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DECISION ANALYSIS—A HELPFUL TOOL FOR CLINICIANS TO ESTABLISH DIAGNOSTIC–THERAPEUTIC GUIDELINES?

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In this paper we focus on the question: Does decision analysis provide a framework to assess the value of diagnostic tests in clinical practice and how can it be used by clinicians in establishing diagnostic–therapeutic guidelines. To study this question we performed two analyses concerning the use of pelvic lymphadenectomy and pedal lymphography for staging prostate cancer. Both analyses yielded similar results as far as the preferred strategy was concerned, yet the approach and set up of the two analyses were different. The first analysis was performed in accordance with the textbooks on decision analysis. However, using this traditional approach we encountered some difficulties: in structuring the decision tree, in eliciting values for the quality of life parameters, and in interpreting the results. These difficulties urged us to modify the approach, presented in the second analysis. In this second analysis, the decision problem was split into several consecutive decision problems which corresponded to the questions posed by the clinicians. Longevity and quality of life were considered separately and the consequences of treatment and testing, which affect the quality of life of the patients, were indicated by just two parameters. Finally, the result of the analysis was expressed in clinically meaningful terms. The second analysis is compared with different approaches presented in the literature for analyzing decision problems involving diagnostic tests. Despite some unresolved methodological problems it is concluded that decision analysis provides a good framework for clinicians to structure and analyze complex decision problems.

The present paper focuses on the question: Does decision analysis provide a framework to assess the value of diagnostic tests in clinical practice and how can it be used by clinicians in establishing diagnostic–therapeutic guidelines.

To study this question we performed a decision analysis to evaluate pelvic lymphadenectomy and pedal lymphography for staging prostate cancer. The analysis was meant to assist clinicians in establishing guidelines for treating patients with clinically localized prostate cancer. At first we used the traditional approach in accordance with the textbooks on decision analysis (1). A decision tree was constructed which incorporated all possible chance events and outcomes relevant to the decision when to perform a lymphadenectomy or lymphography. Quality-adjusted life expectancy was chosen to compare the several diagnostic–therapeutic strategies. However, the tree was very bushy, unintelligible for the clinicians and could not be quantified in a reliable and acceptable way. Moreover, major difficulties were encountered in interpreting and discussing the results with urologists and radiotherapists.

Others have also recognized some of these difficulties when applying decision analysis to clinical problems involving two or more diagnostic tests (2–7). However, this did not make them turn their backs on decision analysis. Polister (8) stated in his article on the problems and

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limitations of decision analysis and clinical intuition: 'The difficulties inherent to decision analytic methods often seems to be lessened when the consequences of not using them are considered'. 'For this reason', he continues, 'the problems have not been a disillusionment to many, but rather a stimulus for the development of better methods and a more appropriate use of existing ones'.

The difficulties we encountered during the first analysis forced us to think of the following questions: 'How to set-up the analysis'?, 'Which parameters to include in the analysis'? and, 'How to present the results of the analysis'? Having considered these questions and being inspired by the discussions with the clinicians we decided to perform a second modified analysis. In this second analysis the decision problem was split into several consecutive decision problems which corresponded to the questions posed by clinicians. Longevity and quality of life were considered separately and consequences of treatment and testing which affected the quality of life of patients were presented by just two parameters. Finally, the result of the analysis was expressed in clinically meaningful terms. In the present paper we present on outline of the two analyses and discuss the difficulties encountered in the first analysis, which urged us to modify the approach presented in the second analysis. The analyses are presented for patients with clinical stage B prostate cancer with a low or intermediate risk of metastases and a well- or moderately differentiated tumor. The curative treatment considered in this paper, is radiotherapy.

We then discuss different approaches suggested by several authors to analyze decision problems involving diagnostic tests, and compare them with our modified analysis. Finally some conclusions are presented on the use of decision analysis as a framework for clinicians to structure and analyze complex diagnostic–therapeutic decision problems.

The first analysis—A traditional approach

The traditional decision analytic approach entails four basic steps (1):

1. identify the decision problem,
2. structure the decision problem,
3. quantify the decision tree,
4. analyse the decision tree.

Step 1: Identify the decision problem

The decision problem concerns the diagnostic work-up of patients with clinically localized prostate cancer, stage B. The problem is defined by the following clinical facts:

- Prostate cancer can only be cured when there are no distant metastases
- Curative treatments, i.e. radical prostatectomy and radiotherapy, are burdensome to patients
- Regional lymph node metastases are considered risk markers; their presence is strongly correlated with the presence of distant metastases
- Pelvic lymphadenectomy is a very accurate, but burdensome test to detect lymph node metastases are also occasionally associated with mortality
- Diagnostic imaging tests, such as CT-scan and lymphography, are less accurate, but without any significant mortality or morbidity.

In the analysis two diagnostic tests are considered in order to identify patients with metastases: pelvic lymphadenectomy and pedal lymphography. Mortality as well as morbidity are taken into account.

Step 2: Structure the decision problem: the tree

The decision problem concerns two diagnostic tests; pelvic lymphadenectomy and pedal lymphography. Lymphography may be followed by lymphadenectomy but not vice versa, hence, six strategies are possible:

Strategy I: Curative treatment without testing.

Strategy II: Lymphadenectomy, followed by curative treatment only if the nodes are negative.

Strategy III: Lymphography, followed by curative treatment only if the lymphogram is negative. If positive, withhold curative treatment.

Strategy IV: Lymphography, followed by lymphadenectomy only if the lymphogram is negative. If positive, withhold curative treatment.

Strategy V: Lymphography, followed by curative treatment when the lymphogram is negative. If the lymphogram is positive perform lymphadenectomy, followed by curative treatment only if the nodes are negative.

Strategy VI: Non-curative treatment.

These six strategies are presented in the decision tree in Fig. 1.

