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ABSTRACT

In 1990, a study was published (Moertel CG, et al 1990) which recommended a new treatment standard for colon cancer: a 52 week course of adjuvant chemotherapy. The study recommended that such a course of chemotherapy administered after surgical resection could increase five year survival from 55% to 71%. However, this recommendation raised several concerns, particularly about the quality of life of patients undergoing such a long course of chemotherapy and the costs to the health care system of such a prolonged therapy. This paper sought to address both of these issues in the context of an economic evaluation.

The cost of surgery plus chemotherapy was estimated and compared with the cost of surgery alone. Descriptions of quality of life were developed from interviews with patients and health professionals, and the time trade off technique was then used to derive utility weights (from a small sample of 16) which were used to adjust length of life to reflect quality, in terms of a "quality adjusted life year" (QALY). Expected survival with and without chemotherapy was based on published data.

Chemotherapy increased the total cost of treating a patient with colon cancer by $7,010 per year, from $6,012 to $13,022. The extra benefit gained from the chemotherapy was 2.4 life years. The cost per extra life year gained was therefore $2,920. Incorporating quality of life reduced this gain to 0.36 QALYs. Thus the cost per QALY gained was $19,472.

The results of this analysis are only tentative, as the quality of life descriptions were not measured over time, but from a cross sectional survey of patients, and the valuations of health states were derived from a small sample. However, the results do demonstrate the importance of quality of life in the evaluation of cancer treatment.

1. INTRODUCTION

The objective of this study was to conduct a preliminary economic evaluation of the joint use of 5-Fluorouracil (5-FU) and Levamisole as adjuvant chemotherapy for patients with fully resected Dukes stage C colon cancer, compared to resection with no chemotherapy. Cost utility analysis is the preferred method of economic evaluation when quality of life is a major outcome of a medical intervention. Adjuvant chemotherapy (chemotherapy used to aid surgery in the cure of disease) for colon cancer meets this criterion because, although it improves disease-free survival and overall survival, it entails longer and more complex treatment. There is currently little information about the physical and psychological burdens experienced by patients undergoing adjuvant therapy. This study used quality of life data to adjust the survival rates to reflect these burdens, and construct 'Quality Adjusted Life Years' (QALYs) as the outcome measure. Adjuvant chemotherapy, particularly the year long regime of weekly treatment, also increases the cost of treating colon cancer. This study analysed the resource consequences to the health service, using Westmead Hospital as the basis for analysis. Costs were combined with health outcomes, using the cost per QALY gained as the measure of cost effectiveness of the treatment.

The study results are preliminary, as they are based on a small sample. However, the primary aim of the analysis was to illustrate the methods that may be used to attempt to quantify quality of life and financial burdens in the evaluation of new treatments. The study provides some tentative, but challenging, results on the efficiency of this treatment.

Section 2 of the paper describes colon cancer as a public health problem in Australia, and provides a review of the clinical treatment of colon cancer. Section 3 describes the methods used in the study, with results presented in section 4. Section 5 concludes with a brief discussion of the results.

2. CLINICAL REVIEW

In Australia, cancer of the colon is the third most common form of cancer (after lung and prostrate) for men, and the second most common (after breast) for women. Colon cancer accounts for around 10% of all new cancers, with a standardised incidence of 25 per 100,000, and a standardised mortality of 14 per 100,000. In an international context, this rate is higher than most of western Europe, although lower than the US (Giles, Armstrong & Smith, 1987). Colon cancer affects predominantly those in their fifties and sixties and virtually no one below the age of forty. As yet there is no established means of preventing colon cancer, nor is there a reliable and cost-effective screening process available. Strategies for reducing mortality thus depend on treatment. As the population ages the incidence of colon cancer can be expected to increase, and so, therefore, can the demand for treatment.

Despite intensive research, treatment for colon cancer has changed little over the last thirty years, with surgery the treatment of choice (Devita, Hellman & Rosenberg, 1989). The extent of colonic resection for potentially curable colon cancer is determined by the biology of local tumour growth and by the associated lymphadenectomy. This is classified by the Dukes system, where stages B and C account for around 70-80% of colon cancer patients. Stage B refers to invasion of the colon wall and C to regional lymph node metastasis. Stage A has a five year survival rate of over 80%, and stage D is incurable (100% fatality). However, although about 70-80% of patients present at a stage where all apparent diseased tissue can be surgically removed, the five year survival rate for these stage B and C patients is around 50%. Recurrence in patients is likely to be due to residual cancer existing at a microscopic stage. For stage C patients the major risk remains disseminated disease, with liver metastasis involved in around 75% of those patients who die due to primary colon cancer.

As the natural history of colon cancer has been better defined, patients at increased risk of recurrence have been identified and studies into various types of adjuvant chemotherapy, methods of application, and forms of combination have proliferated

since the 1950's, but with little consensus on appropriate treatment.

The fluoropyrimidines remain the most widely employed single chemotherapeutic agents for patients with colorectal cancer, and since the introduction of 5-Fluorouracil (5-FU) in 1957 tens of thousands of patients have been treated. Studies into adjuvant chemotherapy have therefore mostly concentrated upon variation in the use of 5-FU, some in combination with other drugs. However, 5-FU does not demonstrably affect survival for all patients, and can cause various unpleasant side effects. Three decades of trials produced no single ideal schedule or dose scheme, and attempts have been made to improve upon these results by combining 5-FU with various other drugs, particularly immunotherapeutic.

Buyse, Zelenluch-Jacquitte, Chalmers et al (1988), to try and clarify the use of adjuvant therapy, performed a meta-analysis of all randomised controlled trials of adjuvant therapy for colon cancer published in English up to December 1986. They found 17 trials of chemotherapy alone (6791 patients), three of immunotherapy alone, and three of combination. The combination of survival data of all these studies showed no overall positive or negative effect. By restricting the analysis to the seven studies in which 5-FU was administered (4700 patients), a 10% reduction in odds of death was found, although this was not statistically significant. Further restriction to 5-FU regimens administered for at least one year showed a statistically significant reduction in odds of death of 17%. They concluded that adjuvant treatment by 5-FU, alone or in combination, may exert a small positive effect (increased 5 year survival by 3.4%), but only if administered in prolonged schedules.

