A Decision-theoretic Network Approach to Treatment Management and Prognosis*

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Abstract

Medical patient management is a complicated process, usually involving a large amount of, possibly uncertain, information. Clinicians may, therefore, require some form of decision support to deal with complicated situations; assistance in exploring various clinical questions, e.g. concerning prognosis and optimal treatment, may be valuable in this respect. Decision-theoretic expert systems provide a suitable framework for such assistance due to the flexibility of the underlying formalisms, with inherent potentials of knowledge reuse. In this paper, the development of a decision-theoretic model of non-Hodgkin lymphoma of the stomach is described, and examined for its clinical usefulness. Central to the model is a probabilistic network that offers an explicit representation of the uncertainties underlying the decision-making process.

Keywords: decision-theoretic expert systems, probabilistic networks, knowledge engineering.

1 Introduction

Medical patient management is a complicated process, usually involving a large amount of, possibly uncertain, information. It is, therefore, not surprising that many computer-based systems, including expert systems, have been developed in the past two decades to offer assistance in diagnosis, treatment management, and assessment of prognosis. The overall goal of the development of these systems was improvement of patient care. However, despite considerable research efforts, few of these systems have actually reached the stage of clinical use. This lack of success in the medical field has been attributed to a number of different factors, both technical and social [12]. This paper focuses on a factor that belongs to the technical realm of expert systems: potentials of reuse of medical knowledge.

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Recent model-based approaches to the development of medical expert systems offer substantial advantages in terms of flexibility and potentials of knowledge reuse, mainly due to the declarative nature of the knowledge embodied in such systems. Frequently employed formalisms to represent knowledge in model-based systems include logic and probability theory, among others. In medicine, using probability theory, possibly augmented with decision theory, is attractive, because it allows for explicitly representing the uncertainties and preferences that go with much of the knowledge used in medical decision making. In particular, adopting probabilistic networks as a framework for building medical expert systems is appealing, because in addition to the advantages linked to using probability theory, qualitative relationships among variables can be represented, in the form of a directed acyclic graph. This feature not only simplifies probability assessment, but also promotes easy understanding of the resulting system. We shall refer to a system that incorporates a probabilistic network, possibly augmented with decision theory, as a *decision-theoretic expert system.* A knowledge base of such a system will be called a *decision-theoretic network.*

There are presently no comprehensive knowledge-engineering methodologies available that can be used in building a decision-theoretic network. In this paper, a further elaboration of a preliminary methodology for building decision-theoretic expert systems for treatment management, as described in [7], is discussed. It is also investigated how decision-theoretic expert systems can be used to deal with a number of questions clinicians are likely to find important: optimal treatment selection, prognostic assessment and generating profiles for specific treatment outcomes. Since all these questions can be answered, in principle, using the same knowledge base of a decision-theoretic expert system, a practical example of knowledge reuse is arrived at.

As an example, medical treatment of patients with non-Hodgkin lymphoma of the stomach (gastric NHL) is discussed. Primary gastric NHL is a relatively rare malignant disorder, accounting for about 5% of gastric tumours. Until recently, the aetiology of gastric NHL was unknown; it is now generally believed that the main factor in the pathogenesis of this disease is a chronic infection with the bacterium *Helicobacter pylori* [3, 18]. Therapy selection for gastric NHL is a complicated process, because only part of the patient findings necessary for therapy selection may be known at a particular stage of the disease, and knowledge of adverse reactions to particular treatments in patient groups may influence treatment selection significantly.

The structure of this paper is as follows. First, we discuss the process of building a decision-theoretic network, which is illustrated by the construction of a decision-theoretic network for gastric NHL. Next, various possible clinical applications of the resulting decision-theoretic expert system are considered. Finally, decision-theoretic networks are compared to conventional prognostic models in medicine.

2 Development of the Gastric NHL Decision Model

In this section, first decision-theoretic networks are introduced; next, the successive steps in the design of the gastric NHL model are reviewed.

2.1 Decision-theoretic Networks

A *probabilistic network*, or *belief network*, is a directed acyclic graph $G = (V(G), A(G))$, consisting of a set of nodes $V(G) = \{V_1, \ldots, V_n\}$, called *probabilistic nodes*, representing discrete random variables, and a set of arcs $A(G) \subseteq V(G) \times V(G)$, representing causal relationships or correlations among random variables. The presence of an arc between two nodes denotes the existence of a direct causal relationship or other influences; absence of an arc means that the variables do not influence each other directly. Associated with a probabilistic network is a joint probability distribution, defined in terms of conditional probability tables according to the structure of the graph:

$$\Pr(V_1, \ldots, V_n) = \prod_{i=1}^{n} \Pr(V_i \mid \pi(V_i))$$

where V_i denotes a random variable associated with an identically named node, and $\pi(V_i)$ denotes the parents of that node. By means of special algorithms for probabilistic reasoning (cf. [9, 5]), a once constructed probabilistic network can be employed to process evidence.

