Pergamon

European Journal of Cancer Vol. 32A, No. 13, pp. 2267–2274, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00279-1

Original Paper

Surveillance Versus Adjuvant Chemotherapy in Stage I Non-seminomatous Testicular Cancer: a Decision Analysis

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In stage I non-seminomatous testicular cancer, the decision between surveillance and adjuvant chemotherapy rests heavily upon the valuation of quality of life. Decision analysis was used to assess at what relapse rate adjuvant chemotherapy is preferred when patients' and clinicians' valuations are considered. Probabilities were obtained from the literature and from experts. Valuations of the disease states were obtained from patients (n = 68) and clinicians (n = 50). Results from the model were compared with a treatment preference question, asking for the relapse rate directly. Adjuvant chemotherapy was preferred at relapse rates above 50% when patient valuations were used. The valuations of the disease states had a strong impact on the decision. Using clinician valuations, adjuvant chemotherapy was preferred at relapse rates above 73%. The relapse rates from the treatment preference question were lower: 46% for patients and 35% for clinicians. The results indicate that when patient preferences are accounted for, adjuvant chemotherapy should be considered more often.

Key words: testicular cancer, quality of life, patient preferences, medical decision making, adjuvant chemotherapy, surveillance

Eur J Cancer, Vol. 32A, No. 13, pp. 2267–2274, 1996

INTRODUCTION

SURVEILLANCE IS widely used in the management of non-seminomatous germ cell tumors of the testis (NSGCT) as an alternative to retroperitoneal lymph node dissection (RPLND) [1–3]. In this surveillance or 'Wait & See' (W&S) policy 26–33% of patients will relapse [1]. Histopathology can predict the risk of relapse [3, 4]. Several studies have stratified patients by the presence of these risk factors and have used adjuvant chemotherapy in the high risk groups. The selection of very low risk patients seems feasible, but that of very high risk patients (risks over 80%) has not been reported. The debate between advocates of surveillance and those favouring adjuvant chemotherapy in these patients is still ongoing [2]. Given the very good prognosis at relapse (95% long-term disease-free survival), the choice is not preeminently guided by survival considerations. The decision entails a weighing of the benefits and side-effects of either early treatment with two cycles of chemotherapy of all patients, or deferred treatment with four cycles of a subset of patients, those who relapse during surveillance. The relapse rate at which the benefits of adjuvant chemotherapy outweigh its disadvantages depends on value judgments: what values are assigned to the quality of life during or following surveillance, chemotherapy and surgery for residual disease? This is a typical example of a dilemma in which patient values are of major importance.

Decision analysis is a useful tool in such a situation in which the probabilities of the outcomes need to be com-

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Received 22 Feb. 1996; revised 11 Jun. 1996; accepted 18 Jul. 1996.

