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# Adjuvant chemotherapy for early colon cancer: What survival benefits make it worthwhile?

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## ABSTRACT

**Background:** We sought to determine the minimum survival benefits that patients judged sufficient to make adjuvant chemotherapy for early colon cancer worthwhile, factors associated with these judgments; and, to compare a self-administered questionnaire with a validated, scripted interview.

**Patients and methods:** One twenty three subjects who completed adjuvant chemotherapy for early colon cancer 3–60 months earlier completed a questionnaire; 97 were randomised to complete an interview before or after the questionnaire. Preferences were elicited by the time trade-off method in 4 hypothetical scenarios. Concordance between the interview and questionnaire was assessed with the intraclass correlation coefficient (ICC).

**Results:** Median age was 65 years (range 19–86), 52% were female and 74% had involved lymph nodes. Over 60% of patients judged an additional 1 month beyond life expectancies of 5 years or 15 years, and an additional 1–2% beyond 5-year survival rates of 85% or 65%, sufficient to make chemotherapy worthwhile. Subjects with tertiary education ( $p = 0.003$ ) or aged 75 years or less ( $p = 0.02$ ) judged larger benefits necessary to make chemotherapy worthwhile. Concordance between the interview and questionnaire was high (ICCs 0.71–0.82).

**Conclusions:** Most subjects judged small survival benefits sufficient to make adjuvant chemotherapy worthwhile. A self-administered questionnaire was a valid and acceptable way of eliciting preferences.

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## 1. Introduction

Adjuvant chemotherapy is the standard treatment for patients with stage III colon cancer. 5-fluorouracil-based regi-

mens improved overall survival rates at 8 years by 10% (from 43% to 53%) for patients with stage III disease in a recent meta-analysis of randomised controlled trials.<sup>1</sup> The addition of oxaliplatin to a 5-fluorouracil-based regimen im-

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proved overall survival rates at 6 years by a further 4% (from 69% to 73%) for stage III patients in the MOSAIC trial.<sup>2</sup> For patients with stage II colon cancer, the benefits of adjuvant chemotherapy are more controversial, and absolute survival benefits shown have been smaller, for example, 3–5% at 5 years<sup>3–5</sup> Guidelines for adjuvant chemotherapy in patients with stage II colon cancer have therefore recommended that it be limited to those with high-risk features.<sup>6,7</sup>

Decisions about adjuvant chemotherapy involve a trade-off between its benefits, harms and inconveniences. The toxicities of 5-fluorouracil, folinic acid and oxaliplatin include those that are common but mild (e.g. fatigue); less common but life-threatening (e.g. febrile neutropaenia); and chronically disabling (e.g. neuropathy). Individual patients assign different importance to the various benefits and harms depending on their personal values, attitudes and circumstances. For adjuvant chemotherapy to be worthwhile, its benefits must be judged to outweigh its harms and inconveniences.

Preference studies determine the benefits judged sufficient to make the harms and inconveniences of treatment worthwhile.<sup>8</sup> Elicited preferences for chemotherapy vary widely between patients, but the minimum benefits required by most patients who have experienced chemotherapy are small.<sup>8–13</sup> For example, 50–70% of women who had adjuvant chemotherapy for early breast cancer judged a 1% improvement in 5-year survival rate sufficient to make their chemotherapy worthwhile.<sup>8,13</sup>

Published studies of preferences for adjuvant chemotherapy in colorectal cancer are limited. Chemotherapy-naïve patients with colorectal cancer were averse to chemotherapy in the first few weeks after their surgery, but their judgements were based on the limited information about chemotherapy.<sup>14,15</sup> Only patients who have had chemotherapy can offer personal insight into the actual harms and inconveniences of the treatment.<sup>11</sup>

The aims of this cross-sectional observational study were to determine the survival benefits that patients with early colon cancer judged sufficient to make the harms and inconveniences of adjuvant chemotherapy worthwhile, and the factors associated with their preferences. Our previous studies elicited preferences with a validated, scripted interview.<sup>13,16–18</sup> A secondary aim of the current study was to validate a self-administered preferences questionnaire for future studies.