The probabilistic-network formalism provides only for probabilistic reasoning. For making therapeutic decisions, certain extensions to the probabilistic-network formalism are required, as offered, among others, by the influence-diagram formalism. Like a probabilistic network, an *influence diagram* is an acyclic directed graph $G = (V(G), A(G))$, except that in addition to probabilistic nodes $O(G) \subseteq V(G)$, two additional node types are distinguished: *decision nodes* $D(G) \subseteq V(G)$ and a *value node* $U \in V(G)$.

As holds for probabilistic networks, arcs between probabilistic nodes in an influence diagram denote direct causal relationships or correlations. Incoming arcs to a decision node indicate information that is required before the corresponding decision can be made. The order of decision nodes in an influence diagram expresses the order in which the decisions are made in the domain. In order to select the most optimal sequence of decisions, assessments of these decisions with respect to other, partially uncertain, information must be available. These assessments, also called *utilities*, are represented by the value node. Incoming arcs of the value node indicate variables on which utilities must be defined, i.e. utilities can be expressed as a *utility function*: $u : C_{\pi(U)} \rightarrow \mathbb{R}$, where $C_{\pi(U)}$ denotes the set of possible instantiations of parents of the value node U.

Various algorithms to evaluate influence diagrams are available, e.g. the algorithm proposed by R. Shachter [11]; the result of evaluation is an optimal sequence of decisions, a *decision strategy*, obtained by computation of the maximum expected utility (MEU) of every decision $D \in D(G)$ given particular evidence E:

$$\mathrm{MEU}(D \mid E) = \max_{d \in D} \sum_{c \in C_{\pi(U)}} u(c) \Pr(c \mid d, E)$$

where possibly $D \in \pi(U)$, and where the evidence E includes previous decisions.

Probabilistic networks and influence diagrams, among others, are considered examples of decision-theoretic networks. The design of a structure for a medical decision-theoretic network model is usually such as to incorporate clinical experience as well as to reflect results from the medical literature. In principle, it is possible to construct such models automatically from a database with patient data. In practice, this is seldom done, due to the prohibitive amount of data and the huge computational resources required. Several researchers, however, have demonstrated that it is feasible to use subjective information, in addition to information drawn from the literature, as a basis for the design of decision-theoretic models (e.g. [1], [4], and [14]). The design of a decision-theoretic network for gastric NHL is next discussed.

Pretreatment Variables	**Treatment Variables**	**Posttreatment Variables**
age	chemotherapy	bone-marrow depression
bulky disease	radiotherapy	early result
clinical stage	surgery	gastric hemorrhage
clinical presentation	combination therapy	gastric perforation
general health status		immediate survival
histological classification		post-CT&RT survival
		post-surgical survival
		5-year result
		therapy adjustment

Table 1: Selected variables.

2.2 Identification of Relevant Variables

The selection of variables for a decision-theoretic network is influenced by the adopted view on the medical domain concerned. Often, knowledge about (patho)physiological mechanisms is used to guide the process of gathering relevant variables (cf. [6, 7]). For the gastric NHL model, however, we have chosen to incorporate only those variables into the model that are widely used by clinicians. The relevance of most of these variables is supported by literature on prognostic factors in primary gastric NHL [2, 10].

First, the information used in the clinical management of primary gastric NHL was subdivided in *pretreatment information*, i.e. information that is required for treatment selection, *treatment information*, i.e. the various treatment alternatives, and *posttreatment information*, i.e. side effects, and early and long-term treatment results for the disease. The selected variables are presented in Table 1. The most important pretreatment variables in the table are the variable 'clinical stage', which expresses severity of the disease according to a common clinical classification, and histological classification, which stands for the assessment by a pathologist of tumour tissue obtained from a biopsy.

Various treatment modalities are in use for gastric NHL, as shown in Table 1. The variables 'chemotherapy', 'radiotherapy', and 'combination therapy' were combined into one variable with name 'CT&RT-SCHEDULE' with possible values: chemotherapy (CT), radiotherapy (RT), chemotherapy followed by radiotherapy (CT-next-RT), and neither chemotherapy nor radiotherapy (none). Possible values for the variable 'surgery' are: 'curative', 'palliative' or 'none', where curative surgery means total or partial resection of the stomach with the complete removal of tumour mass.