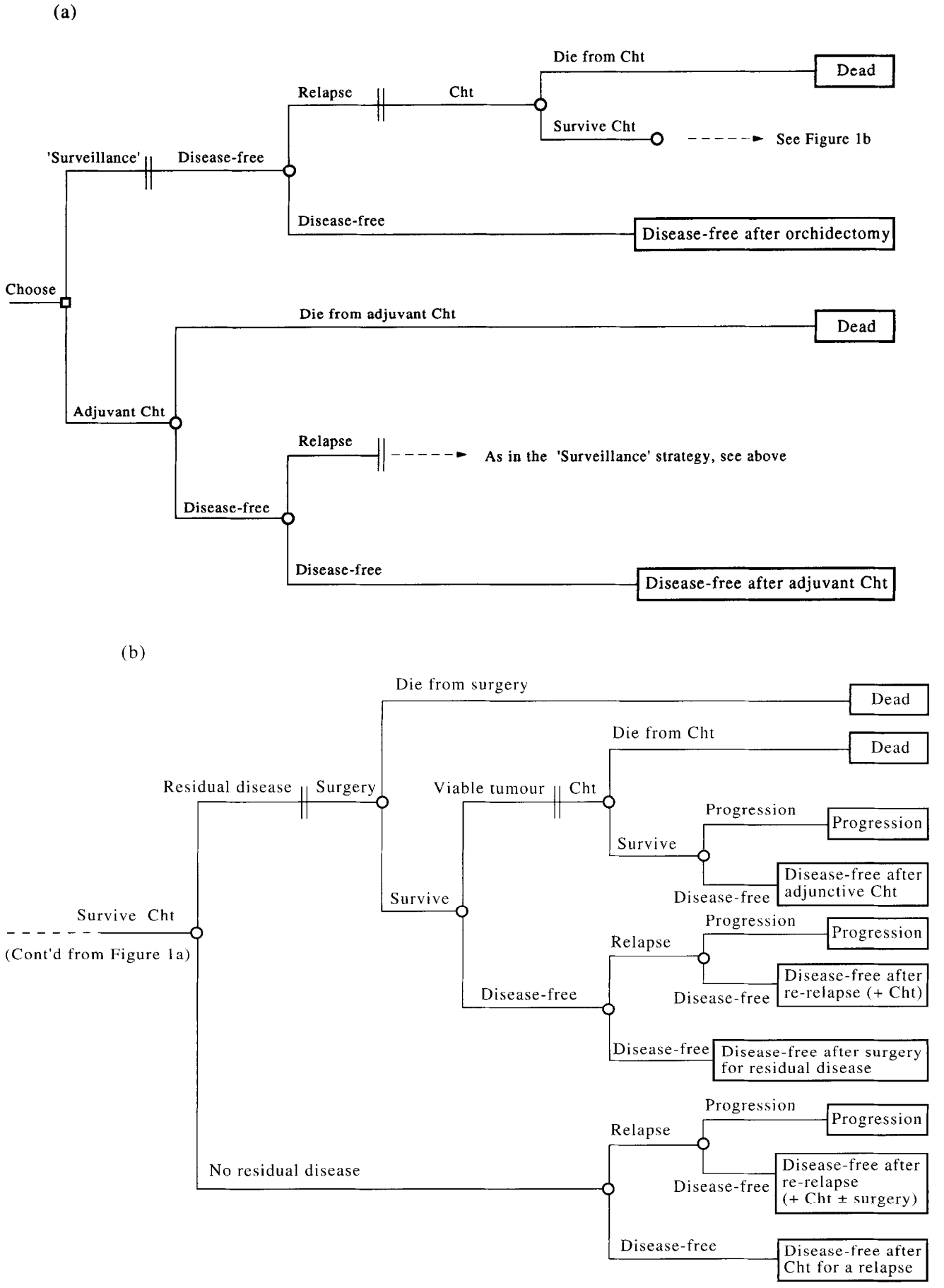

Figure 1. Decision tree for the management of stage I non-seminomatous germ cell tumours of the testis (NSGCT). Two clinical strategies are represented: a surveillance or 'Wait & See' policy and two courses of adjuvant chemotherapy (Cht).

Table 1. Probabilities used in the decision model

Probability of:	Point estimate	Plausible range	References*
Natural mortality	Age-dependent	id.	Netherlands Central Bureau for Statistics
Surveillance			
Relapse	0.27	0.13–0.35	1, **16**, 7, **23**, **25**, 26, 27
Death from chemotherapy	0.005	0.001–0.01	17, 14, 26, 28, 29
Residual tumour after primary chemotherapy	0.16	0.02–0.30	8, 27†, 30
Mortality from surgery for residual disease	0.007‡	0.003–0.011	20, 25, 27, 30
Viable tumour after surgery for residual disease	0.16	0.10–0.35	**19**, 8, 27, 31
Disease-free after adjuvant chemotherapy following surgery for residual disease	0.53	0.41–0.82	**31**
Relapse while disease-free after surgery for residual disease	0.09	0.07–0.10	7, 31, 32
Disease-free after second relapse following surgery for residual disease	0.38	0.36–0.40	8, 32
Relapse while disease-free following primary chemotherapy	0.04§		3
Disease-free following second relapse	0.20‖	0.20–0.25	26