## 2. Patients and methods

### 2.1. Patients

Patients who had completed adjuvant chemotherapy for stage II or III colon cancer 3–60 months prior were identified from departmental databases of the 12 participating centres. The patients were excluded if they received less than 4 weeks of adjuvant chemotherapy or if inadequate English or medical illness precluded successful completion of the study. 126 patients agreed to participate: 26 received chemotherapy as part of the National Surgical Adjuvant Breast and Bowel Project C-07 (NSABP C-07) trial<sup>19</sup> whilst 100 received chemotherapy as part of routine, clinical practice. Of these 100 patients, 3 were

excluded because they had ‘adjuvant’ chemotherapy after resection of metastatic disease, leaving a total of 123 for the final analysis. The patients were interviewed between July 2004 and August 2007. Written informed consent was obtained from each participating patient. Ethics committee approval was obtained from each participating centre.

### 2.2. Preferences

Preferences were elicited by questionnaires and interviews based on the methods of Simes and Coates,<sup>11</sup> and further modified and validated in our subsequent studies.<sup>13,16</sup> All interviews were performed by one of the three research personnel using a standardised script and forms. The questionnaires presented exactly the same hypothetical scenarios as a booklet completed by the patient.

The interview and questionnaire used the time trade-off method to determine the minimum survival benefit that patients judged necessary to make adjuvant chemotherapy worthwhile, based on their own experience of chemotherapy. The two different types of questions were survival time and survival rate questions. Each had two baseline prognoses, for a total of four hypothetical scenarios.

Survival time questions asked the patients to consider adding extra time to a baseline life expectancy. Survival rate questions asked the patients to consider adding extra percentage chance to a baseline survival rate. For example, the patients were asked to choose between life expectancies of 5 years without chemotherapy, or longer life expectancies with chemotherapy. Options were discrete and incremental, for example, ranging from 5 years and 1 day to a maximum of 20 years. Answers to these questions were used to identify the minimum amount of extra time (or percentage) that the patients judged sufficient to make chemotherapy worthwhile.

The baseline prognoses used in this study were life expectancies of 5 and 15 years and 5-year survival rates of 65% and 85%. These values were chosen as reflections of typical prognoses of patients with early colon cancer, and to facilitate comparisons with the data from patients with early breast cancer in our previous studies.

All 123 patients completed the preferences questionnaire. A subset of 97 patients who received their adjuvant chemotherapy as part of routine, clinical practice completed both the interview and questionnaire with the order determined by random allocation. Patients’ ratings of the questionnaire versus the interview were determined with 5-point Likert scales and open responses. Test-retest reliability, framing and anchoring effects of the interview have been evaluated previously.<sup>11,13</sup>

### 2.3. Other assessments

Patients’ demographic and other characteristics were elicited with a study-specific questionnaire. Details of patients’ cancer and treatment were obtained from patients’ medical records. Health-related quality of life during chemotherapy was assessed retrospectively with the Patient Disease and Treatment Assessment Form (Patient DATA Form),<sup>20</sup> a validated, self-rating questionnaire that includes 23 general items about symptoms, functions and global ratings; and 18

specific items about the side-effects and inconveniences of chemotherapy.<sup>13</sup> The ratings from the Patient DATA Form were used to assess the effects of health-related quality of life on patients' preferences.

## 2.4. Statistical methods

Statistical methods were based on those used in our previous preferences studies.<sup>11,13,16–18</sup> The end-points for descriptive purposes were the smallest survival benefits judged sufficient to make chemotherapy worthwhile for each of the four hypothetical scenarios.

The end-point for comparisons and correlations was the average of the responses from the two life expectancy questions (average additional time) to reduce the problems of multiple comparisons. Associations between the average additional time and the various patient, disease, treatment and health-related quality of life variables were assessed with linear regression after normal score transformation<sup>21</sup> of the highly skewed preferences data. Comparisons of health-related quality of life according to treatment received used t-tests for independent samples. All *P* values are two sided and used to indicate levels of support for associations, with lower *P* values indicating stronger associations.