In 1990, Moertel, Fleming, MacDonald et al published the results of a prospective randomised trial consistent with this previous evidence, testing a regimen of 5-FU and Levamisole against surgical controls in patients with completely resected stage B or C colorectal cancer, plus a third arm with Levamisole as a single agent. The study used a sample of 1247 stage B and C patients, all with colon cancer, although the median follow up time was only 3.5 years. Only patients with stage C colon cancer were eligible for randomisation to the Levamisole only arm. Results did not

support the use of 5-FU and Levamisole combined for stage B cases, but did support their use for stage C. Survival rates for stage C patients based on the 3.5 years were 71% for 5-FU and Levamisole against 55% for the surgical controls. The estimated reduction in the death rate was 33%. Levamisole alone was found not to be statistically significant in reducing the death rate.

This publication prompted the United States National Institute of Health in its 1990 Consensus Development Conference to accept 5-FU and Levamisole as the treatment of choice for colon cancer, and to recommend that "at present, the 5-FU and Levamisole regimen is the standard to which new therapies should be compared."

Tiver & Langlands (1991) question the results and the trial methodology on several points, including the extent of morbidity incurred by patients. The authors note that although major toxicity was uncommon, 30% of patients dropped out due to side effects (median time of five months), and one patient died due to toxicity. The authors conclude by stating that

> "a whole range of uncertainties remain as to the value of the various potential adjuvant treatments for colorectal cancer subjected to apparently complete surgical excision. These are likely to persist for some years....Against that background the clinical use of adjuvant therapy seems most appropriately to remain investigational at this time."

The chemotherapy regimen proposed by Moertel, Fleming and MacDonald (1990) has been adopted both in the United States and Australia, with little apparent consideration of cost or efficiency. This study, therefore, was an attempt to answer questions concerning the cost and quality of life implications of this treatment. As stated earlier, the objective was to conduct an economic evaluation of the regimen versus the conventional treatment of surgery alone, adjusting survival for quality of life.

3. METHODS

A cost utility analysis was used to extend the results of Moertel, Fleming and MacDonald (1990). The incremental cost per QALY for surgery plus adjuvant chemotherapy, compared to surgery alone, was estimated. The viewpoint taken for the estimation of costs was that of the health care system. The values for quality of life were derived from patients and non-patients.

3.1 Costing

The new treatment was an 'add on', not a replacement for conventional surgery alone. Surgery alone comprised both the procedure (colonic resection in the absence of rectal cancer) and inpatient stay. The additional chemotherapy costs comprised the costs of the chemotherapy treatment and outpatient visits over the 52 week course. All costs were expressed in 1990/91 prices ($AUS). The average cost of each procedure was calculated on direct labour input, consumables used and a capital and overhead component by the methods advocated by Drummond, Stoddart & Torrance (1990). The method of derivation of each is given briefly below.

Staff costs were based on the observation of medical and nursing staff involved in each procedure. Time spent with each patient was then multiplied by wage rate (at the mid-point on the salary award scale), which was adjusted to include on-costs of overtime and shift penalties, sick and annual leave loading, and superannuation.

Consumables such as drugs, gloves, needles, diagnostic tests etc, were valued at market price and calculated on usage per patient per procedure. In the absence of more accurate data, the costs of diagnostic tests were taken from the Australian Medicare Benefit Schedule.

Overheads, such as lighting, cleaning, administration, etc., were valued from the average floorspace occupied by the unit (or attributable to the units activities) compared to the remainder of the hospital. ie area taken by the unit/area of the

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hospital x department cost/number days.

Capital equipment and building costs were estimated per procedure per patient on an annual equivalent cost basis, discounted at 5%. A sensitivity analysis was performed on this discount rate.

Thus, the cost of surgery was derived by multiplying an observed estimate of the average cost of a surgical oncology bed day (including operating theatre time, pathology tests, medical consultations, etc.), by actual patient usage. The cost of chemotherapy was derived for the average cost per visit multiplied by the number of visits (one per week over 52 weeks). The methods of costing the components (staff, consumables, overheads and capital) were the same in each treatment option.

3.2 Sample

There were two samples used in the quality of life survey. The first comprised patients only, and the second patients and non-patients. First, Dukes C colon cancer patients were interviewed to develop the health state descriptions. Second, values for quality of life were derived from a sample of eight chemotherapy patients with Dukes C colon cancer and eight non-patients. The patients were recruited from chemotherapy clinics at two cancer centres in Sydney over three visits. The non-patients were recruited from other areas, both clinical and administrative, of these same cancer centres.

3.3 Outcome

The procedure for estimating QALYs was as follows. First the health state descriptions (scenarios) were developed (appendix 1). These were based on a patient survey, using qualitative methods. Patients were asked to describe what side effects they experienced, how they felt emotionally and how the treatment was affecting their home life and relationships. The description of quality of life following the surgical procedure was obtained from patients who had just completed a surgical

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operation for colon cancer, but who were either ineligible for the chemotherapy, such as other (non Dukes C) bowel cancer patients, or who were yet to begin chemotherapy. The description of surgery plus chemotherapy came from patients who had been on the chemotherapy programme for varying lengths of time, and who had different experiences of side effects. The surgery health state was used as the good health baseline (Smith in appendix 1) and the chemotherapy states covered three levels of severity of toxicity and side effects; ranging from "best" (Jones in appendix 1), through "medium" (Thomas in appendix 1), to "worst" (Hall in appendix 1).

Second, a questionnaire (appendix 2) was developed to elicit the respondents' utility weights using the time trade off (TTO) technique. The weight was derived as follows. The respondent was presented with a poor health state scenario (surgery plus 12 months chemotherapy) which was expected to be experienced for one year. By process of iteration, the number of years in good health (surgery alone) which the respondent was willing to forgo to avoid the poor health state was elicited. The ratio of the time in the poor health state to the number of years forgone provided the utility value of the poor health state. For instance, if the respondent would be willing to forgo two years in good health to avoid the one year in poor health, then the utility weight would be 0.5 (1/2), such that the year in the poor health state is equivalent to only half a year in good health. This weight is multiplied by the life years to give the QALYs.

The median values for the utility weights were used rather than the arithmetic mean, thus eliminating the influence of an outlier who appeared not to understand the TTO questions, and who also ranked the three chemotherapy health states contrary to all the other respondents. The median of the whole sample was also very close to the mean without this outlier.

The method of adjusting survival for quality of life in this study differs from the conventional QALY technique in two important ways, both related to the nature of the treatment alternatives.