* Point estimates are midpoints of the range, unless the reference is printed in bold. In that case, the reference cited is an overview using a pooled estimate, weighted for the number of patients in each study, and is used as the point estimate. † Refers specifically to low volume disease and is used as the point estimate. ‡ Assuming 50% Retroperitoneal Lymph Node Dissection (RPLND) only and 30% thoracotomy + metastatectomy with or without RPLND [25, 33], with respective mortalities of 0.3% [25] and 1.8% [30]. § Data from reviews pertained to Stage II and ranged from 0.08–0.10 [9, 28, 34], which will be an overestimate for Stage I, so the value from the MRC study [3] was used, following expert opinion. ‖ Following expert opinion; of which 78% was rendered no evidence of disease without surgery [18].

bined with the values assigned to these outcomes. The values are described numerically, as a utility, on a scale from 0–1, in which death is defined as 0 and good health as 1 [5]. The ultimate goal in clinical policy making is maximising long-term quality-adjusted life expectancy. To fulfil this goal, utilities should be obtained from patients who are in the actual health states to be valued, as the patients are the best judges of their own quality of life. Sometimes those of healthcare professionals are used, as their opinion matters in clinical practice. Utilities are combined with life expectancies for different treatment strategies to obtain Quality Adjusted Life Expectancy (QALE). The strategy with the highest QALE is the strategy of choice. The impact of possible errors in—or imprecision of—the data can be assessed in sensitivity analyses. In these analyses, parameters (e.g. probabilities or utilities) which can be expected to affect a decision [5], are determined.

Another way to assess the relapse rate at which adjuvant chemotherapy is preferred, is to ask patients or clinicians directly for their preferences. The answer incorporates the values of the treatment outcomes in an implicit way.

The first aim of our study was to assess, by means of a decision analysis, at what relapse rate a surveillance policy is preferred to adjuvant chemotherapy in clinical Stage I NSGCT, when patient utilities are incorporated. Secondly, we evaluated the effect of substituting clinician utilities for those of patients. Finally, we assessed directly the preferences regarding adjuvant chemotherapy of patients and clinicians, and compared these with the results from the decision analysis.

* Not shown in the figure, but present in the model, is the branch representing the natural mortality.

MATERIALS AND METHODS

Decision model

A decision tree was constructed to examine two strategies: (1) surveillance and (2) two courses of adjuvant chemotherapy followed by close surveillance. This decision tree (Figure 1) is a simplified model of possible events following orchidectomy*. The following assumptions were made: (a) the first 5 years following orchidectomy are of primary importance, as most subjects are considered to be cured after 5 years; (b) no discounting for life years is needed because of the short time span of the analysis and the low mortality rates involved; (c) where adjuvant chemotherapy does not cure, it postpones recurrence by the duration of the chemotherapy.

The expected utility of each strategy was calculated by 'averaging out and folding back' [5]. In this process, the time spent in the disease states in each branch of the tree is multiplied by the utility of the states, to obtain quality adjusted life expectancy. This then is multiplied by the probability of occurrence of the branch, and summed per strategy.

The model was implemented in Decision Maker Version 7.01.

Data used in the model

Probabilities. We carried out a MEDLINE search of the literature from 1990 through 1995 for reviews on NSGCT. Data from these articles were supplemented with data from the state of the art volume *Testicular cancer. Investigation and Management* [6]. Some probabilities could not be obtained from the literature and were based on expert opinion (GS, HJK). Probabilities used for the surveillance strategy are shown in Table 1.

The probability of death from adjuvant chemotherapy was assumed to be half that of chemotherapy for a recur-

Table 2. Utilities of the disease states in the baseline model: means and 95% confidence intervals (CI)

Disease state	Patients			Clinicians		
	n	Mean	(95% CI)	*n*	Mean	(95% CI)
Disease-free following orchidectomy	17	0.953	(0.907, 0.999)	50	0.922	(0.900, 0.943)
Chemotherapy	13	0.924	(0.872, 0.976)	49	0.755	(0.718, 0.791)
Disease-free following chemotherapy	23	0.937	(0.881, 0.994)	49	0.879	(0.851, 0.906)
Disease-free following surgery for residual disease	12	0.934	(0.829, 1.000)	49	0.876	(0.848, 0.903)
Disease-free following surgery + chemotherapy for residual disease	3	0.922	(0.656, 1.00)		–*	