Concordance between the interview and questionnaire was assessed with intraclass correlation coefficients (ICCs) and interpreted according to the guidelines of Landis and Koch.<sup>22</sup> Differences between preferences elicited with the interview and questionnaire for each of the four hypothetical scenarios were assessed with the Wilcoxon rank-sum test for paired data.

We planned to recruit 200 patients: 100 from routine clinical practice and 100 who participated in the NSABP C-07 trial.<sup>19</sup> Subgroups of 100 patients would give 95% confidence intervals no wider than  $\pm 10\%$  for simple proportions. Recruiting patients who participated in NSABP C-07 trial proved more difficult than expected and was stopped at 26 patients.

## 3. Results

### 3.1. Baseline characteristics

Patients' characteristics, disease and treatment details are summarised in Table 1. The median age was 65 years (range 19–86), half were female and most were married or in a de facto relationship. The majority had children and more than half had dependents (children or adults) at home. Most felt that support was available during chemotherapy if they needed it, and had a friend or relative who had died from cancer.

Adjuvant chemotherapy included 5-fluorouracil and folinic acid in all patients, given alone in 79%, in combination with oxaliplatin in 17% and for stage III disease in 74%. When interviewed, half the patients had completed their adjuvant chemotherapy from 1 to 3 years previously and only 11% had suffered recurrence of their cancer.

### 3.2. Experience of treatment

Patients' retrospective self-ratings of health-related quality of life during adjuvant chemotherapy are summarised in Fig. 1.

**Table 1 – Baseline patient, disease and treatment characteristics (n = 123).**

Characteristic	%
Female	52
Age at time of interview (years)	
<50	7
50–59	25
60–69	38
≥70	30
Marital status	
Married or de facto	80
Separated or divorced	7
Widowed	7
Single	5
Has children	87
Has dependent children	17
Has dependents (children +/- adults) at home	60
Support always available during chemotherapy	76
Friend or relative died of cancer	86
Highest level of education	
Primary school (6 years)	4
High school before intermediate (10 years)	20
Intermediate or school certificate (12 years)	24
Trade or technical qualification	22
University or college degree	29
Employment status at the time of interview	
Full-time	18
Part-time	14
Unemployed	1
Student	1
Retired	62
Home duties	4
Stage (TNM)	
II	26
III	74
Adjuvant chemotherapy regimens	
5FU + LV	79
5FU + LV + oxaliplatin	17
Other	4
Disease recurrence before interview	11
Years since completing chemotherapy	
<1	20
1 to <2	23
2 to <3	29
≥3	28

5FU, 5-fluorouracil; LV, leucovorin.

The 10 aspects of health-related quality of life rated most troublesome (highest mean score) included 4 physical symptoms: fatigue, nausea, altered taste and diarrhoea; 4 psychological symptoms: thought of actually having treatment, trouble concentrating, problems coping with treatment and anxiety; and 2 practical issues: problems with needles or injections and inconvenience of treatment. Energy was the most impaired aspect of well-being (lowest mean score), with lesser impairments in global ratings of well-being and mood. Aspects rated substantially worse by subjects who had oxaliplatin (difference in means on a scale from 0 to 10) included numbness or pins and needles (3.6,  $p < 0.001$ ) diarrhoea (2.6,  $p = 0.007$ ), irritability (2.6,  $p = 0.001$ ), anxiety (2.4,  $p = 0.002$ ) and sore hands or feet (2.2,  $p = 0.001$ ).