The result of the lymphography is represented by the chance nodes 9, 14 and 15. The result of the pathohistological examination of the lymph nodes after lymphadenectomy is represented by the change nodes 5 and 7. Pelvic lymphadenectomy is associated with operative mortality and long-term morbidity, represented by chance node 4. Curative treatment, in this analysis equivalent to radiotherapy, is not associated with immediate mortality, but several long-term complications can occur due to radiation, represented by the chance nodes 1, 6, 8 and 11.

The life expectancy (LE) of the patients depends on which treatment that was given; curative or non-curative, (denoted by Tr+ or Tr−), and on the absence or presence of lymph node metastases (denoted by n− and n+), represented by the chance nodes 2–3, 5, 7, 10, 12–13 and 16. Hence, there are four possible outcomes denoted by $LE_{n-,Tr+}$, $LE_{n-,Tr-}$, $LE_{n+,Tr+}$ and $LE_{n+,Tr-}$ (see Fig. 1).

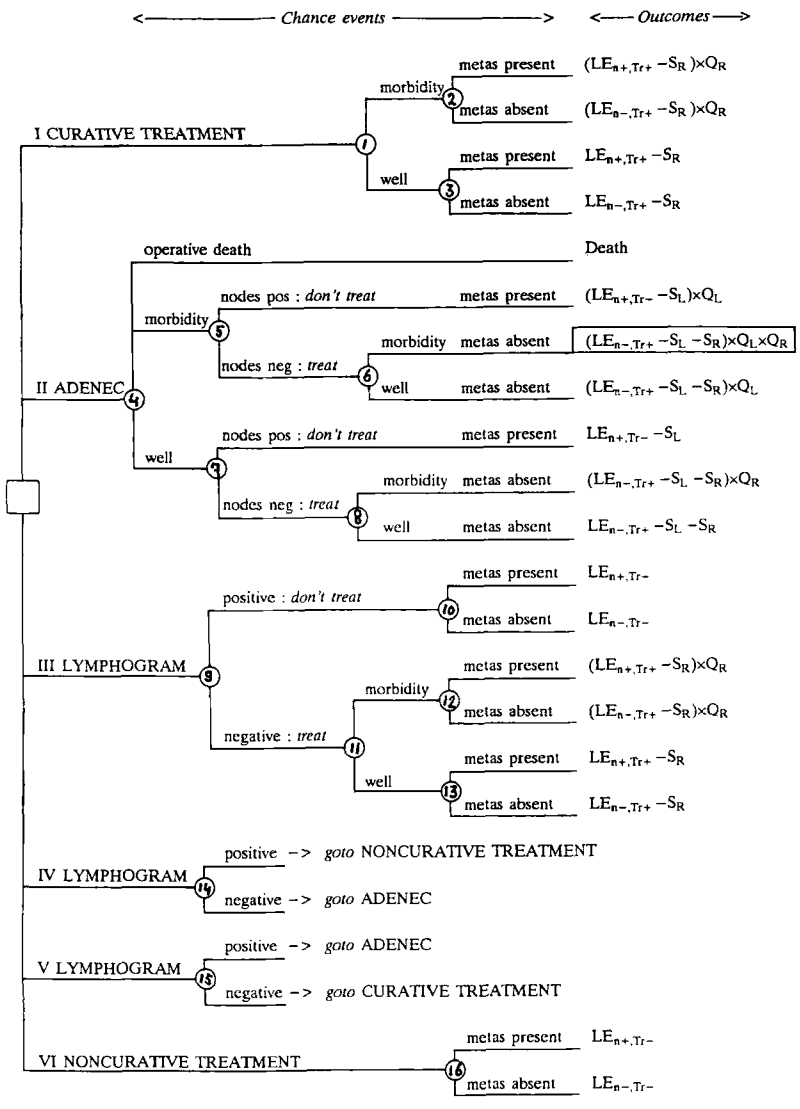

Fig. 1. The decision tree representing the six possible strategies for patients with clinically localized prostate cancer when two diagnostic tests are considered. 'Treat' should be read as 'curative treatment', 'don't treat' as non-curative treatment. For further explanation see text.

Quality-adjusted life years were used as the measure of comparison. In this measure the various attributes of the final outcomes are combined as follows: Life expectancy (LE) is decreased by quality adjustment parameters for short-term morbidity, (S), which are equal to the average time period the patient is suffering from short-term morbidity. Thus, the quality of life during the time period the patient suffers from short-term morbidity is assumed to be zero, which means that the impact of short-term morbidity on the quality of life is slightly overestimated. Life expectancy (LE) is multiplied by quality adjustment factors for long-term morbidity, (Q), since long-term morbidity has an impact on the quality of life of the patient for the remaining years.

For example, the utility for a patient in strategy II, submitted to lymphadenectomy and treated curatively since the lymph nodes were negative but who unfortunately obtained long-term complications of lymphadenectomy and radiotherapy, is given by:

$$U = (LE_{n-,Tr+} - S_L - S_{Tr}) \times Q_L \times Q_{Tr}$$

where $[LE_{n-,Tr+}]$ is the life expectancy of patients without metastases treated curatively, S_L and S_{Tr} are quality adjustment parameters for short-term morbidity of lymphadenectomy (S_L) and curative treatment (S_{Tr}), and Q_L and Q_{Tr} are quality adjustment factors for long-term morbidity of lymphadenectomy (Q_L) and curative treatment (Q_{Tr}). This 'utility' model is frequently used in decision analysis (9–15).

Step 3: Quantify the decision tree

Probabilities. Probabilities assigned to the chance events were based on the literature and are presented in Table 1.