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First, the reference "good health" state was considered to be the surgery alone state, which does not readily correspond to the definition commonly used in QALY analyses as it is not 'free of any ailment'. This definition of good health, surgery alone followed by 'good health', is the best state which the patient already diagnosed with colon cancer could expect. If the study presented a state of 'normal' good health then the surgery scenario would have a weight of less than one, and the chemotherapy states would be correspondingly reduced. However, the QALY gain would remain the same because of the interval scale properties. Thus in the final analysis the cost per QALY gain would be unaffected.

Second, although the 'poor health' state only lasts for one year (ie the 52 week chemotherapy course) the choice offered to respondents was over a longer period to get a value over time, rather than just for the one time period. What respondents were indicating with this trade off was that amount of time at the end of their life which they would be willing to give up to avoid 1 year of chemotherapy now. Thus, overall, the respondents would be willing to give up more years at the end of their life to avoid the "worst" chemotherapy scenario than they would to avoid the "best". For instance the QALY weight of 0.93 for the "best" chemotherapy scenario means that, at a life expectancy of 20 years, the respondents would be prepared to give up 1.4 years at the end of their life to avoid 1 year of chemotherapy now (20-(20x0.93)). For the "worst" health state, with a weight of 0.8, they would give up 4 years (20-(20x0.8)). What we have is therefore **not** a weight on a single year of chemotherapy, but a reflection of what the respondents would give up to avoid it and thus a weight over the whole period. The health states include a time dimension and are not just a preference over states at one point in time. This avoids the necessity to discount future years of survival if one only has a weight for the year of chemotherapy, as the discounting is considered implicit in this application of the TTO technique.

3.4 Survival

The probabilities of survival and recurrence used were those reported by Moertel, Fleming & MacDonald (1990), and the probabilities of experiencing each level of side

effect were derived from Moertel, Fleming and MacDonald (1990) for the "worst" scenario, and from clinical observation in the medical oncology department at Westmead for the others. The probability of experiencing the "worst" health state was 0.30. For "medium" it was 0.45, and "best" it was 0.25.

Twenty years was used as the mean survival time for a successful treatment, as the average age of colon cancer patients is around 55 and life expectancy at this age is 16 years for males and 23 years for females (Giles, Armstrong and Smith, 1987). A five year life expectancy was used for those with recurrent disease (ie recurrence of the cancer within 5 years) because the study by Moertel, Fleming & MacDonald et al (1990) showed that 82% of recurrences, and 60% of anticipated deaths, had occurred within 3.5 years. The assumption of all deaths occurring at the five year point is arithmetically simpler.

4. RESULTS

4.1 Cost.

The cost of surgery plus chemotherapy as treatment for colon cancer patients was found to be $13,022 per patient per 12 month period of treatment. The cost of surgery alone was $6,012. Thus, the incremental cost of the chemotherapy course was $7,010 per patient. The component costs of both the surgery and chemotherapy, derived by the methods outlined above, are presented in table 1. Each procedure has costs broken down into the four broad categories used above - staff, consumables, overheads, and capital - and totals.

TABLE 1

COMPONENT COSTS

1.1 Cost of surgery.

COST CATEGORIES	$ PER OPERATION PER PATIENT
Staff	1547
Consumables	2136
Overheads	2142
Capital equip building	22 163
TOTAL	**6012**

1.2 Cost of chemotherapy

COST CATEGORIES	$ PER 52 WEEKS PER PATIENT
staff	610
Consumables	3271
Overheads	3086
Capital building	41
TOTAL	**7010**

4.2 Sample characteristics

Table 2 shows how well matched the two sample groups (patients and non-patients) were. One can see that they are well matched in terms of marriage, sex and age. However, some characteristics are not matched as closely as one would like. Due to the small sample size in this study, many values are significantly different. This makes it difficult to ensure that these differences are not influencing responses.

TABLE 2

CHARACTERISTICS OF STUDY POPULATION

CHARACTERISTIC	PATIENTS n=8	NON PATIENTS n=8	TOTAL n=16
average age	53.5	49	51.25
age range	36-63	33-63	33-63
sex (male)	4 (50%)	5 (62.5%)	9 (56.25%)
married	7 (87.5%)	7 (87.5)	14 (87.5%)
children	6 (75%)	7 (87.5%)	13 (81.25%)
grandchildren	2 (25%)	4 (50%)	6 (37.5%)
current health good or excellent	6 (75%)	8 (100%)	14 (87.5%)
chronic health problem	1 (12.5%)	2 (25%)	3 (18.75%)
life threatening illness	8 (100%)	3 (37.5%)	11 (68.75%)
relative with bowel cancer	3 (37.5%)	4 (50%)	7 (43.75%)

4.3 Life Years gained.

Figure 1 illustrates the possible outcomes of the study in the form of a decision tree. There are two arms: surgery alone, and surgery plus chemotherapy. The patient initially has the choice of undergoing surgery or undergoing surgery followed by the

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52 week course of chemotherapy. With surgical treatment alone, the patient has a probability of 0.55 of living the full 20 years of remaining life with no recurrence of the disease. They therefore have a probability of 0.45 of having recurrence within 5 years. It was assumed that recurrance would lead to death at the 5 year point.

