Structure and Parameters of a Bayesian Network for Carcinoid Prognosis

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Abstract

In this report, we describe the structure and parameters of a Bayesian network for prognosis of patients that present with carcinoid tumors. The report acts as a reference guide to the carcinoid model, which has been developed in collaboration with an expert physician at the Netherlands Cancer Institute.

1 Preliminaries

This report is divided into two parts. In Section 2, we discuss the construction of the pathophysiological model of the carcinoid model, whereas in Section 3, we discuss the construction of the treatment component of the carcinoid model that is built upon the pathophysiological model. Note that random variables are ordered according to a tree structure, such that $\mathsf{x}_1.\cdots.\mathsf{x}_n.\mathsf{y}$, denotes a random variable y, and where the prefix $\mathsf{x}_1.\cdots.\mathsf{x}_n$ denotes the path through the tree. (Part of) the prefix may be omitted when clear from context. In order to simplify the specification of conditional probability distributions, we will sometimes use $P(\cdot \mid \cdot) = 1_X$, where 1_X is the indicator function that evaluates to one if the expression X evaluates to *true*, and to zero if the expression X evaluates to *false*.

2 The Pathophysiological Model

We proceed as follows. First, we will provide a high-level discussion of low-grade carcinoid tumor pathophysiology by abstracting away from the details. Once this abstract model is in place, we proceed by adding more detail to the pathophysiological component of the model, and quantify this component without taking into regard how treatment influences pathophysiology. Once this component is in place, it can be used to simulate low-grade carcinoid tumor pathophysiology *without interventions*.

Carcinoid tumors are a type of neuroendocrine tumor that can produce high levels of serotonin, kinins, prostaglandins and other vasoactive peptides. They are most commonly found in the midgut [30] and typically behave less aggressively than conventional adenocarcinomas [32]; carcinoids may be present for years without overt symptoms. During the early stages carcinoid tumors often remain undiagnosed, where vague abdominal pain is commonly ascribed to irritable bowel or spastic colon [1]. Progressive carcinoid disease is often accompanied by the *carcinoid syndrome*. This syndrome is mainly characterized by diarrhea caused by increased bowel motility due to serotonin overproduction [22], periodical flushing attacks due to the synergistic interaction between histamine, kinins and prostaglandin released by the tumor into the general circulation, and

less frequently wheezing [39]. Extreme cases of the carcinoid syndrome are known as a *carcinoid crisis*, which may lead to cardiovascular collapse and ultimately death. Often, only if symptoms of the carcinoid syndrome are present, a carcinoid tumor is suspected and the patient is sent for hospitalization. Therefore, in the clinical department of the *Netherlands Cancer Institute* (NKI), most patients that are admitted are already known to have carcinoid disease, most often of the midgut type. Hence, for physicians at the NKI, diagnosis of carcinoids is not of primary concern. However, due to the complex nature of carcinoid disease, and recent advances in carcinoid treatment, the need for appropriate prognostication has increased.

The midgut is the region in which carcinoids are predominantly found, and neuroendocrine tumors that derive from other sites often show markedly different behavior and hence need alternative models for prognostication [40]. Carcinoid tumor histology is determined by mitotic activity and tissue necrosis, and distinguished into well differentiated, or *low-grade* malignancies, and poorly differentiated, or *high-grade* malignancies [2]. A minority of patients presents with high-grade tumors, which grow faster but are biochemically less active and therefore require a different prognostic model. In this paper, we restrict ourselves to carcinoids of the midgut with a low-grade histology. The aim is to describe the construction and validation of a model for the prognosis of carcinoid patients, where the focus is not only on prognostic accuracy, but also on the accurate representation of domain knowledge. This is a non-trivial task, since the domain is complex, where both decision-making and temporal interactions are important. Figure 1 depicts the prior and transition model for the pathophysiological component of the carcinoid model. The prior model was constructed from this transition model by adding additional dependencies that denote associations between variables.

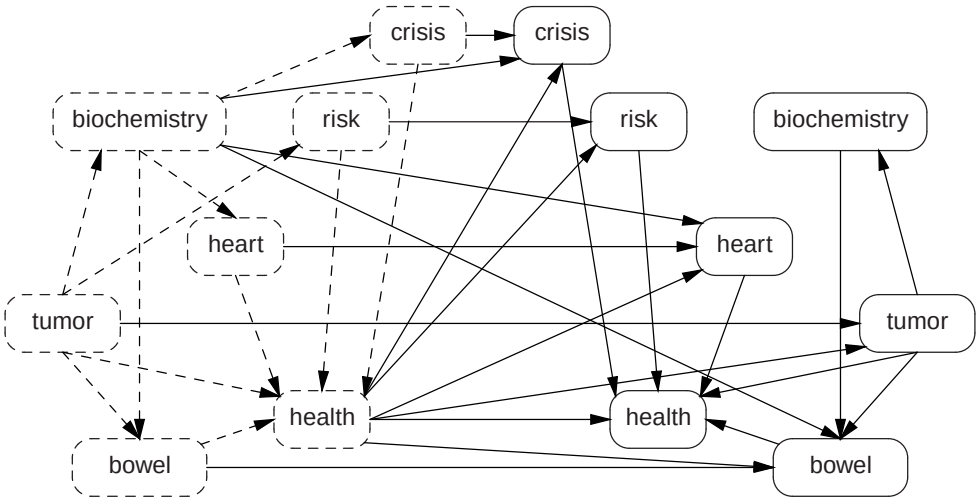

Figure 1: A combination of prior and transition model, representing disease progression for carcinoid tumors. Dashed variables and arcs represent the prior model at the first time point, and solid variables and arcs represent the transition model for the second time point.