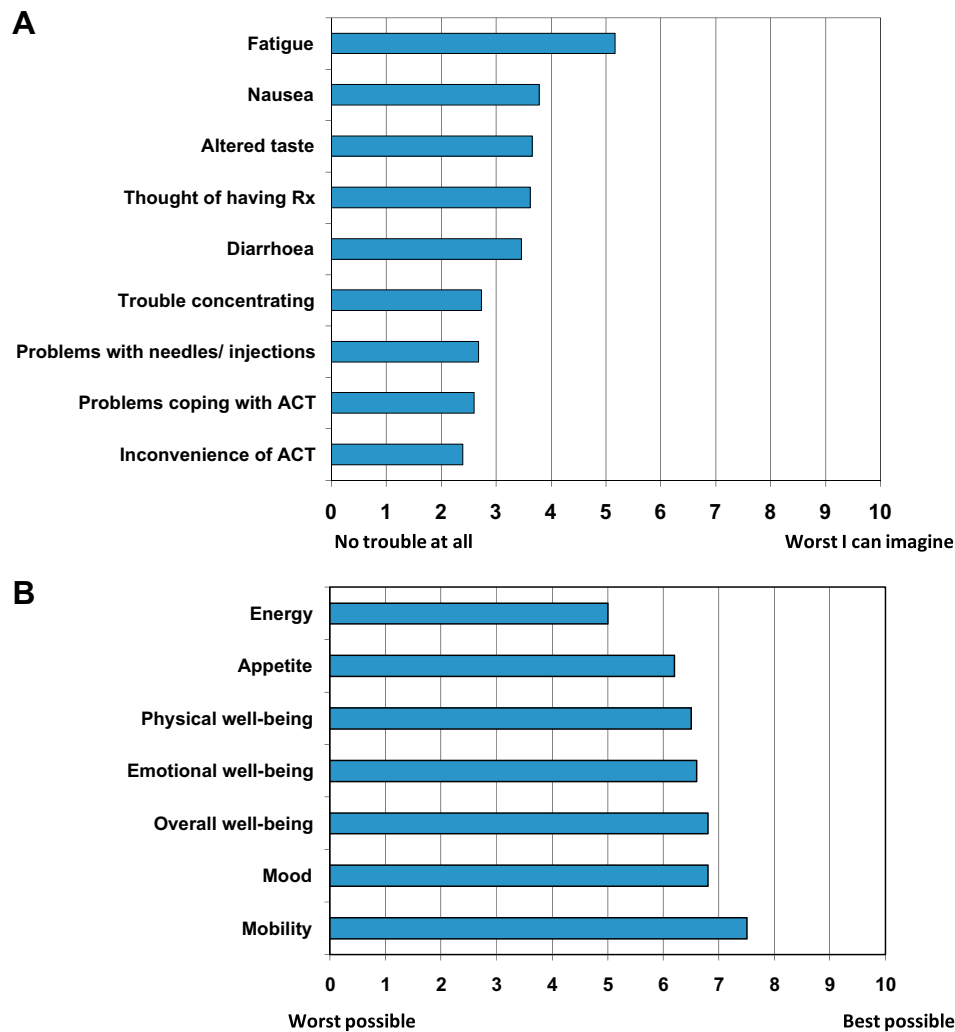


Fig. 1 – Aspects of (A) health-related quality of life and (B) well-being during adjuvant chemotherapy (mean of  $n = 123$ ).

### 3.3. Patients' preferences

Patients' preferences are summarised in Fig. 2. Most patients judged small survival benefits sufficient to make adjuvant chemotherapy for colon cancer worthwhile. For example, more than 60% of patients judged an extra 1 month beyond life expectancies of 5 years or 15 years, an extra 1% beyond a 5-year survival rate of 85%, or an extra 2% beyond a 5-year survival rate of 65% sufficient to make chemotherapy worthwhile. Nevertheless, there was wide variation in the preferences of individual patients. Although half of the patients needed only small benefits (1 day, 0.1%), 1–5% of patients judged even the largest possible survival benefits (15 years, 15% and 35%) insufficient to make chemotherapy worthwhile.