FIGURE 1

DECISION TREE

Average LYs gained from chemotherapy 15.65 (14.2+1.45)
                                      -13.25 (11.0+2.25)
                                      = 2.40
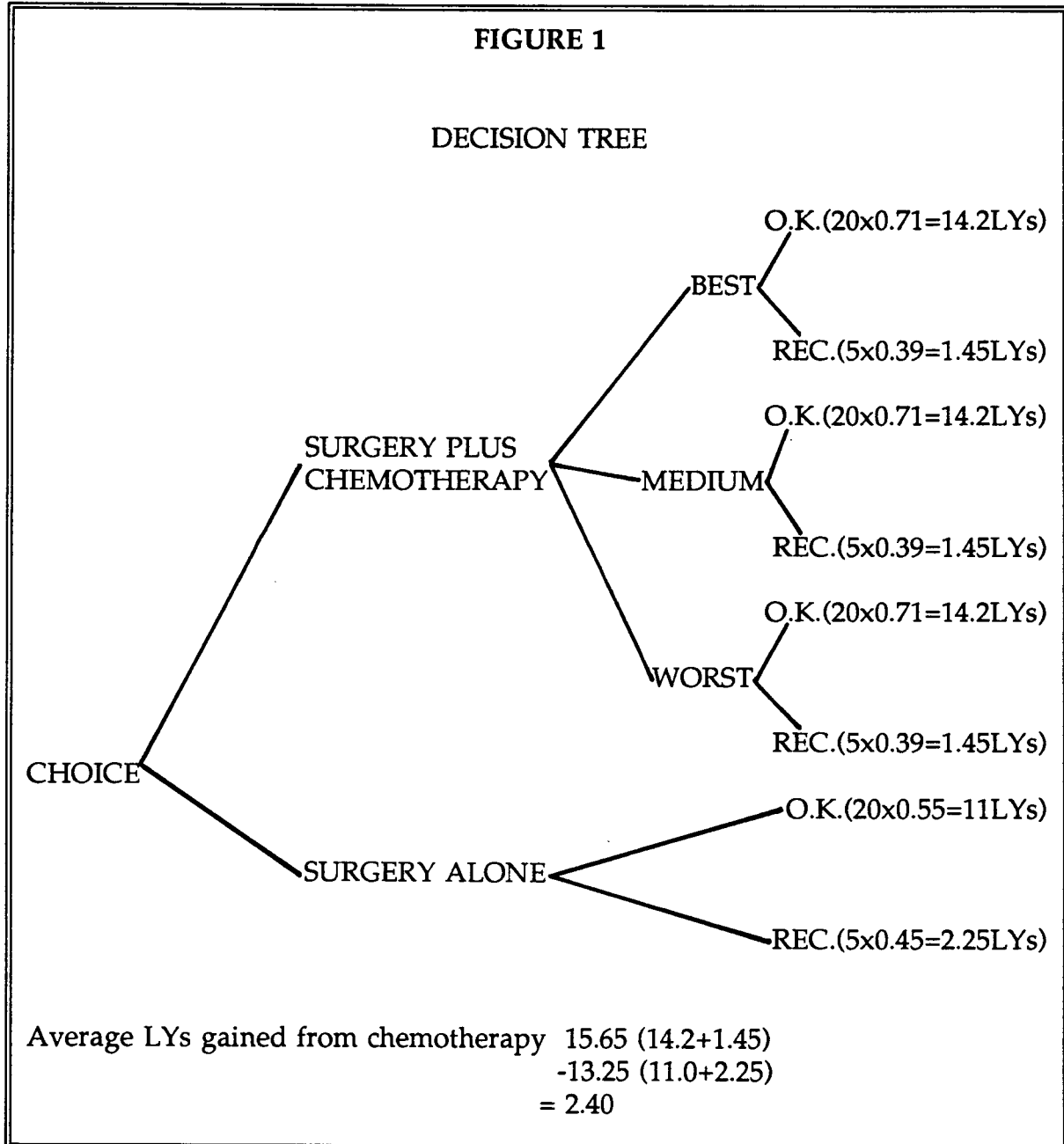
Thus the average life expectancy of a patient undergoing surgery alone is 13.25 ((0.55x20=11.0) + (0.45x5=2.25)).

For the surgery plus chemotherapy there are a number of possible scenarios because

there are different severities of side effect associated with the chemotherapy treatment. Thus, on the surgery plus chemotherapy branch, "best" refers to the least severe side effects, "medium" to moderate side effects, and "worst" to the most severe side effects.

For the chemotherapy option the probability of surviving beyond 5 years has increased to 0.71, with a corresponding decrease in the probability of recurrence within 5 years to 0.39. Probability of recurrence is assumed to be independent of severity of chemotherapy side effects. Thus, the average life expectancy of a patient undergoing surgery and chemotherapy is 15.65 (14.2 + 1.45). The gain from chemotherapy over surgery alone is therefore 2.4 years.

4.4 QALYs gained

However, we also wish to have a measure of **quality** of life under each treatment alternative. For this we simply multiply the life years by a quality weighting derived from the TTO exercise. This is illustrated in figure 2.

For the health state 'best' the weighting derived from the foregoing method is 0.93, and so the QALYs from this treatment and level of toxicity are 14.55. However, there are two other possible scenarios for the surgery plus chemotherapy - medium and worst - which need to be accounted for. This is achieved by using a weighted average of the three scenarios to yield a single average measure for the chemotherapy treatment. The weights are the probabilities of experiencing each different level of toxicity as outlined in section 3.4. Thus for best we have 14.55x0.25 which equals 3.6 QALYs, for medium 13.78x0.45 (6.2) and bad 12.55x0.3 (3.8). The average QALYs expected overall from the surgery plus chemotherapy are therefore 13.61 (3.6+6.2+3.8). The outcome of the surgery remains the same at 13.25 because it has a weight of 1. Thus, the gain with quality of life accounted for is 0.36 (13.61-13.25).

FIGURE 2

DECISION TREE

O.K.(14.2x0.93=13.2QALYs)

BEST

REC.(1.45x0.93=1.35QALYs)

O.K.(14.2x0.88=12.5QALYs)

SURGERY PLUS
CHEMOTHERAPY——MEDIUM

REC.(1.45x0.88=1.28QALYs)

O.K.(1.45x0.80=11.4QALYs)

WORST

REC.(1.45x0.80=1.16QALYs)

O.K.(11.0x1=11.0QALYs)

