness ratios (the cost per Quality Adjusted Life-Year) associated with the decision to opt for a strategy with PET rather than strategy without PET for 50, 60, 70 and 80 year-old patients are £6704, £8385, £10,636 and £13,785, respectively, all of which are well below the notional threshold (of ~£30k) adopted by the National Institute for Health and Clinical Excellence and are broadly in keeping with those originally derived in the HTBS report.

Cost-effectiveness acceptability curves (CEAC) provide an indication of the uncertainty surrounding any conclusions that we may

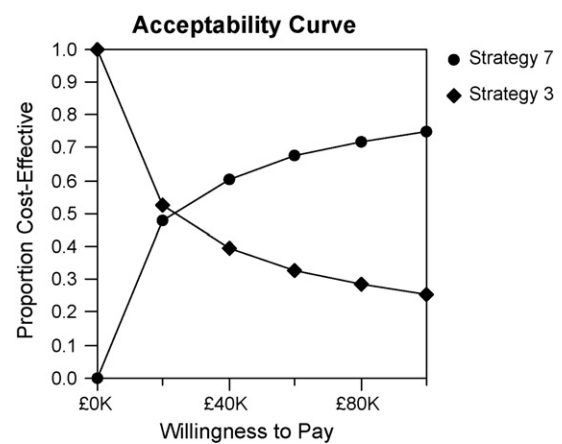


Fig. 2. Cost-effectiveness acceptability curve for 80-year old patients.

wish to draw from the above table. In each case the judgment of whether a particular strategy is “cost-effective” is made against a threshold of £30k, the y-axis indicating the proportion of iterations with an incremental cost-effectiveness ratio below that value. Many CEACs were generated for this study but an example only is provided in Fig. 2 which shows that among the oldest age group (e.g. the 80-year olds), it is clear that neither strategy has a more than 60% chance of being judged cost-effective at the notional threshold lambda of ~£30k. (“Strategy 7” represents the HTBS label for a pathway with PET and “Strategy 3” one without PET.)

The expected value of perfect information associated with each of the three main variables, separately and together, is shown in Table 2. It suggests that variation in patient utility for futile thoracotomy has a much more marked bearing in the two oldest age groups and is likely to be the most dominant variable affecting the overall decision to adopt one or other strategy when all three vary together.

4. Discussion

The National Institute for Health and Clinical Excellence and the recent report from NCRI both emphasize the importance of the health economic perspective to technology appraisal but remind us that the efficiency of a technology is context-specific and so questions of “transferability” inevitably arise [17]. Whether implementing a particular technology will maximize the clinical dividend at acceptable cost will have much to do with the specific clinical context [18]. This report has extended the 2002 HTBS model to conduct a probabilistic sensitivity analysis of the cost-effectiveness of PET scanning in the management of NSCLC and has addressed some specific questions posed in that report. In particular we have updated

Table 2
Expected value of Perfect Information for key variables.

Age	Expected value of perfect information (for each variable and for all variables combined)			
	Utility for futile thoracotomy	PET TPR	CT TPR	All three together
50	-4.66	1.02	0	9.72
60	5.65	1.02	0	24.35
70	40.82	0	0	45.05
80	73.51	0	0	76.42

Figures shown are £ value per patient.

the former report to account for the preferences of real patients (rather than proxies) and determined, using expected value of perfect information analysis, the relative importance of the factors affecting the cost-effectiveness of the technology in this setting.

By accounting for variable patient survival in a Markov model, it has confirmed that a work-up strategy for such patients that includes PET would be cost-effective across a range of age groups. However, the variation between patients in the utility of a futile thoracotomy, particularly among the oldest age groups, is likely to have a greater impact on the cost-effectiveness of the technology than imprecision in the estimate of PET's sensitivity for detecting N2/N3 disease.

The robustness of these conclusions needs to be considered in light of any possible methodological limitations of the analysis.

4.1. The method of utility assessment

Probably the generally held consensus among health economists is that Visual Analogue Scores do not alone provide the best utility measure [19]. However, there have been relatively few studies of the utilities of real patients for the outcomes of surgical and non-surgical treatment of lung cancer. Cykert et al. studied 64 patients (45 of whom had a non-cancerous pulmonary condition) and employed a standard gamble approach to study patient preferences for the outcomes of lung resection. Although the shorter term outcomes such as ventilator dependence had utilities between 0.7 and 0.8 (close to the value used in the HTBS report), the longer term states characterized by, for example, reduced exercise tolerance were associated with much lower utilities, below 0.5. On the other hand Brundage et al. elicited patient preferences using a novel "treatment trade-off" approach but limited their study to comparing radiotherapy and chemotherapy [20]. A further study, by Raab and Hornberger evaluated the patient's attitude to the risk posed by some of the investigations that NSCLC patients might face, such as bronchoscopy, fine needle aspiration and mediastinoscopy [21]. They concluded that risk-taking attitudes among patients, associated with different testing strategies, affect cost-effectiveness in significant ways.