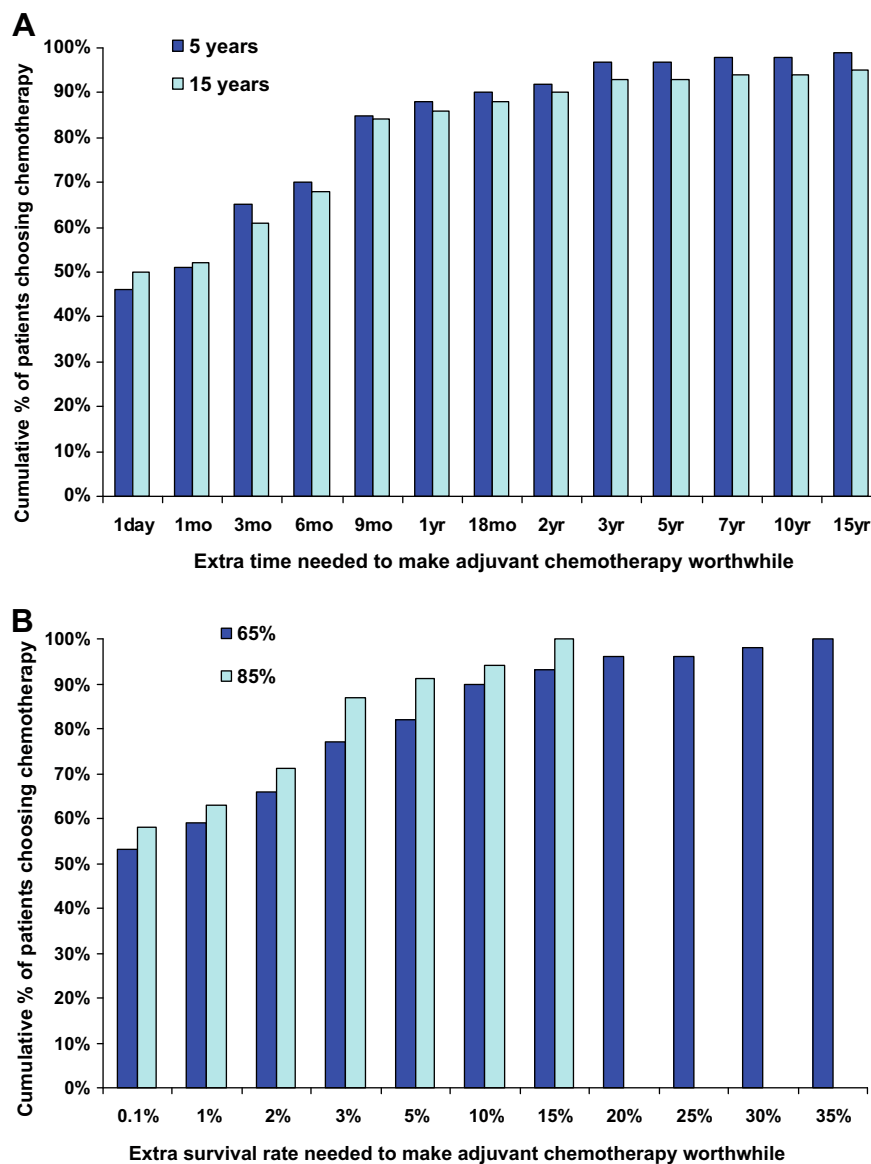
### 3.4. Factors associated with preferences

Tertiary education ( $P = 0.003$ ) and age 75 years or less ( $P = 0.02$ ) were associated with judging larger benefits necessary to make chemotherapy worthwhile. Patients with these characteristics required about 12 months more than the patients

without these characteristics (differences between median benefits judged sufficient). Preferences were not strongly associated with other baseline characteristics of patients, their disease or treatments, or aspects of health-related quality of life during chemotherapy (see Table 2).

### 3.5. Interview versus questionnaire

There were no significant differences in preferences according to whether they were first elicited by interview or questionnaire. Concordance between preferences elicited by interview and questionnaire is shown in Table 3. ICCs were consistent with good to excellent agreement (0.71–0.82). The benefits judged necessary to make chemotherapy worthwhile were somewhat higher when elicited with the interview than with the questionnaire for scenarios with a better prognosis. Patients' ratings of the questionnaire showed that few thought answering it was hard (10%) or stressful (6%) and most were glad that they took part in the study (91%). Over half rated the interview and questionnaire 'about the same' on ease of understanding, clarity and stressfulness.