The most important posttreatment variables included in Table 1 are the variable 'early result', being the endoscopically verified result of the treatment, six to eight weeks after treatment (possible outcomes are: complete remission – i.e. tumour cells are no longer detectable –, partial remission – some tumour cells are detectable –, no change or progressive disease), and the variable '5-year result', which represents the patient either or not surviving five years following treatment.

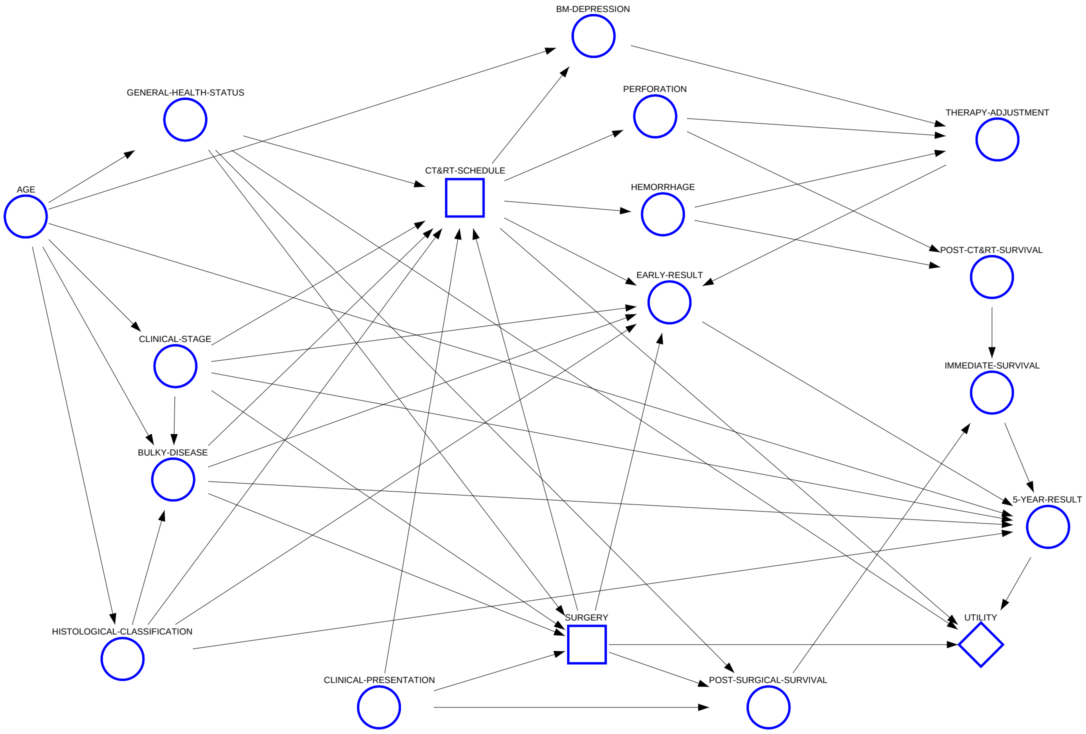

Figure 1: Complete influence diagram for the treatment of gastric NHL.

2.3 Identification of Relationships among Variables

Next, the structure of the gastric NHL model was determined, using causality as the primary modelling concept, supplemented with knowledge of probabilistic dependence between variables. Directed graphs were used as visual aids in the representation of these relationships. During the design process, several nodes in the graph became very complicated, i.e. too many arcs entered these nodes. Since the number of probabilities that must be assessed is proportional to the product of the number of possible values for each of the variables involved, as determined by the number of incoming arcs of each node, probabilistic assessment can easily become unfeasible. To solve this potential problem, a small number of extra nodes was inserted into the graph in accordance with clinical practice, such as THERAPY-ADJUSTMENT, POST-CT&RT-SURVIVAL, POST-SURGICAL-SURVIVAL and IMMEDIATE-SURVIVAL, summarising the effects of other variables. This technique is known as '*divorcing multiple parents*' [8]. These intermediate variables enabled a significant reduction in the number of incoming arcs in the graph, thus facilitating probability assessment.

The influence diagram resulting from this design process is shown in Fig. 1. A probabilistic node is indicated by a circle, a decision node by a box, and a value node by a diamond. The value node present in the diagram was actually added in the last stage of the design process, to be discussed below. Note that the internal structure is still empty: probability and utility information is absent at this stage of design.

AGE	Pr(GHS | AGE)
10-69	good > average > poor
70-79	average > good > poor
80-89	average > poor > good
$\geq$ 90	poor > average > good

Table 2: Qualitative ordering of probabilities, used for assessment.