* Utility of disease-free following surgery for residual disease used in baseline.

rence (two courses are given instead of four). The reported relapse rate in high risk patients receiving adjuvant chemotherapy varies from 0 to 10% [1, 7]. As it can be expected to depend on the relapse rate without adjuvant chemotherapy, it was assumed to be a proportion (10%) of the probability in the surveillance strategy. The probability of viable tumour following surgery for residual disease was assumed to be between 0.16 (the figure following primary chemotherapy in the surveillance arm), and 0.50 (the figure for viable tumour following salvage chemotherapy [8])*. The chance of a second relapse while in remission from a first relapse was taken to be between 0.04 (that of the surveillance strategy) and 0.50 (that following salvage chemotherapy [9]). For these two variables, in the baseline analysis the midpoints, 0.33 and 0.27 respectively, were used. For the remaining probabilities the estimates from the surveillance strategy were used. The effect of varying the probabilities was assessed in sensitivity analysis.

Utilities. Utilities were obtained in interviews with consecutive patients with good prognosis non-seminoma (EORTC/MRC classification: a predicted 3-year disease-free survival of 93% [10]), who were being treated, or had received treatment in the previous 2 years, at the Leiden University Hospital, the Rotterdam Cancer Institute, or the Hospital of the Free University, Amsterdam (72 were approached, 68 (94%) participated). Utilities were assessed by means of a Time Trade-Off question. The patients were asked how many years x in perfect health they would consider equivalent to their remaining life expectancy (y) in the health state of the week before. The utility is x/y (for details see [11]).

The utilities of clinicians were obtained from a questionnaire sent to all medical oncologists, urologists and radiotherapists ($n = 81$) in the same three hospitals. Fifty questionnaires were returned completed (62%). Utilities were obtained by means of a Visual Analogue Scale (see Appendix 1). This method can be applied in a questionnaire, whereas, for the Time Trade-Off, interviews are needed. Group mean scores on a Visual Analogue Scale can be transformed to Time Trade-Off scores by the power function [12]:

$$\text{Time Trade-Off} = 1 - (1 - \text{Visual Analogue Scale})^{1.61}.$$

Utilities were assessed from patients in the five following states: 'disease-free following orchidectomy' ($n = 17$), 'chemotherapy' ($n = 13$), 'disease-free following chemotherapy' ($n = 23$), 'disease-free following surgery for residual disease' ($n = 12$), and 'disease-free following chemotherapy after surgery for residual disease (adjunctive chemotherapy)' ($n = 3$). The utilities are shown in Table 2. We did not assess utilities of the states 'progression' and 'surgery for residual disease'. The impact of these states on the analysis was expected to be small, due to the very infrequent occurrence and the short duration, respectively. Estimates for these utilities were based on the opinion of healthcare professionals familiar with the state. The utilities of 'adjuvant chemotherapy' and 'disease-free following adjuvant chemotherapy' could not be obtained from patients as this treatment is not given in The Netherlands. For these, the respective values of the chemotherapy for relapse states following surveillance were used.

Finally, values had to be assumed for the quality adjustment in the additional model for total life expectancy for the period beyond 5 years. On the one extreme, we assumed that utilities returned to 1 after being cured (i.e. no long-term side-effects of disease or treatment). On the other extreme, utilities of the first 5 years were used as quality-adjustments.

The impact of varying all assumed values was evaluated in sensitivity analyses.

Durations of states. Time to relapse was taken to be 4 months, based on the prospective study of the Medical Research Council [3]. Chemotherapy for a relapse was considered to take 3 months; time between chemotherapy and surgery for residual disease 2 months; surgery and recovery 1 month; chemotherapy following surgery 2 months; time to second relapse following complete remission after induction chemotherapy 6 months, and after surgery for residual disease 1 year; duration of progression 6 months; duration of chemotherapy for second relapse 3 months; duration of adjuvant chemotherapy 6 weeks. Mortality was assumed to occur halfway between the respective time periods.