**Fig. 2 – Cumulative proportions of patients considering whether adjuvant chemotherapy would be worthwhile for various improvements in (A) life expectancies of 5 and 15 years and (B) 5-year survival rates of 65% and 85% (n = 123).**

#### 4. Discussion

Most patients judged small survival benefits sufficient to make adjuvant chemotherapy for early colon cancer worthwhile. The benefits judged sufficient by most patients were smaller than the actual survival benefits observed in meta-analyses and randomised controlled trials of adjuvant chemotherapy for colon cancer. For example, 82% of patients judged an additional 5% in 5-year survival rates sufficient, and 90% an additional 10% sufficient, which compare favourably to the observed absolute overall survival benefits of 5% at 3 years seen with 5-fluorouracil and folinic acid alone,<sup>23</sup> and an extra 4% at 6 years with the addition of oxaliplatin.<sup>2</sup>

The preferences of individual patients were highly variable and there were few strong predictive factors. The most consistent predictors of preferences for adjuvant chemotherapy in a systematic review were the magnitude of benefit, ex-

pected toxicity, personal experience of chemotherapy and having dependent children at home.<sup>24</sup> We did not assess toxicity directly; however, retrospective ratings of chemotherapy symptoms were not strongly associated with preferences. Having dependent children at home was also not a significant predictor, but only 17% of patients in our study had this characteristic.

Two studies have determined preferences for surgical and adjuvant treatment options, including chemotherapy, for cancers of the colon or rectum.<sup>14,15</sup> Both studies elicited preferences in chemotherapy-naïve patients after curative surgery for colorectal cancer, but before the need for adjuvant chemotherapy was known. In contrast to our results, both studies reported an apparent aversion of the patients to chemotherapy and a willingness to trade large amounts of life to avoid it. Other studies comparing patients who have had chemotherapy to those who have not report similar differences. Pa-



**Table 2 – Associations between individual baseline characteristics and preferences: age 75 or less and tertiary education were associated with judging larger benefits necessary to make adjuvant chemotherapy worthwhile.**

Characteristic	P-value
<b>Patients</b>	
Female	0.3
Age at interview $\leq 75$ years	<b>0.02</b>
Had tertiary education	<b>0.003</b>
Was employed at the time of interview	0.9
Has a life partner	0.2
Lives with others	0.2
Has children	0.3
Has dependent children	0.4
Has dependents (children +/- adults)	0.5
Has support available at all times	0.1
Has friend/ relative who died from cancer	0.1
Had $\leq 30$ min to travel to chemotherapy	0.9
<b>Disease and treatment</b>	
Stage II (versus stage III)	0.3
Disease recurrence before interview	0.3
Oxaliplatin-containing regimen	0.4
>2 Years since chemotherapy finished	0.4
Received chemotherapy on clinical trial	0.8
<b>Experience of treatment</b>	
Fatigue	0.4
Nausea	0.9
Thought of actually having treatment	0.1
Trouble concentrating	0.2
Problems with needles or injections	0.5
Problems coping with treatment	0.2
Inconvenience of treatment	0.1
Anxiety (feeling worried)	0.8
Sore mouth or throat	0.7
Irritability (feeling cranky)	0.9
Problems doing what I wanted	0.1
Numbness or pins and needles	0.2
Energy	0.2
Appetite	0.9
Mood	0.5
Mobility	0.2
Overall well-being	0.4

tients who had experienced chemotherapy had more positive attitudes to it than those who had not,<sup>25</sup> and judged smaller benefits sufficient to make it worthwhile in studies of early breast cancer<sup>12,26,27</sup>, metastatic breast cancer,<sup>28</sup> testicular cancer<sup>29</sup> and heterogeneous cancers.<sup>30</sup> Such differences may be partly explained by 'cognitive dissonance reduction'.<sup>31</sup>

This is a psychological coping strategy that minimises regret about past decisions by considering them in a favourable light. A study confined to subjects who have experienced chemotherapy, like ours, will give lower estimates of the smallest benefits sufficient to make adjuvant chemotherapy worthwhile. However the advantage of only including subjects who have experienced chemotherapy is their personal knowledge of what having chemotherapy is actually like, and what it means.