2.4 Qualitative Assessment of Uncertainty and Logical Relationships

It is widely known that it is much easier to assess qualitative relationships between probabilities for particular values of variables, such as ordering relationships, than the probabilities themselves [17]. Such qualitative probabilistic information is often highly accurate. Therefore, the first step in the collection of probabilistic information has been the gathering of such qualitative information, using various techniques. Firstly, the logical relationships between variables were identified. Logical relationships yield probabilistic information with complete certainty, i.e. with probability 1 or 0; usually, logical information will not be a major source of inaccuracy in a model.

Secondly, we have collected information about qualitative probabilistic relationships between values of variables, represented by a number of tables. Table 2 shows the qualitative information that has been used in the assessment of the following conditional probability table:

$$\Pr(\textsc{general-health-status} \mid \textsc{age})$$

For example, the following ordering: good > average > poor for patients with age between 10 to 69 years old, means:

$$\begin{aligned}&\Pr(\textsc{general-health-status} = \text{good} \mid \textsc{age} = \text{10-69}) \; > \\ &\Pr(\textsc{general-health-status} = \text{average} \mid \textsc{age} = \text{10-69}) \; > \\ &\Pr(\textsc{general-health-status} = \text{poor} \mid \textsc{age} = \text{10-69})\end{aligned}$$

The tables with qualitative information proved extremely valuable in validating the numerical probabilities, which were assessed later on, because these numerical values could be checked against this qualitative information.

2.5 Numerical Probability Assessment

After all qualitative information concerning the local probability distributions for the variables in the model was collected, the probabilities were assessed numerically. Various techniques were employed to render subjective, numerical assessment of the probabilities feasible.

Unconditional prior probabilities, such as for the variables AGE, and CLINICAL-PRESENTATION, were assessed in an iterative fashion. Probabilistic information so far as found in the literature on primary gastric NHL was collected, and refined to reflect clinical experience at the Netherlands Cancer Institute.

For the nodes in the network with incoming arcs, *conditional* probabilities had to be assessed. Unfortunately, these conditional probabilities could, almost without exception, not be found in the medical literature. To ease the assessment, a distinction was made between probabilistic nodes with a small number of incoming arcs (less than four) and the nodes

EARLY-RESULT and 5-YEAR-RESULT, which each have six incoming arcs. The assessment of the conditional probabilities for the former non-complicated nodes, and the latter complicated ones, will be discussed separately.

The conditional probabilities for nodes with a small number of incoming arcs were assessed by distributing the probability mass among the various values of the variable corresponding to the node, where each time the values of the conditioning variables were kept fixed. The resulting probabilities were next checked against the tables with qualitative information previously collected. For example, the qualitative information concerning the variable CLINICAL-STAGE expressed that

$$\begin{aligned}&\Pr(\text{CLINICAL-STAGE} = \text{I} \mid \text{AGE} = \text{10-29}) = \\ &\Pr(\text{CLINICAL-STAGE} = \text{II}_2 \mid \text{AGE} = \text{10-29})\end{aligned}$$

which was used as a qualitative constraint for the assessment of four conditional probabilities.

The two more complicated nodes, EARLY-RESULT and 5-YEAR-RESULT, were assessed using a special additive model. First, the conditional probabilities were assessed by conditioning on four to five of the six variables for the value of the variable EARLY-RESULT, which would yield the largest probability in most cases. For the variable EARLY-RESULT, the value 'complete remission' (CR) was chosen as such. Next, the remaining probability mass was distributed among the remaining values for the variable EARLY-RESULT, again conditioning on the same variables. Finally, for both variables, the entire conditional probability table was computed by means of a computer program, that used the following additive model to compute probabilities $\Pr(A \mid C)$, based on partially specified information with respect to collections of variables with values in a given set V:

(1) for each $C \in V$: $\Pr(A \mid C) = \mathbb{P}(A \mid C)$;

(2) for each $C \in \wp(\Delta)\backslash V$, where C contains a value for each variable in Δ:

$$\Pr(A \mid C) = \sum_{\substack{C' \subset C,\, C' \in V \\ \forall C'' \in V,\, C'' \subset C \,:\, C'' \not\supset C'}} \Pr(A \mid C')$$

where $\wp(\Delta)$ denotes the power set of the set of all variables with their values, Δ, and $\mathbb{P}$ denotes the partial specification of the probabilistic information. Note that according to this additive model, the most specific probabilistic information available is always used as a basis for calculating probabilities.

The probabilistic part of the influence diagram was next extracted and examined. The two decision nodes, CT&RT-SCHEDULE and SURGERY, were converted to probabilistic nodes for which prior probability distributions were supplied, based in experience at the Netherlands Cancer Institute. Using a probabilistic reasoning algorithm mentioned in Section 2.1, the prior marginal probabilities of this network were computed; the result is shown in Fig. 2.