The transition model depicts how patient health is influenced by the tumor and other risk factors, such as heart disease (heart), bowel-related problems (bowel), various patient characteristics or risk factors (risk), and carcinoid crisis (crisis.crisis). As discussed, the tumor (tumor) causes the release of certain biochemical compounds (biochemistry), which is responsible for possible carcinoid crisis, and a number of other complications.

2.1 Carcinoid Tumors and Metastatic Disease

Serotonin is thought to be the primary mediator in the development of complications. Serotonin overproduction is caused by the carcinoid tumor in the presence of particular metastases. Hormones released by carcinoid tumors are often destroyed by the liver before they reach the

general circulation to cause symptoms. Therefore, only liver metastases or metastases that release hormones directly into the general circulation such as ovarial, testicular or lung metastases, can produce the carcinoid syndrome. Most of the hormone-producing tumor-mass is accounted for by the liver, and consequently carcinoids are often accompanied by widespread *hepatic metastases*. A localized tumor generally leads to a better prognosis than metastatic disease, with a worse prognosis as the number of metastatic regions increases [24]. Furthermore, the extensiveness of remaining metastatic regions is of high prognostic value. Examples of such metastatic regions are *supraclavicular, peritoneal, retroperitoneal, skin* and *bone* metastases. As the number of such regions is too large to represent exhaustively, we summarize their joint impact by representing the mass that these regions contribute to the total tumor mass, where we assume an equivalence between this mass and the number of regions.

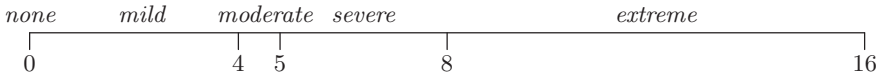

Figure 2: Tumor mass, with mass = *none* equal to 0 units, mass = *mild* equal to $1, 2$ or 3 units, mass = *moderate* equal to 4 units, mass = *severe* equal to $5, 6, 7$, or 8 units, and mass = *extreme* equal to more than 8 units.

In order to quantify the amount of tumor mass that is present within the patient, we define a standard unit of tumor mass as an average sized localized metastatic region, such that tumor.mass ranges from a patient with just a primary localization (0 units) to a patient that shows the maximal amount of metastases (16 units). Although the large number of states of mass allows for a detailed specification of tumor growth (and tumor regression when treatment is administered), it is sometimes useful nor possible to specify how the tumor mass conditions other variables given each state of mass. We therefore map these states to a reduced number of tumor mass categories, as shown in Fig. 2.

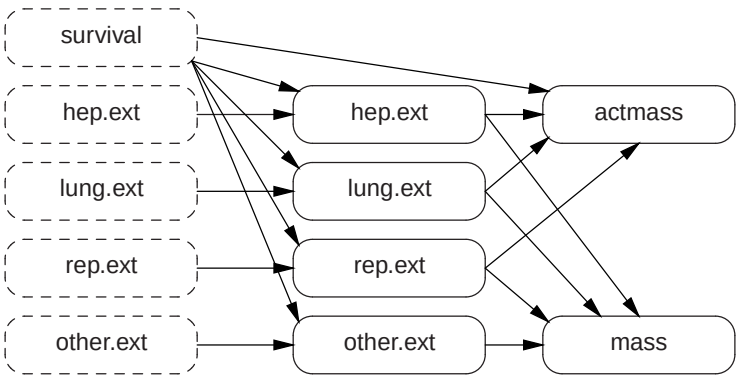

Figure 3: Tumor extensiveness depends on previous extensiveness. As the primary tumor is often small, primary tumor extensiveness is not explicitly represented. Since other.ext also represents abdominal metastases, they may cause abdominal pain. The total tumor mass (tumor.mass) is defined in terms of biochemically active tumor mass (tumor.actmass), consisting of hepatic, lung and reproductive organ metastases, and other biochemically inactive metastases. The conditioning variable health.survival is used to denote that changes only take place if the patient is still alive.

The variable tumor.mass^t has parent variables x.ext^t with $\text{x} \in \{\text{tumor.hep}, \text{tumor.lung}, \text{tumor.rep}, \text{tumor.other}\}$, standing for the extensiveness of hepatic, lung, reproductive organs, and other metastases respectively (Fig. 3). The total tumor mass is then modeled by means of the following additive model:

$$P(\text{mass}^t = y \mid \text{hep.ext}^t = x_1, \text{lung.ext}^t = x_2, \text{rep.ext}^t = x_3, \text{other.ext}^t = x_4)$$
$$= 1_{x_1+x_2+x_3+x_4=y}$$

whereas the biochemically active tumor mass is modeled as:

$$P(\mathsf{actmass}^t = y \mid \mathsf{hep.ext}^t = x_1, \mathsf{lung.ext}^t = x_2, \mathsf{rep.ext}^t = x_3, \mathsf{survival}^{t-1} = yes) = 1_{\min(x_1+x_2+x_3,6)=y}$$

Hepatic metastases are distinguished into a contribution of 0 to 11 units of tumor mass as this accounts for the majority of tumor mass, rep.ext and other.ext each contribute one unit to the total amount of tumor mass, and the variable other.ext takes into account the *number* of other regions, such that $\mathsf{other.ext} = n$, with $n \leq 3$, stands for n metastatic regions, other than liver, lungs or reproductive organs.