CHOICE

SURGERY ALONE

REC.(2.25x1=2.25QALYs)
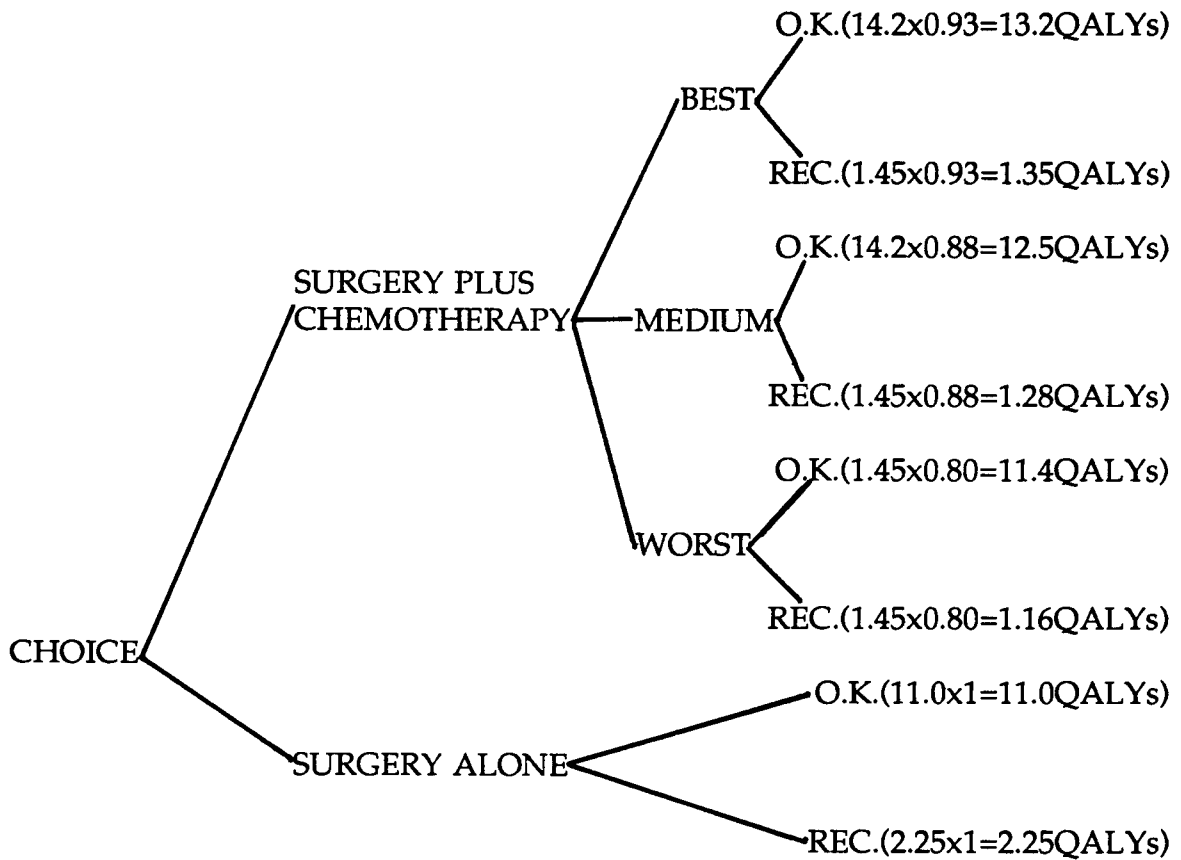
Average QALYs gained from chemotherapy 13.61 (3.6+6.2+3.8)
-13.25 (11.0+2.25)
= 0.36

A summary of the calculations of both life years and QALYs is given in table 3.

TABLE 3

OUTCOME

OUTCOME	LIFE EXPECTANCY	PROB.OF SURVIVAL	LIFE YEARS	UTILITY WEIGHT	QALY
Surgery o.k.	20	0.55	11.0	1.00	11.0
Surgery rec.	5	0.45	2.25	1.00	2.25
Best o.k.	20	0.71	14.2	0.93	13.2
Best rec.	5	0.29	1.45	0.93	1.35
Medium o.k.	20	0.71	14.2	0.88	12.5
Medium rec.	5	0.29	1.45	0.88	1.28
Worst o.k.	20	0.71	14.2	0.80	11.4
Worst rec.	5	0.29	1.45	0.80	1.16

Thus, overall, the study found that surgery alone resulted in an outcome of 13.25 QALYs, and the surgery and chemotherapy option resulted in 13.61 QALYs. The average gain from undergoing the chemotherapy is therefore 0.36 QALYs. This contrasts with the gain in unadjusted life years of 2.4.

4.5 Cost per QALY.

Table 4 shows the cost per life year and the incremental cost per life year. Table 5 shows the cost per QALY, and the incremental cost per QALY gained. The incremental results show the additional cost per unit of benefit in using chemotherapy in addition to surgery.

TABLE 4

COST PER UNADJUSTED LIFE YEAR (LY)

	LY	$ COST	$ COST/LY
Surgery	13.25	6,012	453
Surgery plus Chemotherapy	15.65	13,022	831
Incremental	2.4	7,010	**2,920**

TABLE 5

COST PER QALY/GAIN

	QALY	$ COST	$ COST/QALY
Surgery	13.25	6,012	453
Surgery plus Chemotherapy	13.61	13,022	956
Incremental	0.36	7,010	**19,472**

Surgery alone, followed by good health, was used as the base level of good health, therefore rating a QALY weight of 1. As a result the cost per QALY, $453, is equivalent to the cost per life year. However, it is the **incremental** cost per QALY which is the significant result. It is this which shows the extra resources consumed in treating colon cancer patients with chemotherapy.

4.6 Sensitivity Analysis

Sensitivity analysis was performed on the discount rate used in costing the capital component of the two alternative treatment methods, and also on the QALY values and the cost per QALY values which these resulted in. Table 6 shows that the cost (and therefore cost per QALY) results are not very sensitive to changes in the discount rate for values of 5, 7, and 10%. This result is expected as capital use is only a small proportion of the resource use of the treatments.

TABLE 6

SENSITIVITY ANALYSIS OF DISCOUNT RATE

TREATMENT	5%	7%	10%
surgery	6,012	5,899	5,857
surgery plus chemotherapy	7,010	6,984	6,946
Total	13,022	12,883	12,803

Table 7 shows the effect of using two different subsamples, patients and non patients, to value quality of life and also of using the mean rather than median value. Thus the highest possible QALY gain from undertaking chemotherapy is 0.58 from the non patient sub group, and the lowest is a **loss** of 1.39 from the patient sub group. This illustrates that by using the patient values we would be paying to **reduce** health outcomes.

TABLE 7

SENSITIVITY ANALYSIS OF QALYS

VARIABLE	SURGERY	CHEMO THERAPY	QALY GAIN	$ COST PER QALY GAIN
Median valuation	**13.25**	**13.61**	**+0.36**	**19,472**
Mean valuation	13.25	12.68	-0.57	-
Non Patient median valuation	13.25	13.83	+0.58	12,086
Non Patient Mean valuation	13.25	13.37	+0.12	58,417
Patient Median valuation	13.25	13.01	-0.24	-
Patient Mean valuation	13.25	11.86	-1.39	-
HIGHEST POSSIBLE VALUATION	13.25	13.83	+0.58	12,086
LOWEST POSSIBLE VALUATION	13.25	11.86	-1.39	-

4.7 Conclusion.

The benefit of chemotherapy is an increase in average life expectancy of 2.4 life years: from 13.25 if one undergoes surgical resection alone, to 15.65 from undertaking the chemotherapy course adjuvant to the surgery. However, when quality of life is taken into account the gain falls to 0.36 quality adjusted life years, as the surgery plus chemotherapy treatment now increases average 'quality adjusted' life expectancy to only 13.61.