2.6 Utility Assessment

The assessment of probabilistic information discussed above was succeeded by the assessment of utility information for the value node. The following variables were marked out as being of major importance in deciding about optimal treatment for a patient with gastric NHL:

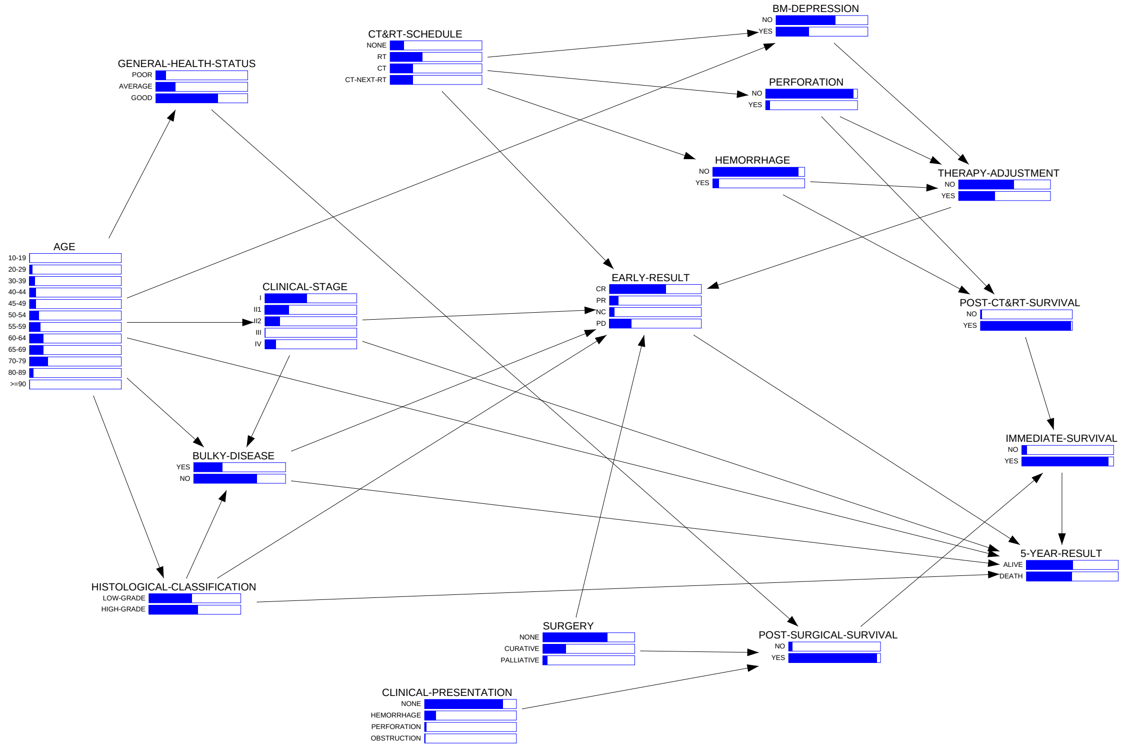

Figure 2: Probabilistic network with prior probability distributions.

(1) general health status, (2) CT&RT schedule, (3) surgery, and (4) 5-year result. Utility assessment was carried out from the patient's perspective.

A number of alternative utility functions were designed, following conventional methods from decision analysis [13]. In the *direct scaling method*, the possible clinical outcomes are assessed using a linear numerical scale, promoting the assessment of these outcomes relative to each other. This methods was applied twice. First, the position of the utilities of particular posttreatment outcomes, as described by the four variables mentioned above, was assessed on a numerical scale ranging from 0 (worst) to 1000 (best). The numerical values were next sorted; the resulting utility function is depicted in Fig. 3. Note that many clinical outcomes were considered equivalent, as is reflected by their identical value according to the utility function. Close inspection of the utility function revealed that the contribution of five-year survival in the numerical assessment had been underestimated. A second utility function was obtained by adjustment of the first utility function, as shown in Fig. 3. Both utility functions display small incremental increases in their function values, showing a more or less even spread of utilities over intervals of the scale, indicating that further refinement may be required.