Table 1

Probability parameters

Probability parameter		Baseline value	Estimated range	References
p:	Probability of metastases			(61–65)
	—low risk	0.08	0.02–0.10	
	—intermediate risk	0.35	0.25–0.40	
r:	Probability of operative death pelvic lymphadenectomy	0.005	0.00–0.012	(63, 66–68)
m_L:	Probability of long-term morbidity pelvic lymphadenectomy	0.05	0.00–0.20	(63, 67–70)
m_{Tr}:	Probability of long-term morbidity radiotherapy	0.12	0.00–0.26	(69)
se:	Sensitivity lymphangiography	0.60	0.50–0.84	(35, 71–73)
sp:	Specificity lymphangiography	0.90	0.98–0.79	(35, 71–73)

Utilities. The DEALE-method was used to calculate the unadjusted life expectancy (16–18). The annual age-specific mortality rate for a male population mean age 62 (i.e. the average age of patients with prostate cancer) was obtained from life tables of the Dutch population, and is equal to 0.062. Ten-year disease specific survival rates were based on available data in literature (19–26) and are presented in Table 2. The calculated unadjusted LEs are given in Table 3.

Quality adjustment parameters for short-term morbidity were set in such a way that they were equal to the average number of days spend in hospital or needed for treatment. Values for the quality adjustment factors for long-term morbidity were derived from direct scaling in consultation with urologists and radiotherapists (27). A value of zero is assigned if life is considered not worth living, i.e. equivalent to death. A value of 1 is assigned if life with a long-term complication is considered to be equivalent to life in good health. Table 3 presents the values of these utility parameters. The utility of each outcome can now be calculated, e.g. the utility of the third outcome of strategy II, which is

$$U = [(12.78 - (7/365.25) - (35/365.25)] \times 0.95 \times 0.85$$

$$= 10.23 \text{ quality adjusted life years.}$$

Step 4: Analysis of the decision tree

Baseline analysis. Table 4 presents the expected utility (EU) of the six strategies for patients with clinical stage B prostate cancer and a low or intermediate risk of metastases, based on the baseline values presented in Tables 1 and 3. For both patient categories strategy V has the highest EU.

Sensitivity analysis. To account for different opinions with respect to the burdens of lymphadenectomy and radiotherapy we calculated the EU of each strategy for two scenarios: (A) in which the burdens of radiotherapy

Table 2

Ten-year disease specific survival for clinical stage-B prostate cancer

	Estimated 10-yr survival in %		
	Baseline value	Range of uncertainty	Variable name
10-year survival for curative treatment			
—in absence of metastases	85	75–85	$S_{n-,Tr+}$
—in presence of metastases	30	20–40	$S_{n+,Tr+}$
10-year survival for non-curative treatment			
—in absence of metastases	70	50–80[c]	$S_{n-,Tr-}$
—in presence of metastases	32	20–45[c]	$S_{n+,Tr-}$
Benefit of curative treatment[a]	15	5–25	B_{Tr+}
Risk of curative treatment[b]	2	0–5	R_{Tr+}

[a] Benefit of curative treatment; $B_{Tr+} = (S_{n-,Tr+} - S_{n-,Tr-})$

[b] Risk of curative treatment; $R_{Tr+} = (S_{n+,Tr-} - S_{n+,Tr+})$

[c] The value for $S_{n-,Tr-}$ is determined by $S_{n-,Tr+}$ and B_{Tr+}, the value for $S_{n+,Tr-}$ is determined by the values for $S_{n+,Tr+}$ and R_{Tr+}.

Table 3

Utility parameters

Utility parameter		Baseline value	Estimated range
$LE_{n-,Tr+}$:	Life expectancy for curative treatment in absence of metastases	12.78	11.01–12.78 yrs
$LE_{n+,Tr+}$:	Life expectancy for curative treatment in presence of metastases	5.48	4.48–6.50 yrs
$LE_{n-,Tr-}$:	Life expectancy for noncurative treatment in absence of metastases	10.23	7.62–11.84 yrs
$LE_{n+,Tr-}$:	Life expectancy for noncurative treatment in presence of metastases	5.68	4.48–6.73 yrs
Q_L:	Quality adjustment factor for long-term morbidity of lymphadenectomy	0.95	0.92–0.98
Q_{Tr}:	Quality adjustment factor for long-term morbidity of radiotherapy	0.85	0.80–0.90
S_L:	Quality adjustment parameter short-term morbidity lymphadenectomy	7 days	4–10 days
S_{Tr}:	Quality adjustment parameter short-term morbidity of radiotherapy	35 days	28–42 days

are weighted heavily compared with the burdens of pelvic lymphadenectomy, and (B) in which the burdens of pelvic lymphadenectomy were weighted heavily compared with the burdens of radiotherapy. This can be obtained by choosing the parameters of the decision tree related to lymphadenectomy and radiotherapy accordingly: for scenario A: $r = 0.00$, $m_L = 0.00$, $S_L = 4d$, $Q_L = 0.98$, $m_{Tr} = 0.26$, $S_{Tr} = 42d$, $Q_{Tr} = 0.80$; for scenario B: $r = 0.012$, $m_L = 0.20$, $S_L = 10d$, $Q_L = 0.92$, $m_{Tr} = 0.00$, $S_{Tr} = 28d$, $Q_{Tr} = 0.90$. The remaining parameters are set at the baseline.

Table 4

Expected utility of the six strategies, expressed in quality adjusted life years, for the baseline analysis, scenario A (favours surgical staging) and scenario B (favours direct curative treatment) for patients with clinical stage-B prostate cancer, mean age 62, and a low or intermediate risk of metastases

Clinical stage-B prostate cancer	Baseline analysis		Scenario A		Scenario B	
Low risk of metastases						
strategy I	11.86	(4)*	11.44	(11)	**12.10**	**(0)**
strategy II	11.79	(29)	**11.47**	**(0)**	11.75	(128)
strategy III	11.68	(69)	11.30	(62)	11.88	(80)
strategy IV	11.60	(99)	11.31	(58)	11.58	(190)
strategy V	**11.87**	**(0)**	11.46	(4)	12.07	(11)
strategy VI	9.87	(730)	9.87	(584)	9.87	(841)
Intermediate risk of metastases						
strategy I	9.93	(26)	9.57	(73)	**10.14**	**(0)**
strategy II	9.98	(7)	**9.77**	**(0)**	9.92	(80)
strategy III	9.87	(47)	9.58	(80)	10.03	(40)
strategy IV	9.85	(55)	9.66	(40)	9.82	(117)
strategy V	**10.00**	**(0)**	9.69	(29)	10.13	(4)
strategy VI	8.64	(497)	8.64)	(413)	8.64	(548)

* Number between brackets presents the loss in quality days with respect to the preferred strategy; i.e., for both patient categories, strategy V for the baseline analysis, strategy II for scenario A, and strategy I for scenario B.