Nevertheless, there have been some spirited defenses of the simpler Visual Analogue Scale approach [22]. One of the few studies to attempt to discover the (*dis*-)utility of wrong diagnoses (relating to pulmonary embolism rather than lung cancer, however) was that by Rosen and Hornberger [21] who also used a VAS approach. Unfortunately the views elicited were those of doctors (not patients) and their method for deriving the utility of *inappropriate* treatment was to subtract the utility of a false positive scan result from the utility of a true negative result. We on the other hand, have used the ratio (FN_{vas}/TN_{vas}) to give an indication of the *dis*-utility of futile surgery, applying these ratios to the utility values used in the previously published HTBS report. We suspect that the appropriateness of a ratio or difference measure would depend on the context, the underlying disease and potential treatment. In Rosen's pulmonary embolism example, a true negative case would not receive any treatment whereas someone with NSCLC whose PET scan is negative will actually receive major surgery.

In designing the patient interview schedule for the present study, a potential patient had to consider potentially four types of risks: (i) the risks that the test gets the wrong result; (ii) the risks that a test itself could have an adverse effect (e.g. bleeding after mediastinoscopy); and (iii) the risks to health outcomes posed by the treatments themselves (dictated by the test results); and (iv) the risks posed as part of the standard gamble technique itself. After a small pilot, we found that it would be very difficult for an already anxious patient to discriminate and weigh these different risks and therefore concluded that the standard gamble approach was not appropriate.

Given the EVPI results (discussed later), it is clear that the method of utility assessment for appropriately and inappropriately treated patients could have a significant bearing on cost-effectiveness analyses in this area especially among older patient groups.

4.2. The analytic approach

Summary cost-effectiveness acceptability curves were employed as the main output of the probabilistic sensitivity analysis. These have been widely interpreted as representing the probability that the intervention is cost-effective given the data. However, this is only valid within a Bayesian framework where parameters are assumed to be random variables with associated probability distributions. In reality, of course, CEACs represent only half the story. A fully Bayesian decision-making approach would also examine the loss function associated with decision-making and examine the expected value of perfect information with regard to collecting more information on uncertain parameters.

A decision to adopt a technology made on the basis of existing information will be uncertain. There will always be a chance that the wrong decision has been made and if it is, health benefits will be foregone. Therefore, the expected cost of uncertainty is determined jointly by the probability that a decision based on existing information will be wrong and the consequences of that decision. The expected value of perfect information thus places an upper limit on the value of doing further research to reduce the uncertainty [23]. Although not all of the model's parameters were studied in this report, the EVPI has been estimated for those that were identified as important in the preliminary sensitivity analysis of the HTBS report.

4.3. Implications for future research

The evolution of diagnostic technologies like PET is never going to stand still and though regulatory bodies such as NICE strive for the highest possible standards of evaluation, the Frybeck and Thornbury hierarchy presents major challenges. While technology assessment is not a one-time exercise, evidence (even in the form of a gold-plated RCT) may be necessary but alone it is not sufficient to improve patient outcomes. Perhaps the greater challenge is to enlighten clinicians and policy makers about how to identify what has most bearing on the cost-effectiveness of new technologies [24]. There are techniques that will also help us decide whether

the pay-back from future studies is likely to be sufficient to justify their expense and whether they should focus on one aspect of the decision problem or another.

In the particular case of PET (or indeed PET-CT) for staging NSCLC, our results clearly show that uncertainty about patient preferences and attitudes to decision-making exceeds the uncertainty about the accuracy of PET for this indication, and research should focus on this. The current study has elicited these before the PET scan and hence before the patients actually experienced the outcomes of that test, using a simple VAS. There is a clear need to investigate the possible impact of different measurement tools, and to extend this work to larger samples of patients and to other cultural settings in which attitudes to risk may differ.