With the *standard reference gamble method*, every possible outcome is assessed in probabilistic terms by determining the risk neutral equivalent of two uncertain outcomes, assuming that the outcome being assessed occurs with absolute certainty. Hence, utility assessment is not carried out in an incremental fashion. A utility function was designed, using the standard reference gamble method; this third utility function is also depicted in Fig. 3. Notice that

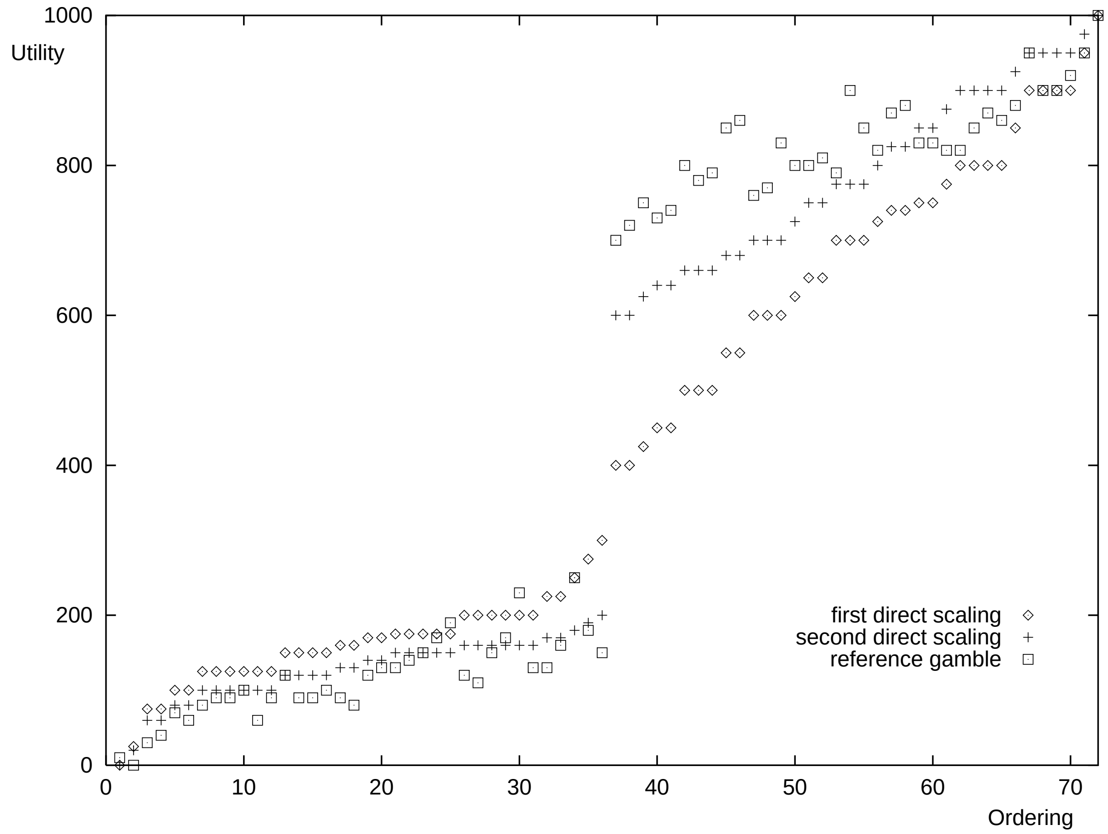

Figure 3: Graphical plot of three utility functions.

this last utility function reveals a bit more variation in its function values as compared to the other two utility functions.

Results obtained by the reference gamble method are generally considered more accurate than those resulting from the direct scaling method; the variation in the values of the last utility function is due to the more subtle expression of differences among the various outcomes. Finally, a fourth utility function was defined, where only the five-year survival following treatment was adopted as a basis for assessment. The function obtained by the reference gamble method was thought to reflect patient's preferences best.

The influence diagram and associated probabilistic network were eventually implemented using an improved version of the *Ideal* probabilistic expert system shell [15].

3 Reusing Medical Knowledge

The main goal of the development of the decision-theoretic model (influence diagram with associated probabilistic network) was to obtain a knowledge base for an expert systems that could be used to explore many different clinical questions. Although the resulting influence diagram is specialised for selecting optimal treatment for a given patient, which is highly dependent on a patient's preferences as expressed by a utility function, the associated probabilistic network offers much flexibility. This can be viewed as an example of knowledge reuse. Some possible clinical uses of the model will be discussed.