We distinguish hepatic metastases into the different types: *localized*, *multiple*, and *diffuse*, as patient treatment depends on these types. Localized hepatic metastases are defined as having at least one, and at most three localized regions, multiple hepatic metastases are confined to at most six localized regions where the diameter of metastatic regions is less than four centimeter, and diffuse metastases can be regarded as diffusely distributed metastatic regions throughout the liver to a limited degree. As hepatic metastases grow, a transition in metastatic type takes place from localized to multiple and finally diffuse hepatic metastases. We estimate the type of the hepatic metastases by taking into account the extensiveness of hepatic metastases. Particularly, we assume that

$$\begin{aligned}
&P(\mathsf{hep.type}^t = \mathit{localized} \mid \mathsf{hep.type}^{t-1} = x, \mathsf{hep.ext}^{t-1} = y) = 1_{x=\mathit{localized} \wedge y \leq 3} \\
&P(\mathsf{hep.type}^t = \mathit{multiple} \mid \mathsf{hep.type}^{t-1} = x, \mathsf{hep.ext}^{t-1} = y) = 1_{x \in \{\mathit{localized}, \mathit{multiple}\} \wedge y = 4} \\
&P(\mathsf{hep.type}^t = \mathit{diffuse} \mid \mathsf{hep.type}^{t-1} = x, \mathsf{hep.ext}^{t-1} = y) = 1_{x=\mathit{diffuse} \vee y \geq 5}
\end{aligned}$$

This reflects the idea that if tumors are of a certain type then there can only be a change to less favorable types; even if tumor extensiveness is reduced. At time $t = 0$, we equate $x \leq 3$ with *localized*, $x = 4$ with *multiple*, and $x \geq 5$ with *diffuse*. The variable hep.degree indicates the amount of hepatic metastases in relation to possible treatments, with

$$\begin{aligned}
P(\mathsf{hep.degree}^t = \mathit{untreatable} \mid \mathsf{hep.ext}^t \in \{0, 7, 8, \ldots, 11\}) &= 1 \\
P(\mathsf{hep.degree}^t = \mathit{present} \mid \mathsf{hep.ext}^t \in \{1, \ldots, 4\}) &= 1 \\
P(\mathsf{hep.degree}^t = \mathit{serious} \mid \mathsf{hep.ext}^t \in \{5, 6\}) &= 1
\end{aligned}$$

Figure 4 depicts these relations.

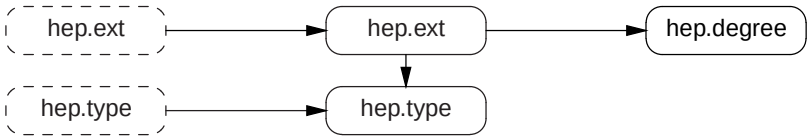

Figure 4: Changes in the type and degree of hepatic metastases due to tumor progression.

It is assumed that metastasis follows a linear growth pattern. For hepatic metastases, the physician has estimated the probability of tumor growth over a three-month period as in Table 1.

This shows a rough correspondence with about a doubling of hepatic metastases within the period of a year [25]. Since the probability of developing metastases is qualitatively different from the growth of metastases, the physician has also specified $P(\mathsf{x.ext}^t = 1 \mid \mathsf{x.ext}^{t-1} = 0, \mathsf{survival}^{t-1} = yes)$ for $\mathsf{x} \in \{\mathsf{hep}, \mathsf{rep}, \mathsf{lung}, \mathsf{other}\}$. The probability of developing metastatic disease is different for each region. The physician estimated that 33 out of 100 low-grade carcinoid patients with no hepatic metastases will see at least a change to mild hepatic metastases within a year. We can use the following equation to convert between an annual probability and a three-month probability [10]:

$$P_m(X) = -\frac{m \ln(1 - P_n(X))}{n}, \tag{1}$$

where P_n is the estimate for n time steps, and m is the estimate for m time steps. Using $n = 4$ and $m = 1$, we obtain $P(\mathsf{hep.ext}^t = 1 \mid \mathsf{hep.ext}^{t-1} = 0, \mathsf{survival}^{t-1} = yes) \approx 0.10$. We estimate the

Table 1: The CPT for $P(\mathsf{hep.ext}^t \mid \mathsf{hep.ext}^{t-1})$.

$\mathsf{hep.ext}^{t-1}$	0	1	2	3	4	5	6	7	8	9	10	11
$\mathsf{other.ext}^t=0$	0.8	0	0	0	0	0	0	0	0	0	0	0
$\mathsf{other.ext}^t=1$	0.2	0.64	0	0	0	0	0	0	0	0	0	0
$\mathsf{other.ext}^t=2$	0	0.36	0.51	0	0	0	0	0	0	0	0	0
$\mathsf{other.ext}^t=3$	0	0	0.49	0.45	0	0	0	0	0	0	0	0
$\mathsf{other.ext}^t=4$	0	0	0	0.55	0.3	0	0	0	0	0	0	0
$\mathsf{other.ext}^t=5$	0	0	0	0	0.7	0.2	0	0	0	0	0	0
$\mathsf{other.ext}^t=6$	0	0	0	0	0	0.7	0.1	0	0	0	0	0
$\mathsf{other.ext}^t=7$	0	0	0	0	0	0.1	0.6	0.05	0	0	0	0
$\mathsf{other.ext}^t=8$	0	0	0	0	0	0	0.3	0.35	0.05	0	0	0
$\mathsf{other.ext}^t=9$	0	0	0	0	0	0	0	0.40	0.25	0.05	0	0
$\mathsf{other.ext}^t=10$	0	0	0	0	0	0	0	0.20	0.30	0.15	0.05	0
$\mathsf{other.ext}^t=11$	0	0	0	0	0	0	0	0	0.40	0.80	0.95	1