Adjuvant chemotherapy seems to have been tolerated well in this study, although the use of oxaliplatin was associated with worse mean scores for several symptoms and aspects of well-being, as expected. Patients with early colon cancer in this study typically rated symptoms and aspects of well-being 1–2 points better than the patients with early breast cancer in a previous study, yet judged similarly small survival benefits sufficient to make chemotherapy worthwhile.<sup>13</sup> Differences in ages may partly explain this result, as the patients with breast cancer were younger than those with colon cancer in this study (median age 55 vs. 65 years).

Trivial benefits of 0.1% or 1 day were judged sufficient by about half our patients with early colon cancer (46–58%). We did not seek explanations as to why such small benefits were judged sufficient, but in previous studies reasons included minimising future regret, parenting concerns, doubts about the information provided and feeling that they had no choice.<sup>18</sup> Misunderstanding is a tempting explanation for judging negligible benefits sufficient to make toxic treatment worthwhile. While problems understanding and incorporating small probabilities in decision making are important, at least for some patients, a benefit of one extra day on a baseline of 5 or 15 years is hard to misunderstand. Preferences appear to have been motivated by more than simple trade-offs between direct benefits and harms of chemotherapy.

It was valid, feasible and acceptable to elicit the preferences of patients with either the interview or questionnaire. Whilst the benefits needed to make chemotherapy worthwhile were somewhat higher when elicited by the interview than the questionnaire for the good prognosis scenarios, the absolute differences between the two methods were small (differences between medians of 0.9% and 2 months) and not clinically significant. The practical advantages of using a questionnaire rather than face-to-face interviews make it our preferred method for future studies.

This study has limitations. Selection bias will result from only including patients who had adjuvant chemotherapy but not those who did not, for example, those who were not

**Table 3 – Concordance of interview and questionnaire (n = 97).**

Baseline prognosis	ICC	Median benefit judged sufficient with interview	Median benefit judged sufficient with questionnaire	Difference between medians from interview and questionnaire	P-value using WRST
65% 5-year survival	0.80	1%	1%	0	0.79
85% 5-year survival	0.75	1%	0.1%	0.9%	<b>0.02</b>
5-year life expectancy	0.82	3 m	3 m	0	0.82
15-year life expectancy	0.71	3 m	1 m	2 m	<b>0.04</b>

ICC, intraclass correlation coefficient; WRST, Wilcoxon rank-sum test; m, months.

referred for, not offered, or declined it. The preferences of these excluded patients are also of interest and worthy of study, however, they are fundamentally different because they are based on indirect knowledge and information, not personal experience. Including only patients who have completed chemotherapy may result in a group of patients with a more favourable prognosis, who consequently judge smaller benefits sufficient to make their 'successful' chemotherapy worthwhile. The few statistically significant predictive factors found may be due to the low prevalence of the tested characteristics. The applicability of our results to contemporary practice may seem limited by the small proportion of patients who received oxaliplatin. However, many patients still receive adjuvant chemotherapy without oxaliplatin, and use of oxaliplatin was not associated with substantially different preferences in our study. This study relies on patients' recollections of what chemotherapy was like, with the potential for recall bias. The lack of association between preferences and the interval since chemotherapy suggests that such bias, if present, is minimal.

The clinical implications of these results are that one size does not fit all for patients considering adjuvant chemotherapy for early colon cancer. Whilst most patients judged small benefits sufficient to make adjuvant chemotherapy worthwhile, individual's preferences varied widely and were not reliably predicted by their baseline characteristics. Clear and detailed review of the incidence and severity of the toxicities likely to be experienced by patients appear to be a very influential part of the decision-making process. Clinicians should explain the pros and cons of adjuvant chemotherapy and allow their patients' views, values, circumstances and priorities to influence discussions and decisions about adjuvant chemotherapy.

Areas worthy of future research include the attitudes and preferences of patients not having adjuvant chemotherapy; changes in preferences over time, particularly before and after having chemotherapy; and preferences for various targeted therapies with their distinct profiles of benefits, harms, inconveniences and costs.

In conclusion, most patients who experienced adjuvant chemotherapy for colon cancer judged small benefits sufficient to make it worthwhile. The preferences of individual patients varied widely and were difficult to predict. Our preferences questionnaire was feasible, valid, acceptable and suitable for future preference studies.

### Conflict of interest statement

None declared.

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