Scenario A favours surgical staging as its burdens are limited yet its benefits are considerable; a very burdensome treatment is avoided for patients with metastases found through lymphadenectomy. Scenario B favours the option to treat a patient without surgical staging as this procedure is assumed to be very burdensome and its benefit (i.e. avoiding curative treatment for those with metastases) is limited as curative treatment is almost without burdens. The EUs of the six strategies are presented in Table 4 for scenarios A and B.

Conclusions: the preferred strategy

The preferred or recommended strategy is the strategy with the highest EU. However, as is shown by sensitivity analysis, this strategy changes when the values of the parameters related to morbidity and mortality of lymphadenectomy and radiotherapy are changed over their plausible ranges.

To determine the preferred strategy we calculated the loss in quality-adjusted life years (expressed in days and presented in Table 4) with respect to the strategy with the highest EU; i.e. strategy V for the baseline analysis, strategy II for scenario A (favours surgical staging), and strategy I for scanario B (favours direct curative treatment). It is obvious that, when looking at these values, for patients with a low risk of metastases strategy I (direct curative treatment) and strategy V (starting with lymphography followed by lymphadenectomy only if the lymphogram is positive) are equivalent. Thus, from a decision analytic view point the consequences of these two strategies are, on average, virtually identical. The decision is a 'toss-up' (28).

For patients with an intermediate risk of metastases strategy V is preferred.

The fact that the therapeutic dilemma for patients with a low risk of metastases is not solved by the decision analysis, (the decision is a 'toss-up'), does not imply that the analysis is of no value. Also, clinical trials, for example, do not always solve therapeutic dilemmas but this does not mean that the information they provide is useless. This is also the case with decision analysis. The conclusion that strategy I and V are equivalent for patients with a low risk of metastases is as important as is the conclusion that for patients with an intermediate risk of metastases strategy V is preferred.

The differences in quality-adjusted survival between the 'best' and 'second best' strategy are small, varying from 4 to 29 quality adjusted days. This may seem insignificant in view of all the clinical uncertainties in the management of patients with clinically localized prostate cancer stage-B. However, one has to remember that these uncertainties are taken into account in the analysis. Even a small difference in expected utility between two strategies cannot be neglected when establishing diagnostic therapeutic guidelines or when advising a patient upon testing and treatment.

Difficulties with the traditional analysis

Structuring the decision problem

The first step of a decision analysis is breaking the problem down to its components, and to identify the relevant variables. However, if this is done in a very realistic and comprehensive way the decision tree becomes very bushy. Therefore, the models that are used simplify reality almost without exception.

Moreover, we could not represent the decision problem in a decision tree without making several assumptions; conditional independence of the occurrence of long-term morbidity, a constant annual mortality rate, risk neutrality with respect to longevity of life, and a constant quality adjustment factor over time. Some of these assumptions could have been avoided by using a Markov model (29), others could not. However, the assumptions which formed the basis of the model did not present the major problem in this stage of the analysis; clinicians know that making assumptions is almost unavoidable when a model is used.

The major problem we encountered was the fact that the decision tree did not seem to reflect the questions posed by the clinicians. They were seeking answers to two questions: 1) When should a pelvic lymphadenectomy be performed for staging prostate cancer? and 2) Can non-invasive diagnostic tests, such as lymphography, help to select patients for staging lymphadenectomy? These were also the questions presented in the literature (30–35). However, with a decision tree as presented in Fig. 1 we investigated, in the opinion of the clinicians, a somewhat different question, namely: 'What is the preferred diagnostic–therapeutic strategy when two tests are considered; lymphadenectomy and lymphography? We then realized that we had to split the problem into several consecutive decision problems, which corresponded to the questions posed by the clinicians.

Eliciting values for the quality adjustment factors

The second major problem using the traditional approach was encountered in assigning values to the quality adjustment factors for long-term morbidity. Individual patients preferences should be measured and used in an analysis. However, the analysis was not set up to investigate the best choice for a given patient, but to assist clinicians in establishing diagnostic–therapeutic guidelines for treating patients with prostate cancer. So the first question was: Whose utilities should be measured? Patients who are under treatment? Who have been treated? Prospective patients? Other questions were: Which method should be used? How should the questions and gamble outcomes be framed? What to choose as anchor points? Many authors posed these questions and showed that the values obtained are depending on method, age, sex and socio-economic status, length of time spent in a given health status, and the actual situation of the patient (27, 36–42). In spite of all this we asked clinicians, involved in treating patients with prostate cancer, to assign values to the quality adjustment factors by direct scaling, and used these values in the analysis. Although the same method is used in several analyses (9, 10, 12, 14) it remained unsatisfactory.

Presenting the results of the analysis

When we presented the results of the analysis by QALYs per strategy and by 'sensitivity graphs', the clinicians got the impression that the whole decision problem was reduced to comparing numbers and lines. We fully agree with Cebul who in his paper 'Look at the chief complaints' (43) mentioned that 'the style of presentation of decision analytic papers is arcane and emphasizes quantitative methods'.