incidence of other metastases by updating the odds-ratio as follows:

$$\frac{p}{1-p} = k \cdot \frac{q}{1-q},$$

where p is the probability of incidence of other metastases, k is a multiplication factor, and q is the probability of incidence for hepatic metastases. From clinical experience we estimate that the incidence of lung metastases is 0.08 times as likely as experiencing hepatic metastases:

$$\frac{p}{1-p} = 0.08 \cdot \frac{0.10}{1-0.10}$$

such that $P(\mathsf{lung.ext}^t = 1 \mid \mathsf{lung.ext}^{t-1} = 0) \approx 8.9 \cdot 10^{-3}$. We estimate that the incidence of reproductive organ metastases is 0.03 times as likely as experiencing hepatic metastases:

$$\frac{p}{1-p} = 0.03 \cdot \frac{0.10}{1-0.10}$$

such that $P(\mathsf{rep.ext}^t = 1 \mid \mathsf{rep.ext}^{t-1} = 0) \approx 3.3 \cdot 10^{-3}$. From clinical experience we estimate that the incidence for other metastases is on average 0.16 times as likely as experiencing hepatic metastases. By straight computation we obtain

$$\frac{p}{1-p} = 0.16 \cdot \frac{0.10}{1-0.10}$$

such that the probability p of developing other metastases during follow-up is estimated to be $1.6 \cdot 10^{-2}$ given $\mathsf{tumresp}^t = \mathit{none}$. By assuming that the occurrence of a metastatic region is independent of occurrences of other regions, the CPT can be completed as shown in Table 2.

Table 2: The CPT for $P(\mathsf{other.ext}^t \mid \mathsf{other.ext}^{t-1})$.

$\mathsf{other.ext}^{t-1}$	0	1	2	3
$\mathsf{other.ext}^t=0$	0.984	0	0	0
$\mathsf{other.ext}^t=1$	0.016	0.984	0	0
$\mathsf{other.ext}^t=2$	0	0.016	0.984	0
$\mathsf{other.ext}^t=3$	0	0	0.016	1

Other metastases in the abdomen can cause severe abdominal pain, and we estimate:

$$\begin{aligned} P(\mathsf{bowel.abdpain}^t = \mathit{present} \mid \mathsf{other.ext}^t = 1) &= 1 \cdot 10^{-3} \\ P(\mathsf{bowel.abdpain}^t = \mathit{present} \mid \mathsf{other.ext}^t = 2) &= 2 \cdot 10^{-3} \\ P(\mathsf{bowel.abdpain}^t = \mathit{present} \mid \mathsf{other.ext}^t = 3) &= 3 \cdot 10^{-3} \end{aligned}$$

We also need to specify the prior probability that metastases are present. The estimates for the prior probability of having hepatic metastases of a given degree, for patients that enter the clinic, are as follows:

Table 3: The CPT for $P(\mathsf{hep}^0.\mathsf{ext})$.

$\mathsf{hep}^0.\mathsf{ext}$	0	1	2	3	4	5	6	7	8	9	10	11
$P(\mathsf{hep}^0.\mathsf{ext})$	0.20	0.03	0.04	0.10	0.13	0.22	0.13	0.05	0.04	0.02	0.02	0.02

The prior probabilities that metastases are present have also been estimated, but note that these estimates are valid only for patients that arrive at the NKI, due to the fact that patients that are sent to this clinic often have advanced metastatic disease.[1] For $\mathsf{rep.ext}^0$ we estimate $P(\mathsf{rep.ext}^0 = 1) = 0.02$, and for $\mathsf{lung.ext}^0$ we estimate $P(\mathsf{lung.ext}^0 = 1) = 0.15$. The prior for $\mathsf{other.ext}^0$ is estimated as $P(\mathsf{other.ext}^0 = 0) = 0.88$, $P(\mathsf{other.ext}^0 = 1) = 0.08$, $P(\mathsf{other.ext}^0 = 2) = 0.02$ and $P(\mathsf{other.ext}^0 = 3) = 0.02$.

2.2 Neuroendocrine Properties

Plasma *chromogranin A* (biochemistry.cga) levels, can be used as a marker of tumor load, in terms of neuroendocrine activity [19] and tumor mass [5]. We distinguish *normal* (< 120 μg/L), *elevated* (120-3000 μg/L) and *extreme* (> 3000 μg/L) cga levels, and patients with extreme cga levels have a significantly poorer 5-year survival than patients with elevated cga levels [9]. The variable cga^t has parent variables $\mathsf{biochemistry.bioresp}^t$and $\mathsf{tumor.mass}^t$.

The biochemical response stands for the possible biochemical response of treatment, and may lead to reductions in cga levels. The biochemical response is quantified by means of the criteria in Table 4, where biochemical activity is defined in terms of the production of cga and the release of neuroendocrine substances such as serotonin.

Table 4: The criteria for biochemical response.

Biochemical Response	**Criteria**
Complete remission (*cr*)	Normal biochemical activity.
Partial remission (*pr*)	$> 50\%$ decrease in abnormal biochemical activity.
Progressive disease (*pd*)	No response of treatment.
Stable disease (*sd*)	$> 50\%$ decrease or $< 25\%$ increase in abnormal biochemical activity.
No treatment (*nt*)	No treatment given.