Treatment preference

The direct choice of patients was assessed during the interview in which the utilities were measured, by means of a Treatment Preference method [13]. We offered the patient a hypothetical choice between two policies. In the adjuvant chemotherapy policy, the relapse rate was fixed at 5%, in surveillance the probability was varied until the respondent switched his preference (Appendix 2). Data were only available from the last 51 patients, due to late introduction of the method ($n = 11$ disease-free during surveillance, 10 chemotherapy, 19 disease-free following chemotherapy, and 11 disease-free following RPLND (± adjuvant chemotherapy)). The mean relapse rate was

* The rationale for these assumptions is as follows. The patient has not been pretreated heavily, so chemotherapy for a relapse after adjuvant chemotherapy is different from salvage chemotherapy. However, it is not similar to chemotherapy for a relapse during surveillance either.

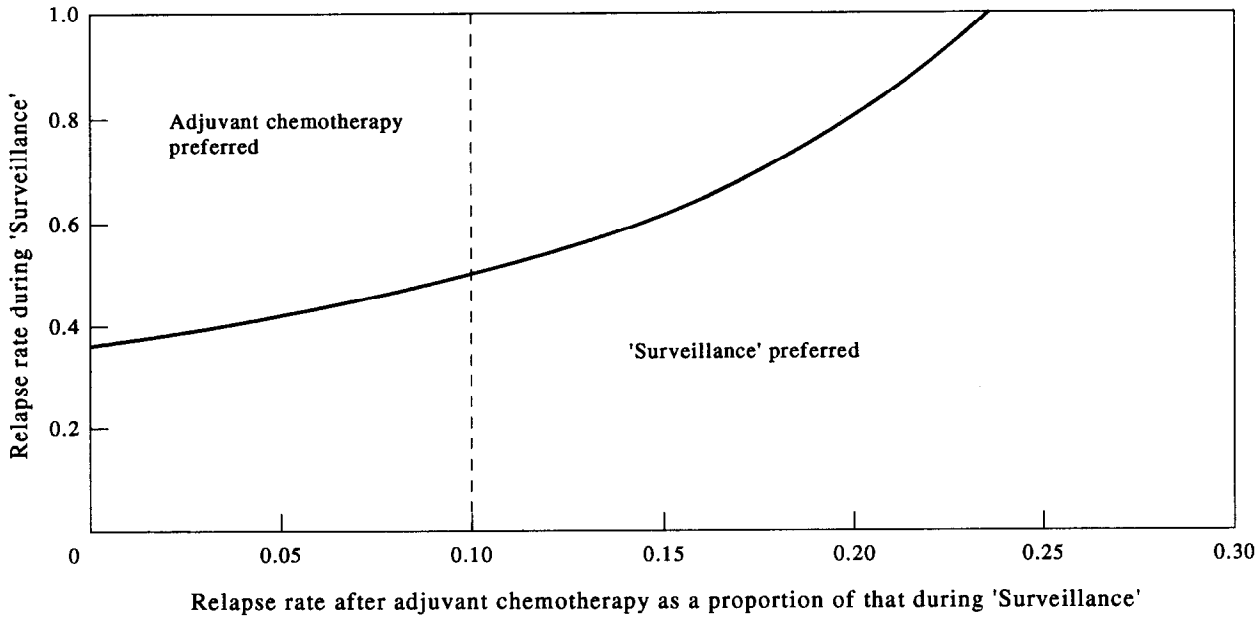

Figure 2. Two-way sensitivity analysis for the relapse rate following adjuvant chemotherapy: effect on the relapse rate during surveillance above which adjuvant chemotherapy became the preferred strategy.

weighted according to the expected distribution of patients over the disease states, to make it comparable with the rate resulting from the decision model.

The treatment preference of clinicians was obtained by the aforementioned questionnaire. We asked the clinicians to imagine the situation in which it would be possible to identify a 'high risk' group of Stage I NSGCT patients, and to indicate at what minimal relapse rate they would consider treating these patients with two or three courses of adjuvant chemotherapy (bleomycin, etoposide and cisplatin).