Expected utilities, even when they are expressed in QALYs, are actually a very meager result of an analysis comparing different diagnostic–therapeutic strategies. Clinicians are not used to thinking in terms of QALYs but in terms of survival and morbidity. This is also the way in which outcomes of clinical studies are presented in the literature.

Interpreting the results—the preferred strategy

The analysis was presented during a working conference on uro-oncology in our region. Immediately upon the

presentation of the results a vivid discussion arose between radiotherapists and urologists.

The urologists would not accept that, for patients with a low risk of metastases, strategy I (curative treatment without testing) and strategy V (starting with lymphography) were considered equal, as the percentage of patients treated curatively with metastases was not the same for the two strategies. Nor would they accept that strategy V was preferred for patients with an intermediate risk of metastases, since in their opinion it was unacceptable that some patients with metastases were treated curatively (due to a false negative result of the lymphography).

It was not till then that we realized that the objective of the urologists was to minimize the number of patients with metastases who received curative treatment. Radiotherapists were of a different opinion: they thought it acceptable to occasionally treat a patient with metastases, because otherwise too many patients without metastases would have to submit to pelvic lymphadenectomy. Their objective was to maximize quality-adjusted life years.

This difference in objectives between urologists and radiotherapists was not discovered until at the end of the analysis. Furthermore, we had not explained beforehand that in decision analysis maximization of the EU is used to select the preferred strategy, and, as shown by Elstein et al. (44, 45), maximization of the expected utility is not always the criterion considered by clinicians when reaching a decision. In their study physicians aimed at minimizing the risk of endometrical cancer.

The second analysis—A modified approach

The second analysis consisted of six steps, which are briefly presented in this paper, using formal notations. A more detailed description of the analysis in clinical terms has been presented elsewhere (46, 47). The question of when to perform a lymphadenectomy was answered by step 1 and 2. Step 3 to 6 led to answering the question: 'Can lymphography help to select patients for staging lymphadenectomy?'

Step 1. Determine the 'fall back' treatment strategy

To decide when to perform a pelvic lymphadenectomy, one must compare the option 'lymphadenectomy followed by curative treatment only when the nodes are negative' (strategy II) with the preferred treatment choice in case the test is not considered. Hence, one must know what the treatment decision would be (curative or non-curative) in case of no additional testing; the so-called 'fall back treatment'.

To determine the fall back treatment we used a very simple decision tree, presented in Fig. 2, similar to the one described by Pauker & Kassirer (48). Apart from the probability of metastases (p) there are 5 utility parameters in that tree. Four utility parameters relate to survival;

$S_{n+,Tr-}$: 10-year survival rate of patients with metastases, not treated curatively,

R_{Tr+}: risk of curative treatment; i.e., the difference in 10-year disease specific survival between non-curative and curative treatment of patients with metastases.

$S_{n-,Tr+}$: 10-year survival rate of patients without metastases, treated curatively

B_{Tr+}: benefit of curative treatment; i.e. the difference in 10-year disease specific survival between curative and non-curative treatment of patients without metastases.

Consequently, the survival rate of patients with metastases treated curatively is given by $(S_{n+,Tr-} - R_{Tr+})$, and the survival rate of patients without metastases not treated curatively is given by $(S_{n-,Tr-} - B_{Tr+})$ (see Table 2).

There is one utility parameter, Cc, which relates to quality of life and which indicates the inconveniences and morbidity of curative treatment (in this analysis radiotherapy) and which, in short, is called the burdens. Cc represents a reduction in 10-year disease specific survival which compensates for the burdens of treatment. Values for $S_{n+,Tr-}$, R_{Tr+}, $S_{n-,Tr+}$ and B_{Tr+} were obtained from the literature or estimated by oncologists (see Table 2). However, quantifying Cc in terms of survival is very difficult; it therefore was considered to be the soft parameter in this analysis.

In decision analytic terms the fall back treatment strategy is curative treatment if the expected utility of curative treatment (denoted by EU_{Tr+}) exceeds the expected utility of non-curative treatment (denoted by EU_{Tr-}). Using the decision tree of Fig. 2, $EU_{Tr+} > EU_{Tr-}$ if:

$$p \times (S_{n+,Tr-} - R_{Tr+} - Cc) + (1 - p) \times (S_{n-,Tr+} - Cc) > p \times S_{n+,Tr-} + (1 - p) \times (S_{n-,Tr+})$$

which is equivalent to

$$Cc < (1 - p) \times B_{Tr+} - (p \times R_{Tr+}) \qquad [1]$$

When substituting values from the plausible ranges for B_{Tr+}, R_{Tr+} and p (see Tables 1 and 2) in inequality [1], the value for the right part ranged from 4% to 24.5% (baseline value 13.6%) for patients with a low risk of metastases, and from 1% to 18.75% (baseline value 9%) for patients

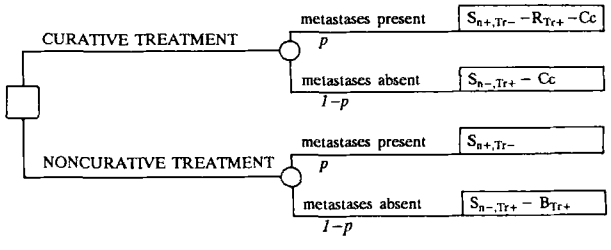

Fig. 2. Decision tree to determine the fallback treatment choice. For further explanation see text.

with an intermediate risk of metastases. Radiotherapists agreed that, for both patient categories, Cc did not outweigh this increase in 10-year disease specific survival obtained by curative treatment. Hence, inequality [1] held, and we concluded that the fall back treatment strategy is 'curative treatment'.

Step 2. Determine when a pelvic lymphadenectomy should be performed

Pelvic lymphadenectomy should be recommended when the expected utility of the decision 'perform a lymphadectomy' minus the expected utility of the fall back treatment strategy is greater than zero; i.e., when the net expected value of lymphadenectomy, NEV_L exceeds zero.