In [18], a group of 124 patients with gastroenteropancreatic neuroendocrine tumors was analyzed. Here 53% of patients with secreting tumors and no metastases had normal cga levels and 47% of these patients had elevated cga levels. Based on clinical expertise, and taking these observations into account, we estimate the distribution shown in Table 5. We use $\Omega_{\mathsf{bioresp}} = \{pd, sd, pr, cr\}$, and if $\mathsf{bioresp} = cr$ then $\mathsf{cga} = normal$.

Biochemically active carcinoid tumors also produce serotonin (biochemistry.5-ht), which can be estimated from the the measurement of 5-hydroxyindole-3-acetic acid (biochemistry.5-hiaa) concentrations in a 24-hour urine sample, as a metabolite of serotonin. Following [38] we distinguish *normal* (< 40 μmol/L), *elevated* (40-200 μmol/L) and *extreme* (> 200 μmol/L) 5-hiaa levels, and assume that 5-hiaa levels follow 5-ht levels. Likewise, we assume a direct relation between release and 5-HT since we have no further knowledge concerning the relation between the tumor and the production of other biochemical compounds. Therefore, $P(\mathsf{5\text{-}ht}^t = x \mid \mathsf{release}^t = y) = 1_{x=y}$.

[1] For the general patient population, we would also condition the probability of hepatic metastases on the localization of the primary tumor, since incidentally found appendiceal tumors have a smaller probability of metastatic disease.

Table 5: Estimate of the distribution $P(\mathsf{cga}^t \mid \mathsf{mass}^t, \mathsf{bioresp}^t)$.

mass^t	*none*	*mild*	*moderate*	*severe*	*extreme*
$\mathsf{bioresp}^t$			*pd*		
$\mathsf{cga}^t = normal$	.53	.10	.05	.05	.05
$\mathsf{cga}^t = elevated$	.47	.80	.85	.80	.65
$\mathsf{cga}^t = extreme$	0	.10	.10	.15	.30
$\mathsf{bioresp}^t$			*sd*		
$\mathsf{cga}^t = normal$	.59	.20	.16	.15	.13
$\mathsf{cga}^t = elevated$	.41	.75	.79	.78	.72
$\mathsf{cga}^t = extreme$	0	.05	.05	.07	.15
$\mathsf{bioresp}^t$			*pr*		
$\mathsf{cga}^t = normal$	.65	.30	.26	.25	.21
$\mathsf{cga}^t = elevated$	.35	.70	.74	.75	.79
$\mathsf{cga}^t = extreme$	0	0	0	0	0

The variable $\mathsf{biochemistry.release}^t$ has parent variables $\mathsf{actmass}^t$ and $\mathsf{bioresp}^t$ since release is determined by the amount of hormone producing tumor-mass and the possible biochemical response of treatment. In order to complete the distribution, we have assessed the conditional probabilities for release for the various biochemical responses, as shown in Table 6. Note again that if $\mathsf{bioresp} = cr$ then $\mathsf{release} = normal$.

Table 6: The CPT for $P(\mathsf{release}^t \mid \mathsf{actmass}^t, \mathsf{bioresp}^t)$.

$\mathsf{actmass}^t$	0	1	2	3	4	5	6
$\mathsf{bioresp}^t$				*pd*			
$\mathsf{release}^t = normal$	1	.05	.03	.02	.01	.01	.01
$\mathsf{release}^t = elevated$	0	.75	.60	.45	.35	.11	.05
$\mathsf{release}^t = extreme$	0	.20	.37	.53	.64	.88	.94
$\mathsf{bioresp}^t$				*sd*			
$\mathsf{release}^t = normal$	1	.14	.11	.11	.09	.03	.02
$\mathsf{release}^t = elevated$	0	.76	.66	.64	.63	.53	.51
$\mathsf{release}^t = extreme$	0	.10	.23	.25	.28	.44	.47
$\mathsf{bioresp}^t$				*pr*			
$\mathsf{release}^t = normal$	1	.24	.17	.16	.14	.05	.04
$\mathsf{release}^t = elevated$	0	.76	.83	.84	.86	.95	.96
$\mathsf{release}^t = extreme$	0	0	0	0	0	0	0

2.3 Carcinoid Syndrome

As mentioned, the most prominent clinical sign of carcinoid disease is the carcinoid syndrome, which is caused by high levels of circulating bioactive substances [39]. Although many of these substances are thought to play a role in the disease, the exact interactions are as yet unclear, and in practice, diagnosis relies on the assessment of serotonin overproduction by measuring urinary 5-HIAA levels. Sometimes, an excessive release of bioactive substances may lead to a *carcinoid crisis*; a very severe case of carcinoid syndrome which is characterized by severe flushing, severe diarrhea and vomiting. A crisis may lead to dehydration, acute hypotension and may ultimately cause cardiovascular collapse, which is a life-threatening situation. It is thought to arise from an excessive release of vasoactive substances into the general circulation [26]. The cascade of events that occurs after a crisis is not modeled explicitly as we are interested only in the influence of a crisis on patient survival (Fig. 5).

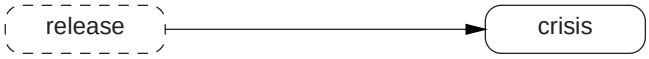

Figure 5: Excessive release (biochemistry.release) may induce a carcinoid crisis.