RESULTS

Results from the decision model, patient perspective

Baseline analysis, 5-year survival. When no quality-adjustment was used, adjuvant chemotherapy was preferred over surveillance; survival was 99.4 and 98.1%, respectively. In the baseline quality-adjusted analysis, Surveillance was preferred to adjuvant chemotherapy: QALEs were 56.24 and 55.72 months, respectively, an advantage of under 16 days. Results were similar for all ages. The relapse rate during surveillance at which adjuvant chemotherapy was preferred was 51%.

Sensitivity analyses

Probabilities. The decision was highly sensitive to the relapse rates in both strategies. In Figure 2, the impact is seen of simultaneous variation of the probabilities of relapse during surveillance and of relapse following adjuvant chemotherapy. If adjuvant chemotherapy eradicates all microscopic disease, it is preferred at a relapse rate during surveillance of 36%. If adjuvant chemotherapy does not reduce the relapse rate to less than 23% of that during surveillance, it is never preferred.

The decision was insensitive to changes in the other probabilities.

Utilities. The decision was highly sensitive to changes in the utilities, particularly in the utilities of 'disease-free during surveillance' and 'disease-free after adjuvant chemotherapy' (Figure 3). Adjuvant chemotherapy was preferred if the utility of 'disease-free during surveillance' was less than 0.941, i.e. not much lower than the baseline value of 0.953 (Figure 3a), and well within the 95% confidence interval. Of the patients, 24% had assigned lower values. Had their scores been used, adjuvant chemotherapy would have been preferred.

The utility of 'disease-free after adjuvant chemotherapy' may be expected to be higher than its baseline value (that of 'disease-free after chemotherapy for a relapse'), as the chemotherapy dose is lower and the prognosis is better. At values of 0.947 and higher, adjuvant chemotherapy was preferred (Figure 3b). Of our patients, 78% had higher values. If one assumes the utility of this state to be the same as that of 'disease-free during surveillance' then adjuvant chemotherapy is preferred at a relapse rate as low as 9%.

Durations. The result of the analysis was not sensitive to changes in the various durations within a clinically realistic range.

Extension to lifelong survival. If quality-adjustment is based on the utilities of the first 5 years, surveillance is preferred. QALEs were 46.81 years versus 46.49 years for adjuvant chemotherapy, an advantage of 3.8 months. Without quality-adjustment beyond 5 years (assuming all utilities to be 1.0), QALEs were 49.09 years for surveillance and 49.30 for adjuvant chemotherapy, a difference of 2.5 months in favour of chemotherapy. Thresholds for the relapse rate were 42% in the former, and 14% in the latter case.

Results from the model: clinician perspective

When clinician utilities were used, surveillance was preferred. QALEs were 53.93 and 52.10 months, respectively, a difference of 55 days. The relapse rate at which adjuvant chemotherapy was preferred was 74%. The utility of 'disease-free after adjuvant chemotherapy' can be assumed to be in the range of 0.879 (the baseline value, i.e. that of 'disease-free after chemotherapy for a relapse') to 0.922 (the utility of 'disease-free during surveillance'). At this latter

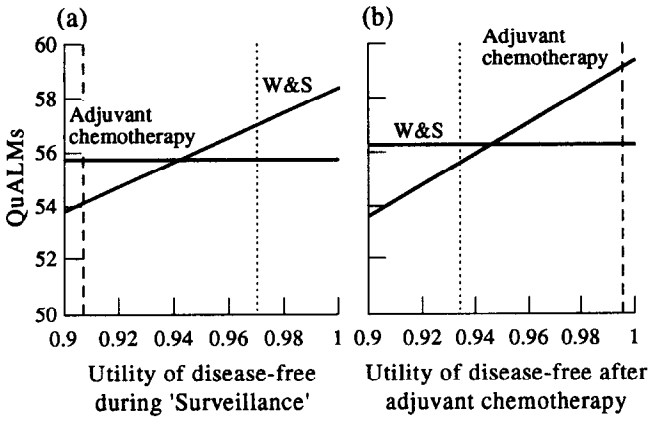

Figure 3. Sensitivity analysis for the utility of the states disease-free during surveillance (a) and disease-free after adjuvant chemotherapy (b): effect on QuALMS (. . . ., baseline value; - - - -, 95% confidence interval).

value, adjuvant chemotherapy was preferred at a relapse rate of 11%.