The chemotherapy treatment essentially doubles the cost of treatment of colon cancer patients from $6,012, with surgery alone, to $13,022 with surgery plus chemotherapy. Thus the extra cost per life year gained is just under $3,000, compared to just under $20,000 per QALY gained.

5. DISCUSSION

Surgical resection has been the principal form of colon cancer treatment (Devita, Hellman and Rosenberg, 1989). Recently chemotherapy has been shown to have a significant effect on patient outcome, at least in terms of survival (Moertel, Fleming MacDonald et al, 1990). Tiver & Langlands (1991) have argued that there are doubts over the clinical efficacy of the chemotherapy, particularly with respect to patient quality of life. This study has attempted to provide data in this area.

Our results show a gain of 0.36 QALYs per patient from chemotherapy. The cost of achieving this gain is $19,472 per QALY, compared to $2,920 per life year. However, several qualifications have to be placed on the robustness of these results.

First, the cost of each treatment alternative, although accurately reflecting cost to Westmead, may not be generalisable to other institutions. For instance the cost to a dedicated cancer unit may be lower, but higher to institutions with high 'hotel' costs. It is, however, likely that the cost of the chemotherapy will be of a sizeable magnitude wherever used.

Second, the costs are based solely on a health system viewpoint. There may be additional costs to the patients and their families, for example travel costs in attending for treatment. It could be argued that patients and families are prepared to bear these costs as no one dropped out of the treatment programme due to personal costs. Thus, time costs may be considered as incorporated in the measure of benefit.

Third, the life year estimates are only approximate. All deaths due to colon cancer were assumed at five years after diagnosis which leads to an overestimate of life years for both treatments. Twenty years was selected as mean survival, based on an average patient age of 55. However, variations in life expectancy occur by age and sex. Furthermore, Moertel, Fleming and MacDonald (1990) found that older patients received a greater survival benefit than younger, which would affect the result for

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this subgroup. However, an earlier study (Laurie, Moertel and Fleming, 1989) reported the opposite effect; that treatment was more effective in younger patients. Future research should therefore perform survival analysis by subgroup.

Fourth, the result is sensitive to the QALY weights used. Given the small sample and the variation in weights, the resultant QALY values should not be generalised.

The results of the analysis are preliminary. The primary aim of the study was to provide an example of how the tools of economic evaluation may be used to provide a more comprehensive picture of the effects, and therefore efficiency, of treatments, rather than conclusive evidence. This study does show how a neglect of quality of life may lead to an over estimation of the benefits of this treatment.

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APPENDIX 1

<u>Mr/s Smith.</u>

Imagine that your present good health is interrupted by a bowel problem, diagnosed as colon cancer. You are taken into hospital and an operation successfully removes the tumour.

Physically the operation causes a certain amount of pain and discomfort and you must take things easy for a few weeks. After this time your life returns to normal with no lasting physical effect, although you become more careful with your diet.

Mentally the initial shock of the disease and surgery wears off with time, and your health returns to normal.

As the years go by you remain in good general health. This means that you tire more easily and feel more aches and pains as time passes. You continue to have a positive outlook and stable, fulfilling relationships.

You live the remaining years of your life in good health.

<u>Mr/s Jones.</u>

Imagine that your good health is interrupted by a bowel problem which is diagnosed as colon cancer. You are taken into hospital where an operation successfully removes the tumour. This is followed by a course of chemotherapy which involves a visit to the hospital each Wednesday morning for a period of 12 months.

Initially you experience a feeling of nausea after each episode of treatment and feel a little less energetic for a couple of days. You experience occasional nose-bleeds and become more conscious of your diet. Gradually these effects wear off after a few weeks and you complete the treatment with no side effects whatsoever.

Your mental state also improves as the treatment progresses. Initially you and your partner are anxious about the disease recurring. However, as the treatment progresses your outlook becomes more positive, your relationships return to normal and the anxiety subsides. You go back to work and your social and home life return to normal.

You continue in this state for the length of the treatment. After the 12 months is over you return to a normal healthy life for the remaining years of your life.

Mr/s Thomas.

Imagine that your good health is interrupted by a bowel problem which is diagnosed as colon cancer. You are taken into hospital where an operation successfully removes the tumour. This is followed by a course of chemotherapy which involves a visit to the hospital each Wednesday morning for a period of 12 months.

Physically your health is reduced because of the treatment. You feel nausea after each episode of treatment and have less energy, but this improves slightly during the week. Your skin becomes dry, your hair begins to thin slightly, you have more frequent nose-bleeds and occasional bouts of diarrhoea and wind. You organise your life to accommodate these effects and live as normally as possible.

Mentally your health remains below normal. You experience anxiety over the recurrence of the disease, and bouts of depression brought on by the treatment side effects. This makes you irritable and agitated. Your partner is coping well but your relationships with family and friends suffer due to your lack of energy making social trips less frequent. You find that meeting fellow patients each Wednesday therapeutic. You give up work for the 12 month period.

You live in this state for the period of treatment. After the 12 months you return to a normal healthy life for the remaining years of your life.

Mr/s Hall.

Imagine that your good health is interrupted by a bowel problem which is diagnosed as colon cancer. You are taken into hospital where an operation successfully removes the tumour. This is followed by a course of chemotherapy which involves a visit to the hospital each Wednesday morning for a period of 12 months.

Physically your health is considerably reduced because of the treatment. You feel nausea after each episode of treatment and experience frequent vomiting. You feel extremely lethargic, and spend each day sitting around the house watching T.V. Your skin becomes very dry and sensitive, you experience substantial hair loss, and have frequent nose bleeds. You experience a great deal of diarrhoea and wind. You feel withdrawn from your family and friends, and contact with them is now rare. Your relationship with your partner is strained.

Mentally you are particularly depressed because of the treatment side-effects and the possibility of disease recurrence. Sometimes you contemplate suicide. Each Wednesday serves as a reminder of the disease. You are also concerned about your appearance following the hair loss and some weight gain.

You continue in this state for the period of the treatment. After the 12 months you return to a normal healthy life. You live in this state for the remaining years of your life.