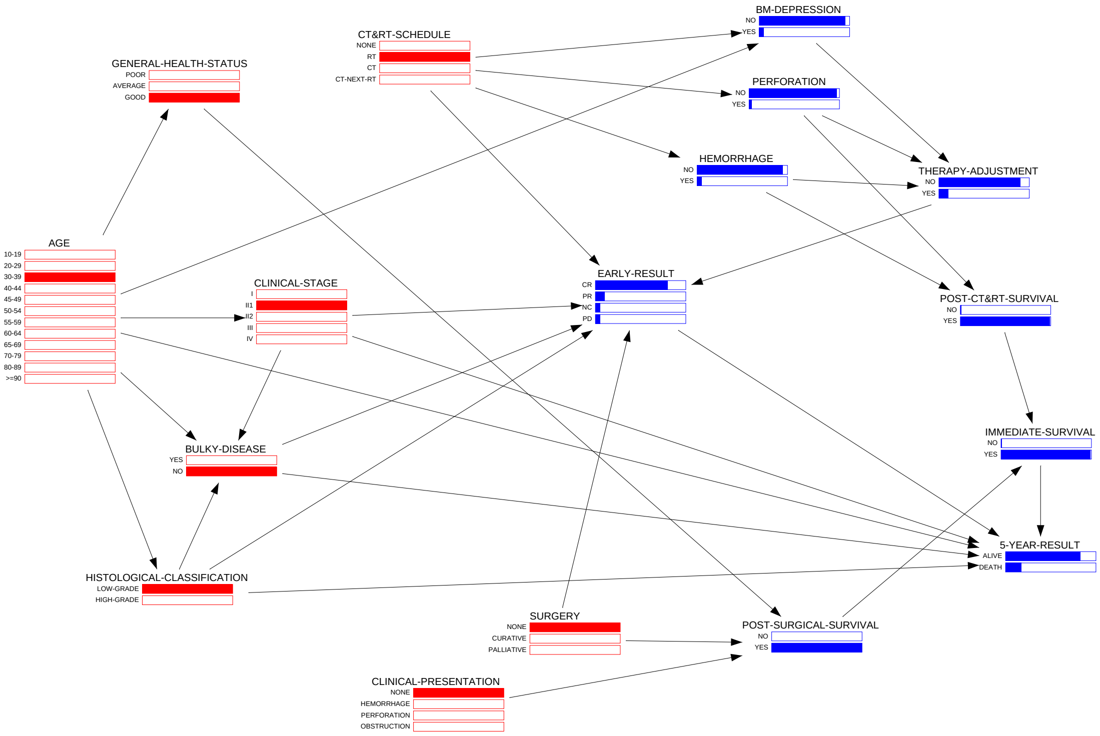

Figure 4: Prognostic prediction, assuming that the patient has been treated with radiotherapy.

3.1 Prognostic Prediction

The probabilistic network for gastric NHL can be applied to the data of a specific patient, yielding prognostic information about the patient, given particular patient features and therapeutic decisions. For example, in Fig. 4 all pretreatment variables have been entered. If we assume that this patient will be treated with radiotherapy only, the probabilistic network can be employed to indicate the future likelihoods of the various possible consequences (side effects, remission, death, etc.) of the chosen therapy, given the clinical characteristics of the patient. For this patient, there is a probability of 0.80 that all tumour cells have been eradicated, and the probability of surviving at least 5 years following treatment is 0.82. Others clinical questions can be explored along similar lines. Note that it is not necessary that all patient data are available. It is even possible to leave the therapy choice open, and to examine consequences of the 'average' therapy.

3.2 Selection of Optimal Treatment

By reverting to the original influence diagram in Fig. 1, it is possible, using Shachter's reasoning algorithm described in Section 2.1, to determine which treatment is optimal for the patient introduced above. The treatment advice generated by the system depends on the utility function reflecting patient preferences. Taking the two utility functions discussed in Section 2.6, where the former was obtained by the direct scaling method and the latter by the standard reference gamble method, yielded the same optimal treatment: radiotherapy with expected utility of 833 and 825 (on a scale from 0 to 1000), respectively. The small difference in expected utility can be explained by the fact that for the utility function assessed by the standard reference gamble, inconvenience to the patient from radiotherapy was rated higher than for the utility function obtained by the direct scaling method.

Adoption of the utility function in which only the expected five-year survival following treatment was taken into account yielded a more drastic treatment: chemotherapy followed by radiotherapy with expected utility equal to 831. A utility equal to 1000 is associated with a survival of five years or longer, and a utility of 0 with surviving less than five years, which is interpreted as treatment failure.

Note that in this way alternative treatment strategies associated with various utility function can be examined. These alternatives are a result of differences in patient preferences. Using the corresponding probabilistic network shown in Fig. 2, the predicted prognosis for a particular treatment for a specific patient can be examined, and used as a further guide in clinical decision making.

3.3 Risk Profiles

Above, we have essentially used the decision-theoretic model of gastric NHL for prognostic assessment, where in the last case we have also determined the optimal treatment for a specific patient. The same model, however, can also be used to reason in the reverse direction: it is possible to start with the final results of treatment, and to generate probabilistic profiles that fit these final results. For this purpose, we use again the purely probabilistic version of the model. Consider for example the situation where we have been able to reach complete remission after treatment, but were required to adjust treatment, resulting in death within five years. The resulting profile is depicted in Fig. 5.