Treatment preferences of patients and clinicians

The mean score for the patients was 46%*, that for the clinicians 35%. Medical oncologists were the least willing to offer adjuvant chemotherapy (at a risk of relapse of 44%), urologists and radiotherapists indicated an approximately equal risk of relapse (31 and 29%, respectively).

DISCUSSION

Surveillance is widely used in Stage I NSGCT. We used decision analysis to assess at which relapse rate adjuvant chemotherapy would be preferred. At a relapse rate of 51% or higher, adjuvant chemotherapy was preferred over a surveillance policy. The decision was a 'close call': in the baseline analysis, surveillance was better than adjuvant chemotherapy by only 16 days. In our model, we did not include a possible third strategy, nerve sparing RPLND, as it is not used in any of the three participating institutes. The choice between surveillance and RPLND has been discussed extensively in the literature e.g. [1, 2, 3, 16], and, in many centres in The Netherlands and other parts of Europe, surveillance is used as an alternative to RPLND.

The figures for the medical oncologists and the patients in the direct treatment preference question are strikingly similar (46 and 44%), and are even somewhat lower than the rates in high risk groups identified in some of the prognostic models [3, 4, 14]. Cullen found that the majority of clinicians and patients would prefer adjuvant chemotherapy in a high risk situation [14]. It should be noted that the relapse rate given by the patients is not the same as that which would have been obtained from patients actually facing the decision (the mean for the patients in the surveillance strategy in our study was 52%, data not shown). The actual experience with disease and treatment (in case of a relapse) influences the preference. However, in this way, direct treatment preference and preference according to the decision model can be compared.

The analysis was very sensitive to the utilities of some states. Clinicians' utilities have been shown to be lower than those assigned by patients in our study as in most other studies. These differences stress the need for an explicit incorporation of patient preferences in decision making.

Both the results from our decision analysis and the direct preferences of patients and clinicians would imply that, at a risk of relapse of 40 to 50%, adjuvant chemotherapy would be a policy worth being considered, in the context of a trial at least. Using the prognostic index of the Medical Research Council [4], patients with three or four of the following risk factors would be eligible: vascular invasion, lymphatic invasion, absence of yolk sac elements, and presence of embryonal carcinoma. This is the only index that has been validated as yet in an independent patient population [3].

Given the sensitivity of the decision to the utilities, randomisation may not be deemed ethical by some. Also, it will be difficult to enrol enough patients to show statistically significant differences in a trial. An alternative might be the so-called preference trial [15]. Patients, after informed deliberation, choose their own preferred treatment. The actual consequences of patients' choices can be assessed prospectively, as well as patients' quality of life and utilities. New evidence (e.g. from improvement of the relapse prediction models) can also be accommodated.

For some of the probabilities, empirical estimates were scarce. Even in large studies, the number of patients experiencing adverse outcomes, such as second-relapses, is small, and the percentage unstable. Most of the data on secondary therapy pertain to stage II tumours and do not fit our model. For the adjuvant chemotherapy strategy, even fewer data were available. For this reason, meta-analytical techniques were only used for parameters for which sufficient literature was available (pooled estimates, weighted by the numbers of patients in the studies). To assess the validity of the probabilities used, we carried out an analysis using survival as an endpoint, and compared the results with survival data from the literature. Survival for the surveillance strategy was 98.1%, in between the 98% reported by Schmoll [16] and the 99% reported by Sternberg [7]; both are overviews of large patient numbers. The long-term disease-free rate following chemotherapy for residual viable cells at resection was 62% in our analysis, within the range of the 59% reported by Bajorin and Bosl [17], the 65% reported by Hudes and coworkers [18], and the 50–80% found in an overview by Steyerberg and coworkers [19]. This concordance with the literature supports the validity of the probabilities used.