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<u>Mr/s Cameron.</u>

Imagine that your are in good health for your age. This means that your physical health is generally good and mentally you have a positive outlook on life and enjoy a good relationship with family and friends.

Now imagine that you have an accident which puts you in hospital for a short while. You experience a certain amount of discomfort and pain from the physical injuries, but after you are discharged your life soon returns to normal, except for a loss of sight. This means that you now require help from family and friends with general mobility and to carry out daily tasks such as shopping. You have to give up work and cannot carry on with your usual lifestyle.

Mentally you become frequently depressed about this disability and find it hard to accept. However your relationships with your partner and friends are good and you find a lot of comfort in this.

You live like this for the remaining years of your life.

APPENDIX 2

QUESTIONNAIRE

NAME..

ADDRESS (if known)..........................

        ....

TELEPHONE No................................

PLACE OF INTERVIEW..........................

DATE OF INTERVIEW...........................

TIME INTERVIEW COMMENCED....................

Thank you for agreeing to take part in this study. The purpose of the study is to find out how people feel about various health states.

The results of this study will be used to help plan and improve health services.

Remember that the responses you give will be treated in **confidence** and will be used **anonymously,** only group results will be used.

You don't need to know anything about the health problems I will describe or about the medical treatment involved.

I am **interested in your opinion** so remember that means there are no right or wrong answers, **just your own views**.

But first of all I would like to find out some information about yourself if that's ok.

1. What is your age?

    [WRITE NUMBER OF YEARS]   . . . .

2. Are you married?

    [CIRCLE ONE ANSWER]   NEVER MARRIED

                                           MARRIED/DE FACTO

                                           SEPARATED/DIVORCED

                                           WIDOWED

3. Have you any children?

    [CIRCLE ONE ANSWER]   YES

                                                    NO

    [If yes] what are their ages?

    [RECORD OLDEST AND YOUNGEST]   OLDEST

                                                YOUNGEST

4. Have you any grandchildren?

    [CIRCLE ONE ANSWER]   YES

                                                    NO

5. Have you ever had a life threatening illness?

    [CIRCLE ONE ANSWER]   YES

                                                    NO

    [If so] what illness have you had?
            when were you diagnosed?

    diagnosis   No. years ago

    . . . .

6. Have you ever had an operation?

[CIRCLE ONE ANSWER]   YES

                                                                           NO

[If so] what operation did you have?
        when was that?

Operation   No. years ago

. . . .

7. Have you a chronic condition?

[CIRCLE ONE ANSWER]   YES

                                                                           NO

[If so] what is that condition?
        how long have you had it?

Condition   No. years ago

. . . .

8. How would you describe your health compared to
   other people your age?

                                                                   POOR

[READ ANSWERS]
                                                                   FAIR
[CIRCLE ONE ANSWER]
                                                                   GOOD

                                                           EXCELLENT

Now we are going to look at some health conditions
which **could happen to anyone with bowel cancer.**
I am going to ask you to **imagine** yourself in these
conditions, although they do not necessarily
reflect your current or future health state.
Occasionally, people become upset when talking about
illness. We can end the interview at any time if you
tell me you find the questions distressing and you
would rather not go on.

Shall we go on?

First of all, let's read this description of **Mr/s Smith**.

    [PAUSE AND READ]

Throughout the interview I will be reminding you of
Mr/s Smith, because we want to make some comparisons with
it. **Imagine that you are Mr/s Smith** and this is how you
will spend your life.

Warm up exercise

Now let's read this description of **Mr/s Cameron**.

    [PAUSE AND READ]

    [NOW GET TIME BARS READY TO SHOW]

9. Imagine that your life expectancy is 15 years, the time
represented by this **blue bar**.

    [POINT TO BLUE BAR]

I am going to offer you a choice. You could spend
15 years in **Mr/s Cameron's** health state or you could live
a **shorter** time, [.. PINK TIME BAR..] in good health
like **Mr/s Smith** which is represented by this other bar.

    Which would you choose?

    **[WORK THROUGH THE PAGES OF TIME BAR CHOICES
    AND SAY: NOW I'M GOING TO OFFER YOU ANOTHER
    CHOICE... THEN ASK WHICH YOU WOULD CHOOSE NOW?]**

    **[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF
    TIME BAR CHOICES AND RECORD THE VALUE OF "A"
    AS INDICATED]**

                                      A=

So you're saying you would choose to be .....
for .... yrs rather than .... for
........yrs.

or if respondent is indifferent

You can't choose between **Mr/s Cameron** for 15
yrs and **Mr/s Smith** for .... yrs.

[CONFIRMATION]

[NOW CHANGE TO 10 YEARS TIME BAR]

10. **I'm now going to offer you another choice.**
    you could spend 10 years in **Mr/s Cameron** health state
    or you could live a **shorter** time [..PINK BAR..]
    in **Mr/s Smith's** health state.

    Which would you choose?

    **[WORK THROUGH THE PAGES OF TIME BAR CHOICES
    AND SAY: NOW I'M GOING TO OFFER YOU ANOTHER
    CHOICE... THEN ASK WHICH YOU WOULD CHOOSE NOW?]**

    **[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF
    TIME BAR CHOICES AND RECORD THE VALUE OF "A"
    AS INDICATED.]**

                                                    A=

So you're saying you would choose to be .... for
...... yrs rather than ..... for.... yrs.

or if respondent is indifferent

You can't choose between **Mr/s Cameron** for 10 yrs and
Mr/s Smith's good health for ...... yrs.

[CONFIRMATION]

Thank you. That's the first part of the interview
over.

****

11. **Now here are three descriptions of people who have
    been treated for colon cancer.** What I'm going to
    do is read these through with you and ask you to put
    them in the order which you think best ranks them from
    the **best** (closest to **Mr/s Smith**) to the **worst** (furthest
    from **Mr/s Smith**).

                                              NAME

     [RECORD READING ORDER]   1st.............

                                       2nd............

                                       3rd............

But before we do this I want to point out that to
start with you may find that the descriptions all
seem very similar, and so it is important that you
take as much time as you want. Ok?

        [GIVE RESPONDENTS DESCRIPTIONS AND READ THEM OUT
        LOUD TAKING CARE TO HIGHLIGHT THE DIFFERENCES]

                                          NAME
[RECORD RESPONDENT'S ORDERING]
                                       1st..............

                                       2nd.............

                                       3rd.............