We need to estimate the probability that a patient will experience a crisis in the coming three months, conditional on the current release of biochemical substances. It is assumed that $P(\text{crisis}^t = yes \mid \text{release}^{t-1} = normal) = 0$, and if a crisis occurs then appropriate response will prohibit the occurrence of another crisis. The physician estimated

$$\begin{aligned} P(\text{crisis}^t = yes \mid \text{release}^{t-1} = elevated) &= 5 \cdot 10^{-5} \\ P(\text{crisis}^t = yes \mid \text{release}^{t-1} = extreme) &= 1.3 \cdot 10^{-3} \end{aligned}$$

For the prior distribution for crisis, a dependency between release^{0}and crisis^{0}was introduced, since a high current release increases our belief that a crisis has occurred in the past. We use the probability $P(\text{crisis}^0 \mid \text{release}^{t-1})$ as a crude estimate of $P(\text{crisis}^0 \mid \text{release}^0)$.

Serotonin is known to cause diarrhea and is used as a correlate of the vasoactive substances that cause flushing. Which substances are exactly responsible for flushing remains unclear. The severeness of diarrhea and flushing is subjective, but here we associate moderate diarrhea and flushing with the need for symptomatic or no medication, and severe diarrhea and flushing with the need for carcinoid specific medication. Sometimes, the increased bowel motility that causes diarrhea leads to severe abdominal pain. We define carcinoid syndrome as a combination of diarrhea and flushing, disregarding less frequently occurring symptoms (Fig. 6).

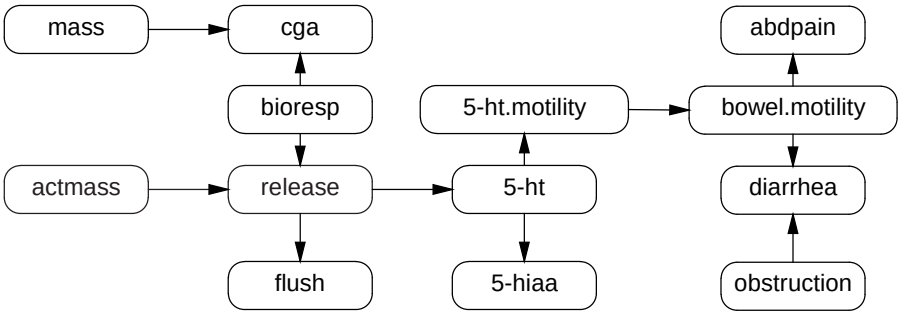

Figure 6: Serotonin overproduction, as measured by the urinary 5-hiaa concentration, arises from the release of biochemical substances into the general circulation by active hepatic, reproductive organ or lung metastases, and is associated with carcinoid syndrome, defined as the presence of diarrhea and flushing. Elevated cga levels are associated with tumor load.

The variable biochemistry.flush^t has parent variable biochemistry.release^t. Moderate flushing is defined as a degree of flushing that requires no medication, and the avoidance of certain dietary products such as alcohol. Severe flushing is defined as a degree of flushing that would require carcinoid specific medication such as somatostatin analogues. Again, we use the estimate $P(\text{flush}^t \mid \text{5-ht}^t)$ in order to define $P(\text{flush}^t \mid \text{release}^t)$ as shown in Table 7.

Table 7: The CPT for $P(\text{flush}^t \mid \text{release}^t)$.

release^t	*normal*	*elevated*	*extreme*
flush^t = *none*	0.70	0.50	0.20
flush^t = *moderate*	0.29	0.30	0.30
flush^t = *severe*	0.01	0.20	0.50

The variable biochemistry.diarrhea^t has parent variables bowel.motility^t and bowel.obstruction^t. Moderate diarrhea is defined as a degree of diarrhea that requires symptomatic medication such

as loperamide and codeine. Severe diarrhea is defined as a degree of diarrhea that would require carcinoid specific medication such as somatostatin analogues. It is reported that 39% of patients that present with bowel obstruction experience cessation of diarrhea, which ultimately leads to vomiting [14]. We equate no diarrhea with normal bowel motility, moderate diarrhea with increased bowel motility, and severe diarrhea with severe bowel motility, such that the completed distribution is given by Table 8.

Table 8: The CPT for $P(\mathsf{diarrhea}^t \mid \mathsf{bowel.motility}^t, \mathsf{obstruct}^t)$.

$\mathsf{bowel.motility}^t$	*normal*		*increased*		*extreme*	
$\mathsf{obstruct}^t$	*absent*	*present*	*absent*	*present*	*absent*	*present*
$\mathsf{diarrhea}^t = none$	0.38	0.55	0.30	0.5	0.28	0.45
$\mathsf{diarrhea}^t = moderate$	0.62	0.45	0.54	0.4	0.20	0.15
$\mathsf{diarrhea}^t = severe$	0	0	0.16	0.1	0.52	0.4