To calculate NEV_L we added the option 'perform a lymphadenectomy' in the decision tree of Fig. 2 and pruned the branch NON-CURATIVE TREATMENT (see Fig. 3). There is one new utility parameter in this tree, Cl, indicating the morbidity and inconvenience for patients associated with lymphadenectomy, in short the burdens of lymphadenectomy. The parameter is similar to Cc, difficult to quantify but unavoidable.

Using the tree of Fig. 3 the net expected value of lymphadenectomy is given by:

$$\begin{aligned} NEV_L = EU_L - EU_{Tr+} &= (1-r) \times [p \times (S_{n+,Tr-} - Cl) \\ &+ (1-p) \times (S_{n-,Tr+} - Cl - Cc)] \\ &- [p \times (S_{n+,Tr-} - R_{Tr+} - Cc) + (1-p) \\ &\times (S_{n-,Tr+} - Cc) \end{aligned}$$

which can be rewritten as

$$\begin{aligned} NEV_L = \{&(p \times R_{Tr+}) - r \\ &\times [p \times S_{n+,Tr-} + (1-p) \times S_{n-,Tr+}]\} \quad [2a] \\ &+ \{Cc - [(1-r) \times (1-p) \times Cc] \\ &- (1-r) \times Cl\} \quad [2b] \end{aligned}$$

$$NEV_L = NEV_{L,S} + NEV_{L,B}$$

We divided NEV_L into two parts: part [2a], denoted by $NEV_{L,S}$, which incorporates only utility parameters related to survival, and part [2b], denoted by $NEV_{L,B}$, which incorporates the two utility parameters Cc and Cl.

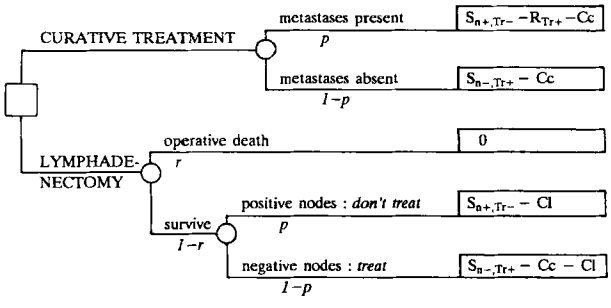

Fig. 3. Decision tree to determine when to perform a pelvic lymphadenectomy for staging prostate cancer.

$NEV_{L,S}$ can be calculated because the values of the parameters are known (see Tables 1 and 2). For patients with a low risk of metastases $NEV_{L,S}$ ranged from -1.0% to $+0.5\%$ (baseline value -0.2%) 10-year disease specific survival, and for patients with an intermediate risk of metastases from -0.9% to $+2.0\%$ (baseline value $+0.4\%$). This led to the conclusion that the decision to perform a lymphadenectomy does not depend on survival considerations, but rather on the burdens associated with curative treatment and lymphadenectomy. Consequently the NEV_L can be considered, by approximation, to be equivalent to $NEV_{L,B}$:

$$\begin{aligned} NEV_L &\approx NEV_{L,B} \\ &= Cc - [(1-r) \times (1-p) \times Cc] - (1-r) \times Cl \quad [3] \end{aligned}$$

Equation [3] can be rewritten as a function of the percentage of patients treated curatively and the percentage of patients submitted to lymphadenectomy in each branch of the decision tree of Fig. 3.

$$NEV_{L,B} = (N_1 - N_2) \times Cc - (M_2 - M_1) \times Cl$$

with: N_1, percentage of patients exposed to the burdens of curative treatment in branch CURATIVE TREATMENT (i.e. 100%); N_2, percentage of patients exposed to the burdens of curative treatment in branch lymphadenectomy i.e., $(1-r) \times (1-p) \times 100\%$; M_2, percentage of patients exposed to the burdens of lymphadenectomy in branch lymphadenectomy, i.e., $(1-r) \times 100\%$; and M_1, percentage of patients exposed to the burdens of lymphadenectomy in branch CURATIVE TREATMENT, i.e. 0%.

Lymphadenectomy should be performed in $NEV_L > 0$, which is equivalent to:

$$(N_1 - N_2) \times Cc - (M_2 - M_1) \times Cl > 0$$

and can be rewritten as

$$\frac{Cc}{Cl} > \frac{M_2 - M_1}{N_1 - N_2} \quad (4)$$

The value of Cc/Cl for which the two choices presented in the decision tree of Fig. 3 are equivalent, the so-called threshold value of Cc/Cl, can now be calculated, as the percentage of patients exposed to the burdens of curative treatment and lymphadenectomy for the decision CURATIVE TREATMENT and lymphadenectomy are known. Now we only have to assess whether the ratio Cc/Cl exceeds the calculated threshold value in order to answer the question as to when to perform a pelvic lymphadenectomy.

However, we also have to investigate whether lymphography can help to select patients for staging lymphadenectomy. Moreover, adding lymphography to the diagnostic work-up will change the percentage of patients exposed to

the burdens of lymphadenectomy and curative treatment and, subsequently, the threshold value of Cc/Cl. Thus, before assessing the position of the ratio Cc/Cl relative to the threshold values, we add lymphography to the diagnostic work-up and (re)calculate the threshold value.

Step 3–4. Add lymphography to the diagnostic work-up and calculate threshold values for Cc/Cl for each strategy

Since lymphography is neither associated with mortality nor with morbidity, the utilities of the decision problem do not change when lymphography is added to the diagnostic work-up. Possible strategies when adding lymphography are strategies III, IV and V, presented in Fig. 1. However, from the first analysis we know that only strategy V has to be considered.

Using Bayes theorem and the values for the sensitivity and specificity of the lymphography as presented in Table 1, we calculated the percentage of patients exposed to the burdens of curative treatment and lymphadenectomy for strategy I, II and V (47). Substituting these percentages in equation [4] we calculated the threshold value of Cc/Cl for which strategy I and V are equivalent, and the threshold value for which strategy II and V are equivalent (see Fig. 4).