[CONFIRM THE ORDERING WITH THE RESPONDENT]

12. Now let's start with the health description which you
    considered was the **worst** in comparison to **Mr/s Smith**.

    I am going to offer you a choice. You could spend 15 years in
    [3rd] health state. That is the time represented by the blue
    bar. Or you could live a **shorter** time [..PINK BAR..] in **Mr/s
    Smith's** health state, represented by this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
 I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
 WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
 CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

                                                        A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

                    OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for .... years.

[CONFIRMATION]

            [NOW CHANGE TO 10 YEAR TIME BAR]

13. **I am now going to offer you another choice**.
    You could spend 10 years in **[3 rd]** health state.
    That is the time represented by the blue bar. Or a
    shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
    this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
 I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
 WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
 CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

                                                        A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

You can't choose between .... for .... years and
.... for 10 years.

[CONFIRMATION]

[NOW CHANGE TO FIVE YEAR TIME BARS]

14. **I am now going to offer you another choice.**
    You could spend 5 years in **[3rd]** health state.
    That is the time represented by the blue bar. Or a
    shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
    this other bar.

Which would you choose?

**[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]**

**[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]**

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 5 years.

[CONFIRMATION]

[NOW CHANGE TO 15 YEAR TİME BARS]

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15. Now let's take the health description which you
thought was the second worst - remember **[READ OUT]**

I am now going to offer you another choice.
You could spend 15 years in **[2nd]** health state.
That is the time represented by the blue bar. Or a
shorter time [..PINK BAR..] in **Mr/s Smith,** represented by
this other bar.

Which would you choose?

**[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]**

**[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]**

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

                         OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 15 years.

[CONFIRMATION]

                    [NOW CHANGE TO TEN YEAR TIME BARS]

16. I am now going to offer you another choice.
You could spend 10 years in **[2nd]** health state.
That is the time represented by the blue bar. Or a
shorter time [..PINK BAR..] in **Mr/s Smith,** represented by
this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

                    OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 10 years.

[CONFIRMATION]

                [NOW CHANGE TO FIVE YEAR TIME BARS]

17. I am now going to offer you another choice.
    You could spend 5 years in **[2nd]** health state.
    That is the time represented by the blue bar. Or a
    shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
    this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

                    OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 5 years.

[CONFIRMATION]

[NOW CHANGE TO 15 YEAR TIME BARS]

18. Now let's look at the health state you thought was
closest to **Mr/s Smith**. **[READ OUT]**

I am now going to offer you another choice.
You could spend 15 years in **[1st]** health state.
That is the time represented by the blue bar. Or a
shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
this other bar.

Which would you choose?

**[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]**

**[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]**

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

                    OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 15 years.

[CONFIRMATION]

[NOW CHANGE TO TEN YEAR TIME BARS]

19. **I am now going to offer you another choice.**
You could spend 10 years in **[1st]** health state.
That is the time represented by the blue bar. Or a
shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 10 years.

[CONFIRMATION]

[NOW CHANGE TO FIVE YEAR TIME BARS]

20. **I am now going to offer you another choice.**
You could spend 5 years in **[1st]** health state.
That is the time represented by the blue bar. Or a
shorter time [..PINK BAR..] in **Mr/s Smith**, represented by
this other bar.

Which would you choose?

[WORK THROUGH THE PAGES OF TIME BAR CHOICES AND SAY: NOW
I'M GOING TO OFFER YOU ANOTHER CHOICE... THEN ASK WHICH
WOULD YOU CHOOSE NOW?]

[FOLLOW THE INSTRUCTIONS ON THE OPPOSITE SIDE OF TIME BAR
CHOICES AND RECORD THE VALUE OF "A" AS INDICATED]

A=

So you're saying you would choose to be .... for ....
years rather than .... for .... years.

OR IF RESPONDENT IS INDIFFERENT

You can't choose between .... for .... years and
.... for 5 years.

[CONFIRMATION]

Well thank you for answering those questions on the
health descriptions of colon cancer.

I'd now like to finish the interview with a few
questions about how you found the interview as
well as a few more details about yourself.

21. Have you ever had bowel cancer in the past ?   YES

    [CIRCLE ONE ANSWER]   NO

22. Has a relative you've been close
    to or a close friend of yours
    ever had bowel cancer?   YES

    [CIRCLE ONE ANSWER]   NO

23. How difficult was it to rank the
    3 health states?   VERY EASY

    [READ OUT SCALE]   EASY

    [CIRCLE ONE ANSWER]   DIFFICULT

                                      VERY DIFFICULT

24. How difficult was it to use the
    time bars method?   VERY EASY

    [READ OUT SCALE]   EASY

    [CIRCLE ONE ANSWER]   DIFFICULT

                                      VERY DIFFICULT

25. Some people say they are quite
fatalistic about death. They
say if your time is up, your
time is up and there's nothing
you can do about it.
How strongly do you agree with this
statement?   STRONGLY AGREE

[READ OUT SCALE]   AGREE

[CIRCLE ONE ANSWER]   DISAGREE

                                    STRONGLY DISAGREE

26. Did you find the interview at all
distressing?
                                                    YES
[CIRCLE ONE ANSWER]
                                                    NO

27. Is there anything else that influenced
your answers to these questions that
you would like to add?

[WRITE DOWN BRIEF DESCRIPTION]

. . . .

Thank you very much indeed.

TIME INTERVIEW COMPLETED   . . . .

LENGTH OF INTERVIEW   . . . .

28. Status of interview   COMPLETED

    [CIRCLE ONE ANSWER]   BROKEN OFF

                                               REFUSED

    If not complete, please explain

    ....

29. Was anyone other than respondent present?
                                               YES
    [CIRCLE ONE ANSWER]
                                               NO

    If yes, who

    ....

30. Please rate how difficult the respondent
    found each of the measurement techniques,
    in your opinion.
                                               VERY EASY
    ORDERING
                                               EASY
    [CIRCLE ONE ANSWER]
                                               DIFFICULT

                                        VERY DIFFICULT

                                               VERY EASY
    TIME BARS
                                               EASY
    [CIRCLE ONE ANSWER]
                                               DIFFICULT

                                        VERY DIFFICULT

31. How distressed was the respondent
    during the interview?
                                               NOT AT ALL
    [CIRCLE ONE ANSWER]
                                               A LITTLE

                                               SOME

                                               VERY

32. Any other comments or impressions of this
    interview.

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