4 Conclusions

A number of prognostic models of NHL, and of gastric NHL in particular, have been developed in the past. Examples of such models are those developed by Valicenti et al. [16], by Radaszkiewicz et al. [10], and by Azab and colleagues [2]. These models are based on univariate and multivariate analysis of data from patients with gastric NHL. Although these statistical techniques are useful for identifying relevant prognostic factors, the resulting models are of limited value from a clinician's point of view. As Wyatt and Altman have noted, many medical prognostic models have never reached the stage of actual clinical use [19]. An important reason why these prognostic models are not widely used in a clinical setting may be their restrictive nature: they cannot be used to explore different clinical questions.

In contrast to other researchers, we have chosen to develop a decision-theoretic expert system, using the techniques of decision-theoretic networks, i.e. probabilistic networks and influence diagrams, as a basis for a model of gastric NHL. The design of a medical decision-theoretic network model is guided by the clinical experience of medical specialists, who are capable of indicating the random variables that are of importance in medical decision making, as well as the relationships, causally or otherwise, that hold between these variables. This information, supplemented with information from the medical literature and from clinical databases, forms a suitable basis for building decision-theoretic network models. A major advantage of a decision-theoretic expert system over other types of expert systems is that

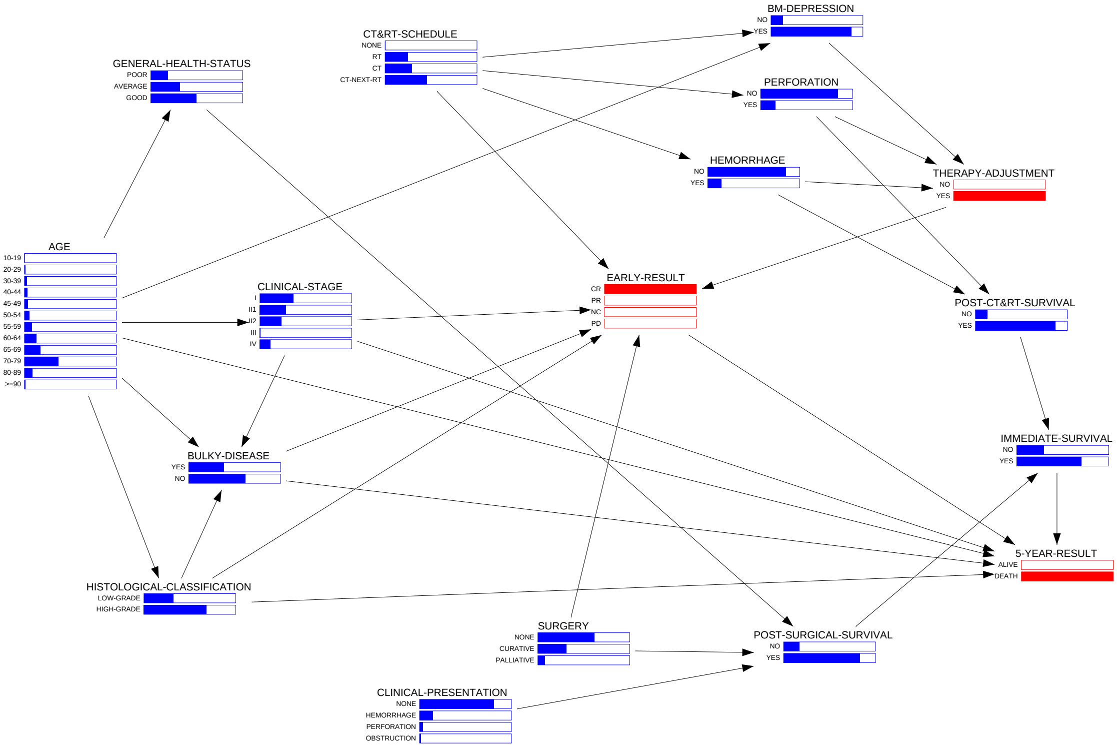

Figure 5: Risk profile for patients with therapy adjustment, complete remission, but death within five years following therapy.

many different clinical questions can be explored quite easily, as illustrated by the various examples above.

The present basis of the system discussed in this paper is clinical experience, supplemented with information gathered from the medical literature. Although it has been previously shown that such information may be a sufficient basis for the development of a reliable decision-support system [4], further improvement may be expected from adapting the underlying decision-theoretic network model using data from a large, reliable clinical database. We are currently planning to use data from the Netherlands Cancer Registry for improving the system, as well as for evaluation of the underlying decision-theoretic network model.

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