There are multiple independent causes that contribute to increased bowel motility. Therefore, it is convenient to specify the combined influence of these causes by means of the following *leaky noisy-max* model:

$$P(\mathsf{bowel.motility}^t = e \mid \mathbf{C}) = \sum_{\mathbf{z}:\ max(\mathbf{z})=e} \prod_{C_i \in \mathbf{C}} P(z_i \mid C_i) \tag{2}$$

where $\mathbf{C}$ represents the set of independent causes of bowel motility. We use $C.\mathsf{motility} \in \mathbf{Z}$ to represent the intermediate variable belonging to a cause C. We also assume a leak cause leak that is always present, for which we estimate

$$\begin{aligned} P(\mathsf{leak.motility}^t = increased \mid \mathsf{leak.cause}^t = present) &= 0.10 \\ P(\mathsf{leak.motility}^t = extreme \mid \mathsf{leak.cause}^t = present) &= 0.01 \end{aligned}$$

and for serotonin, we have the following estimates:

$$\begin{aligned} P(\mathsf{biochemistry.motility}^t = increased \mid \mathsf{5\text{-}ht}^t = elevated) &= 0.50 \\ P(\mathsf{biochemistry.motility}^t = extreme \mid \mathsf{5\text{-}ht}^t = elevated) &= 0.25 \\ P(\mathsf{biochemistry.motility}^t = increased \mid \mathsf{5\text{-}ht}^t = extreme) &= 0.1 \\ P(\mathsf{biochemistry.motility}^t = extreme \mid \mathsf{5\text{-}ht}^t = extreme) &= 0.8 \end{aligned}$$

2.4 Carcinoid Heart Disease

Carcinoid heart disease is often a consequence of enlargement and distortion of the endocardium and subendocardium of the tricuspid valve, leading to tricuspid insufficience and decompensatio cordis [36]. CHD may lead to right heart failure which is the cause of death in approximately half of carcinoid patients [27]; as the pump function of the heart deteriorates the patient's general health status deteriorates rapidly. A trend can be seen between the degree of right atrium dilatation, and the level of the *brain natriuretic peptide* (BNP); especially its biologically inactive N-terminal fragment NT-pro-BNP [37]. CHD related mortality is dependent on the progression of carcinoid heart disease in the patient, which is defined as tricuspid valve thickening with additional severe or extreme regurgitation. The dependencies between variables are shown in Fig. 7.

The variable $\mathsf{heart.chd}^t$ has parent variables $\mathsf{heart.regurg}^t$ and $\mathsf{heart.thick}^t$ and is a deterministic variable, whose states are fully determined by the states of its parent variables. Following the definition of chd in [36], we define:

$$P(\mathsf{chd}^t = yes \mid \mathsf{thick}^t, \mathsf{regurg}^t, \mathsf{survival}^{t-1} = yes) = 1_{\mathsf{thick}^t = yes \wedge \mathsf{regurg}^t > moderate}$$

CHD is a dangerous condition since it has a high associated mortality rate. This is expressed in terms of a strong negative influence on a patient's general health status.

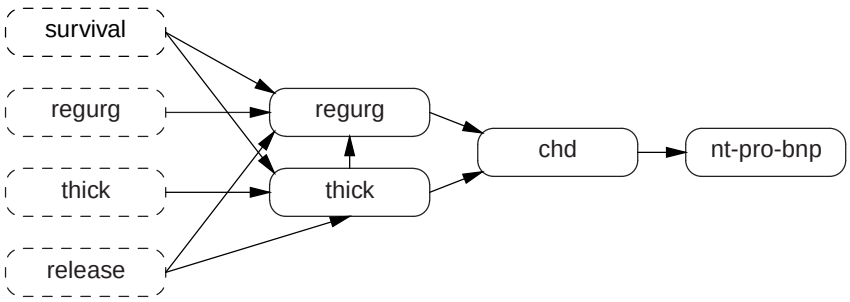

Figure 7: The release of biochemically active substances may lead to an increase in cardiac valve thickening. This causes a retraction of the tricuspid valve and ultimately cardiac valve regurgitation. Note again that change takes place only if $\mathsf{survival} = yes$.

The expert physician found it difficult to estimate the effect of the release of biochemically active substances, since the role of serotonin and other substances with regard to the development of chd is not clear [17]. In order to make the task feasible, we equate this release with the release of 5-hiaa, which is an observable finding. Furthermore, the expert found it difficult to estimate the required probabilities for a period as short as the follow-up time of three months. Therefore, instead the probabilities were assessed for a yearly interval, and transformed to a three-month period, again making use of Eq. (1):

$$\begin{array}{lcl} P(\mathsf{thick}^t = yes \mid \mathsf{release}^{t-1} = normal, \mathsf{thick}^{t-1} = no, \mathsf{survival}^{t-1} = yes) & \approx & 0.005 \\ P(\mathsf{thick}^t = yes \mid \mathsf{release}^{t-1} = elevated, \mathsf{thick}^{t-1} = no, \mathsf{survival}^{t-1} = yes) & \approx & 0.013 \\ P(\mathsf{thick}^t = yes \mid \mathsf{release}^{t-1} = extreme, \mathsf{thick}^{t-1} = no, \mathsf{survival}^{t-1} = yes) & \approx & 0.062 \\ P(\mathsf{thick}^t = yes \mid \mathsf{release}^{t-1}, \mathsf{thick}^{t-1} = yes, \mathsf{survival}^{t-1}) & = & 1 \end{array}$$

where the latter follows from the fact that tricuspid valve thickening is irreversible. The prior distribution for thick^0 is conditioned on $\mathsf{release}^0$, since thickening depends on the release of neuroendocrine substances by the tumor. We estimate

$$\begin{array}{lcl} P(\mathsf{thick}^0 = yes \mid \mathsf{release}^0 = normal) & = & 0.01 \\ P(\mathsf{thick}^0 = yes \mid \mathsf{release}^0 = elevated) & = & 0.10 \\ P(\mathsf{thick}^0 = yes \mid \mathsf{release}^0 = extreme) & = & 0.40 \end{array}$$