Step 5–6. Assess the position of the ratio Cc/Cl relative to the calculated threshold values and determine the recommended strategy

The next step in our approach was to ask clinicians to determine the value of the ratio Cc/Cl relative to the calculated threshold values. For this purpose we developed a questionnaire in which the clinician was asked for his/her preferences for specific choices. The characteristic question in the questionnaire was:

What do you prefer:

a) *To treat 100 patients curatively without performing a pelvic lymphadenectomy and accept its burden for all patients including X patients who cannot be cured due to the presence of undetected lymph node metastases.*

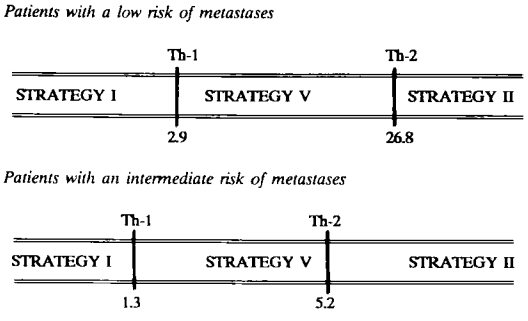

Fig. 4. Utility threshold Th-1 for the choice between strategy I and V and utility threshold Th-2 for the choice between strategy V and II, for patients with clinically stage-B prostate cancer and a low or intermediate risk of metastases.

b) *To perform a pelvic lymphadenectomy for these 100 patients (and accept its burden for these 100 patients) in order to find out that X of them do have lymph node metastases. Consequently, as a result of performing the lymphadenectomy, these X patients will be spread the burdens of curative treatment.*

c) *Are you indifferent between options 'a' and 'b'?*

Specific numbers for X which related to the calculated threshold values were used in the questionnaire. The questionnaire was presented to 67 Dutch radiotherapists during a conference (47).

Analysis of the questionnaire resulted in identifying intervals for the ratio, and led to the identification of the recommended strategy. With radiotherapy as treatment modality the preferred strategy for patients with a low risk of metastases was strategy I; curative treatment without any additional testing, and for patients with an intermediate risk strategy V, starting with lymphography and followed by lymphadenectomy only when the results of the lymphogram is positive. In case of a negative lymphogram the patient should be treated curatively. So for this latter patient category lymphography can help to select patients for staging lymphadenectomy.

Comparison of our approach with the literature

We presented two analyses, performed to evaluate pelvic lymphadenectomy and pedal lymphography for staging prostate cancer. Both analyses yielded similar results as far as the preferred strategy was concerned. However, the approach and set up of the two analyses were different. The first analysis was performed using the traditional approach according to the textbooks on decision analysis. Difficulties which we encountered using this approach urged us to modify the approach presented in the second analysis. In this second analysis the decision problem was split into several consecutive decision problems which corresponded to the questions posed by the clinicians. The decision trees we used were very simple. The consequences of curative treatment and lymphadenectomy which might have an impact on quality of life of the patients were represented in the decision trees by only two utility parameters. A utility threshold analysis was performed and the result of the analysis could be expressed by means of the number of patients exposed to the burdens of curative treatment and lymphadenectomy.

It is obvious that by performing the second analysis we had not solved the problems encountered during the first analysis, but had rather gotten around them. Reading the literature on decision analysis we realized that several authors had suggested and used an approach different from the traditional one for analyzing decision problems involving diagnostic tests. Their reason for proposing a different approach was, that they considered 'a full deci-

sion analytic approach of such problems often infeasible'. We will discuss these papers, and compare them with our second analysis.

To avoid a complex analysis Greenes et al. (2–4) introduced two performance measures of diagnostic tests: assignment potential, AP, characterizing the chance that, as a consequence of performing the test, the probability of disease will exceed the decision threshold, and assignment strength, AS, characterizing the average extent to which a decision threshold will be exceeded when the post-test probability of disease does exceed the decision threshold. These two measures can be computed if the prior probability of disease, the test characteristics and the treat/don't treat decision threshold are known. This treat/don't treat decision threshold must be expressed as 'probability of disease' and can be obtained by performing an analysis in which the choices TREAT and DON'T TREAT are compared or they could be estimated directly by clinicians (49). AP and AS can only be used to decide whether a test should be performed if the burdens of the test can be considered negligible compared with the burdens of treatment. For burdensome tests one has to perform a decision tree analysis to determine the net expected value of testing.

Glasziou & Hilden (5, 6) developed a method to analyze decision problems in which several diagnostic investigations need to be considered simultaneously. They described a step-by-step method for the construction and use of decision tables. For their approach the prior probability of disease, test characteristics and treat/don't treat decision threshold must also be known. Although the use of decision tables might be convenient in daily practice it does not provide insight in the decision problem as do AP and AS. The method described the Glasziou and Hilden is also only applicable to non-burdensome tests; they advise to include burdensome tests into a decision tree as a separate strategy.

Greenes et al. as well as Glasziou & Hilden divide decision problems involving diagnostic tests into two consecutive decision problems. Their first problem concerns the treat/don't treat decision threshold, which is equivalent to our first step 'What is the fall back treatment strategy?'. Their second decision problem is to determine when to use a non-burdensome diagnostic test. For this purpose they use a probability threshold approach. The main difference with out approach is that we performed a utility threshold analysis to determine when to use the non-burdensome test.

When a diagnostic test is associated with mortality or morbidity, the first decision problem has to be extended to determine when this burdensome test should be performed; the second step in our modified approach.

Phelps & Mushlin (7) described how to evaluate new diagnostic technologies and how to determine whether they should be introduced in medical practice. They assume that there are data to determine the treat/don't treat decision threshold. Their first step is to determine what the fall back treatment strategy is for the patient population for which the new technology might be used. The second step is to determine whether the net expected value of testing exceeds zero under the assumption that the test yields perfect information. If the answer to this question is NO there is no need for further evaluation; i.e. to determine by clinical study what the characteristics of the test are.