It is possible, indeed likely, that if the patients were interviewed three or six months after treatment (whether futile or otherwise) some patients may regret their previous choices and though there are validated scales with which to measure regret [25], it is not clear whether retrospective views are necessarily better than prospectively stated ones or how they should be used in cost-effectiveness appraisals of diagnostic tests. This is clearly also an area meriting further study. However, on a more fundamental point, health economists are still divided about whether cost-effectiveness models should use the utilities of patients themselves or those of a random sample of population [26]. We believe most people would agree that when the avoidance of a mutilating but potentially useless thoracotomy is at stake, ethical clinical practice would guide us to seek out the patient's own viewpoint.

More generally, the impact of patient preferences and desires on the cost-effectiveness of PET scanning, and other diagnostic tests has been investigated less thoroughly than the impact of increased technical accuracy. Our results suggest that further attention should be paid to the preferences of patients. Perhaps, as Woolf and Johnson have suggested, medical advances have "break-even" points that are more dictated by the fidelity with which they are delivered than by the underlying technology itself [27].

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Contributions: F.K. conceived and designed the study, undertook the analysis and drafted the manuscript. K.C. provided training and guidance on the Treeage models. I.B. quality assured the model structure against the original HTBS model and assisted in the analysis of the previous meta-analyses. S.E. provided cancer registry follow-up data for NSCLC patients in Scotland and along with all authors, contributed to the final version of the manuscript.

Appendix A

A.1. Utilities assigned: base case

Stage of disease	Treatment	Utility	Based on
N0/N1, M0	Surgery	0.88	Earle's figure for local disease
N2/N3, M0	Surgery	0.65	Berthelot's figure for advanced disease which responds to treatment
N0/3, M1	Surgery	0.65	Berthelot's figure for advanced disease which responds to treatment
N0/N1, M0	Non-surgical treatment	0.65	Berthelot's figure for advanced disease which responds to treatment
N2/N3, M0	Non-surgical treatment	0.65	Berthelot's figure for advanced disease which responds to treatment

Appendix A (Continued)

Stage of disease	Treatment	Utility	Based on
N0–3, M1	Non-surgical treatment	0.65	Berthelot's figure for advanced disease which responds to treatment

A.2. Inputs to the HTBS economic model: base case

Variable	Input/assumption
Base-case patient	62-year-old fit for surgery or non-surgical treatment
Prevalence of N2/N3	30%
FDG-PET sensitivity	CT-negative 86%; CT-positive 92%
FDG-PET specificity	CT-negative 90%; CT-positive 76%
Mediastinoscopy:	
Specificity	100%
Sensitivity	72%
CT and PET mortality	0%
Mediastinoscopy mortality	0.5%
Surgery mortality	3.7%
Life expectancy (LE) after surgery	N0/1, M0 4.5 years
	N2/3, M0 1.8 years
	M1 0.5 years
LE after palliation	N0/1, M0 2.6 years
	N2/3, M0 1.8 years
	M1 0.5 years
Cost of thoracic FDG-PET	£677
Cost of mediastinoscopy	£375
Cost of surgery	£3,419
Non-surgical treatment:	
Radical radiotherapy	£2,102
Chemotherapy	£4,003
Best supportive care	£3,371

Appendix B

The wording of the elicitation task was as follows:

"What we want you to do is to assign a score, from 0 to 100, according to your strength of preference for each of the outcomes after the various possible results of your scan. You may indicate your score on the horizontal line on the SHOWCARD, which has been anchored at one end by the "The best possible outcome" and at the other by "The worst possible outcome". Give your response imagining that you would be receiving the treatment recommended, based on the PET scan results".

Scenario 1.

Your PET scan indicates that there is no significant spread of the disease (that would otherwise rule out surgery) and this corresponds to the true state of reality. Thus surgery would be indicated and will be offered in an attempt to cure the disease.

Scenario 2.

Your PET scan suggests that the disease has spread (to an extent that surgery is unlikely to be offered), but this does not correspond to the true state of reality, that is to say, actually the spread of the disease is *not significant*. Nevertheless, based on the scan results you will not be offered surgery, and other treatments such as chemotherapy or radiotherapy will be deemed more appropriate for you.

Scenario 3.

Your PET scan indicates that there is no significant spread but in reality this is not the case. Any surgery you will be offered on the basis of the scan results, will not cure the disease.

Scenario 4.

Your PET scan indicates that the disease has spread beyond a point when surgery can cure the disease and this corresponds to the true state of reality. Surgery will not be offered and other treatments, such as radiotherapy or chemotherapy, represent better options to control symptoms of the disease at this stage.