Negative sequelae that may have an impact on the—assumed—utility of 'disease-free following adjuvant chemotherapy' are chemotherapy-induced infertility and secondary tumours. Given the low dose of chemotherapy, the chances of these outcomes occurring are small. Even after chemotherapy for a relapse, the recovery from fertility may be quite high, while patients on surveillance also have impaired fertility [20]. A recent review on secondary tumours concluded that the risk of solid tumours is not significantly elevated. The risk of leukaemia was increased for the doses of etoposide used, but this was beyond the scope

* This is a weighted average, based on the actual distribution of patients over disease states (74% disease-free during surveillance, 21% disease-free after chemotherapy, 5% disease-free after RPLND).

of our analysis [21]. In a recent study, no adverse late sequelae were detected within a median follow-up time of more than 6 years [22].

An objection raised against adjuvant chemotherapy may be that the benefits do not outweigh the financial costs. However, for patients in whom a recurrence has been prevented, the costs of treatment of the recurrence are avoided. Moreover, if one could reduce the intensity of follow-up after adjuvant chemotherapy, this may largely compensate for the costs of the chemotherapy itself. Another aspect to be taken into account in the decision is the feasibility of regular, qualified follow-up, a prerequisite for surveillance. This argument is often raised in the discussion about the choice between surveillance and nerve sparing RPLND [16, 23] and might hold similarly for the choice between surveillance and adjuvant chemotherapy. The argument is particularly relevant given the reports on late relapses that advocate life-long follow-up [24].

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Acknowledgements—We would like to acknowledge Jan Molenaar, Ger Dahmen, Dr A. H. van Hattum, Thérèse van Eijk and Marjo Schuurmans for their assistance in patient selection; Maartje Heyboer for assistance in interviewing the patients and for data management; colleagues of the Medical Decision Making Unit for their comments on an earlier version of this paper; and all patients and clinicians for their contribution to this study. The research presented in this paper was supported by The Netherlands Cancer Society (grant IKW 90-13).

APPENDIX 1

Visual analogue scale questions posed to clinicians

Would you indicate on the lines below, anchored on the left by death and on the right by perfect health, how you would value the **average** health state of one of your patients in the respective state (based on your clinical experience). The question does not pertain to prognosis, but to how good or how bad you judge the patients in the respective health states to be feeling. Please do not just think

about physical aspects, but also about psychological and social aspects that are influenced by the disease and treatment.

Please indicate your judgment by marking the line at that point at which you think the average of your patients in the health state is located.

Health state 1

A patient 6 months after orchidectomy, in a surveillance protocol (monthly follow-up visits).

death perfect health

Health state 2

A patient with a good prognosis stage II tumour, at the follow-up visit following the second of four courses of BEP chemotherapy.

Health state 3

A patient with a good prognosis stage II tumour, at the monthly follow-up visit, 3 months after the last of four courses of BEP chemotherapy.

Health state 4

A patient with a good prognosis stage II tumour, at the monthly follow-up visit, 6 months after a retroperitoneal lymph node dissection (adjunctive, following four courses of BEP chemotherapy).

APPENDIX 2

Treatment preference question posed to patients

The patient is asked to imagine that the testicular tumour were detected now. It would be a somewhat different form, for which two treatment options would be available. The two strategies are explained, and the following treatment card is shown:

Treatment A. Surgery followed by a surveillance policy

- Chances of the disease recurring **25%**; in that case treatment with chemotherapy.

Treatment B. Surgery followed by chemotherapy

- All patients suffer from side-effects of chemotherapy.
- Chances of the disease recurring 5%; this implies that **25%** – 5% = **20%** of the patients benefit from chemotherapy.
- A large number of patients receive unnecessary chemotherapy.

We began with a relapse rate during surveillance of 25%, and asked the patient which scenario he/she preferred. If he/she preferred the surveillance scenario, we raised the relapse rate by means of a bracketing procedure (ping-pong wise, offering alternating high and low relapse rates). If he/she preferred the chemotherapy scenario, we lowered the relapse rate in the same way. The point of indifference was sought. It was stressed that the choice would not affect survival.