As they depart from technology assessment they first focus on the cost of testing, while a researcher with a clinical background would be inclined to focus first on the ability of the test to discriminate between diseased and non-diseased individuals. However, their method embodies ideas we also used in our modified approach; start the analysis by determining the fall back treatment strategy and try to avoid unnecessary complex data collection. In our second modified analysis we were able to avoid explicitly measuring the burdens of treatment and lymphadenectomy in terms of survival.

With regard to quantification of parameters of a decision tree the paper of Nease & Bonduelle is interesting (50). They described the test/treatment decision problem, similar to Pauker & Kassirer (48), yet they chose a utility parameter for threshold analysis. They stated that 'the threshold approach of utilities should be considered seriously because, almost all models of medical outcomes suffer from severe difficulties in adequately modeling patient preferences'. For similar reasons our modified approach embodied a utility threshold analysis.

Laupacis et al. argued in the New England Journal of Medicine that 'the number of patients to be treated might be preferred to QALYs as a measure of outcome when comparing treatment alternatives' (51). For the assessment of the value of diagnostic tests the same holds true, as most diagnostic tests do have a direct impact on survival (they are not associated with significant mortality), but affect only the number of patients to be treated. In our analysis adding lymphography to the diagnostic work-up only affected the number of patients exposed to the burdens of curative treatment and lymphadenectomy. The questionnaire as well as the result of the analysis were therefore expressed in the percentage of patients submitted to lymphadenectomy and curative treatment in each strategy.

A very nice example of how results of an analysis can be presented in a clinically meaningful way is the analysis of Brandeau & Eddy (52) concerning protocols for working up an asymptomatic patient with a positive faecal blood test. Instead of performing a formal decision analysis they just answered a number of questions for each protocol such as; What proportion of malignant and premalignant cancers will be detected? What are the complication rates? What are the costs? Neither did they calculate the Life Expectancy nor the number of Quality Adjusted Life Years for the different strategies. Nevertheless their analy-

sis was much more informative than the traditional decision analysis performed by Malenka et al. (53) who, for choosing the optimal strategy for staging non-small cell lung cancer, only presented life expectancies as the result of the analysis.

Discussion

In the introduction we raised the question: Does decision analysis provide a framework to assess the value of diagnostic tests in clinical practice and how can it be used by clinicians in establishing diagnostic–therapeutic guidelines. We have shown that many difficulties arose when we attempted to use formal decision analysis to solve a particular diagnostic–therapeutic decision problem in prostate cancer; difficulties which urged us to modify the first analysis.

Two of these difficulties are inherent to the expected utility theory: first, the assignment of values to quality adjustment parameters which reflect patient preference for certain health status, and second, the selection of the preferred strategy by maximizing the overall expected utility. Although QALYs and maximization of EU are theoretically attractive concepts to compare alternative choices, they proved to be major obstacles when applying decision analysis in daily care. Clinicians and patients are not familiar with the concept of assigning values to a health status which express its quality of life. Moreover, instruments to measure quality of life are crude and still experimental. It is even not yet clear what the best set of descriptions of quality of life is (54). It also can be questioned whether maximization of the overall expected utility should be the criterion for choosing the preferred choice in clinical decision making. In practice a different criterion, or even several criteria, might be used to make a decision. Elstein et al. (44) showed that the choices of the physicians in his study were consistent with what they considered to be the most important objective: minimizing the risk of endometrial cancer. On the other hand they were not consistent with the result of the analysis, although they had agreed with the structure and quantification of the decision tree.

Does this imply that decision analysis is not a useful tool for clinicians? It is one of these theories which comes and goes without having contributed to clinical practice? In my opinion the answer to both questions should be NO. Decision analysis provides a good framework to structure and analyze complex decision problems. However, it cannot be used to provide the ultimate answer to any decision problem. To cite Kassirer & Pauker (55) 'The principal purpose of decision analysis is not to provide a single optimal patient management strategy, but rather to explicate the competing issues in a problem domain'. In this respect decision analysis can be a very helpful tool for clinicians.

Just taking the first step of an analysis can help when facing a complex decision problem. The alternative choices and all factors relevant to the decision must be made explicit, so that they can be discussed among clinicians or between the clinician and his patient. Also the objective of either the patient or the doctor must be considered explicitly. This first step of an analysis is probably the most difficult one as doctors are not used to explicate their reasoning.

Furthermore, the assignment of values to probabilities in a decision tree has advantages above implicit reasoning when we think of the many heuristics and biases in probabilistic reasoning of humans (56). And despite all the methodological problems of measuring quality of life that are not yet solved, decision analysis offers the clinicians a model to study the impact of patient preferences on the selection of therapy (57, 58).

One major advantage of using a decision analytic framework is the possibility to perform a sensitivity analysis; i.e., testing the stability of the outcome of the analysis over a range of structural assumptions, probability estimates and value judgments. In this way, parameters which are most crucial to the decision can be identified, white spots of knowledge be detected and the impact of different perceptions of risks and benefits of treatments on the decision can be assessed.

Decision analysis has made progress, there is no doubt about it (55, 59). Experience in structuring decision problems has grown and has become more realistic by the introduction of Markov models (29). Sensitivity analysis can now be carried out by using Monte Carlo simulations (60). Computer programs have been developed to analyze decision trees. However, despite all these improvements, Pauker & Kassirer (55) concluded that decision analysis has not achieved widespread acceptance in regular clinical practice. Greater effort should therefore be put into research that is aimed towards making decision analysis a useful tool for clinicians to ration their decisions and evaluate their daily practice. We should not forget that, with or without decision analysis, we have to make decisions every day, the very best way we can.

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