Appendix C

Initial survival analysis using STATA

```
. use "C:\FRANK\Lung cancer\Operable lung cancer.dta", clear
. table clone
```

clone	Freq.
surgical - localised disease	244
surgical - regional spread	148
non surgical - regional spread	351
none or non-surgical - metastatic spread	567

```
. stset time84 ,failure(status84=1)
```

```
failure event: status84 == 1
obs. time interval: (0, time84]
exit on or before: failure
```

```
-----
5906 total obs.
  4 event time missing (time84>=.)
5902 obs. remaining, representing
5551 failures in single record/single failure data
73216.08 total analysis time at risk, at risk from t = 0
                                     earliest observed entry t = 0
                                     last observed exit t = 84
```

Cox Model analysis (stratified by clone) showing lack of significance of gender.

```
. stcox age gender , strata(clone) nohr
```

Stratified Cox regr. -- Breslow method for ties

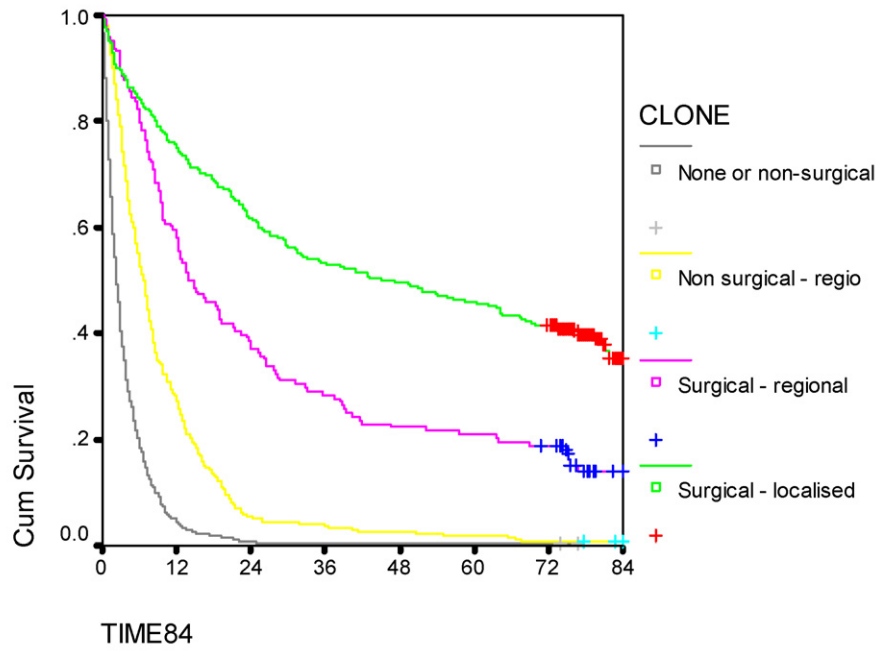
No. of subjects =	5902	Number of obs =	1310
No. of failures =	5551		
Time at risk =	73216.07904		
Log likelihood =	-6030.9131	LR chi2(2) =	27.14
		Prob > chi2 =	0.0000

_t	Coef.	Std. Err.	z	P> z	[95% ConfInterval]
age	.0171902	.0034484	4.99	0.000	.0104315 .0239488
gender	-.0726527	.0624793	-1.16	0.245	-.1951098 .0498044

Stratified by clone

Appendix C (Continued)

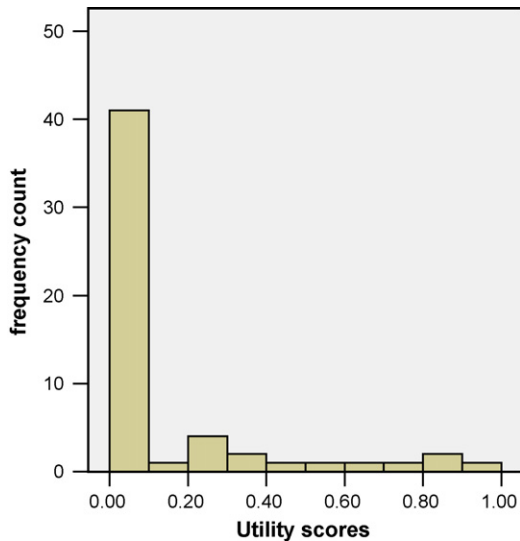
Survival Functions



Clone	Median Survival Time	Standard Error	95% Confidence Interval
Surgical - localised disease	45.00	9.59	(26.19, 63.81)
Surgical - regional spread	13.85	2.31	(9.31, 18.38)
Non surgical - regional spread	6.74	.39	(5.98, 7.51)
None or non-surgical - metastatic spread	2.30	.16	(2.00, 2.61)

Appendix D

Distribution of utility weightings used in the Monte Carlo simulation.



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