The variable regurg^t has parent variables regurg^{t-1}, thick^t, $\mathsf{release}^{t-1}$, and $\mathsf{survival}^{t-1}$. Since regurgitation is a result of tricuspid valve thickening, we assume that

$$P(\mathsf{regurg}^t = none \mid \mathsf{regurg}^{t-1}, \mathsf{thick}^t = no, \mathsf{release}^{t-1}, \mathsf{survival}^{t-1}) = 1.$$

Furthermore, we assume that regurgitation is *irreversible* conditional on the presence of thickening:

$$P(\mathsf{regurg}^t = x \mid \mathsf{regurg}^{t-1} = x', \mathsf{thick}^t \neq no, \mathsf{release}^{t-1}, \mathsf{survival}^{t-1}) = 0$$

for $x < x'$. We also assume that regurgitation can only worsen gradually, such that

$$P(\mathsf{regurg}^t = x \mid \mathsf{regurg}^{t-1} = y, \mathsf{thick}^t, \mathsf{release}^{t-1}, \mathsf{survival}^{t-1} = yes) = 0$$

for all $x, y \in \Omega_{\mathsf{regurg}}$ for which there is a $z \in \Omega_{\mathsf{regurg}}$, such that $x < z < y$. Finally, if $\mathsf{release}^{t-1} = normal$ then we assume that there is no change in regurgitation, such that

$$P(\mathsf{regurg}^t = x \mid \mathsf{regurg}^{t-1} = x, \mathsf{thick}^t, \mathsf{release}^{t-1} = normal, \mathsf{survival}^{t-1}) = 1.$$

The remaining probabilities were assessed for an annual interval, and using the approach of Eq. (1), we obtain the CPT depicted in Table 9. The situation for extreme regurgitation at $t-1$ is not shown, since regurgitation is irreversible.

Table 9: Table for $P(\text{regurg}^t \mid \text{regurg}^{t-1}, \text{thick}^t = yes, \text{release}^{t-1})$.

thick^t	*yes*											
release^{t-1}	*normal*				*elevated*				*extreme*			
regurg^{t-1}	*no*	*mi*	*mo*	*se*	*no*	*mi*	*mo*	*se*	*no*	*mi*	*mo*	*se*
$\text{regurg}^t = no$	.97	0	0	0	.841	0	0	0	.8	0	0	0
$\text{regurg}^t = mi$	.03	.98	0	0	.159	.891	0	0	.2	.87	0	0
$\text{regurg}^t = mo$	0	.02	.98	0	0	.109	.937	0	0	.13	.913	0
$\text{regurg}^t = se$	0	0	.02	.98	0	0	.063	.9	0	0	.087	.87
$\text{regurg}^t = ex$	0	0	0	.02	0	0	0	.1	0	0	0	.13

Table 10: The CPT for $P(\text{regurg}^0 \mid \text{thick}^0, \text{release}^0)$.

release^0	*normal*		*elevated*		*extreme*	
thick^0	*no*	*yes*	*no*	*yes*	*no*	*yes*
$\text{regurg}^0 = none$	1	0.50	1	0.20	1	0.10
$\text{regurg}^0 = mild$	0	0.33	0	0.30	0	0.30
$\text{regurg}^0 = moderate$	0	0.12	0	0.30	0	0.30
$\text{regurg}^0 = severe$	0	0.03	0	0.15	0	0.20
$\text{regurg}^0 = extreme$	0	0.02	0	0.05	0	0.10

The variable regurg^0 is also assumed to have parent variable thick^0, and is estimated using available clinical expertise (Table 10). The variable $\text{heart.nt-pro-bnp}^t$ has parent variable chd^t. Here, we follow the results of [37], and distinguish nt-pro-bnp into *normal* (< 200 ng/L) and *elevated* (≥ 200 ng/L) concentrations. Since all chd patients had elevated nt-pro-bnp levels, we obtain $P(\text{nt-pro-bnp}^t = elevated \mid \text{chd}^t = yes) = 1$, and since 4 out of 23 non-chd patients had elevated nt-pro-bnp levels, we obtain $P(\text{nt-pro-bnp}^t = elevated \mid \text{chd}^t = no) = 0.174$.

2.5 Mesenterial Fibrosis

Mesenterial fibrosis (bowel.mesfib) may lead to obstruction and/or ischaemia, with finally necrosis and perforation of the bowel wall [17]; life threatening situations, that are often accompanied by acute abdominal pain (Fig. 8). Note that mesfib is conditioned by tumor.primloc (primary tumor localization), since only small-bowel tumors may cause mesenterial fibrosis.

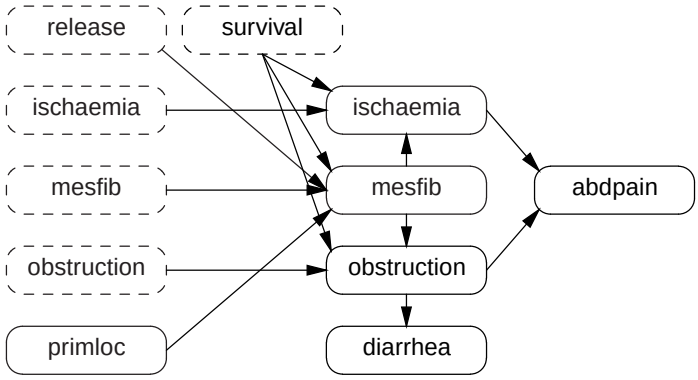

Figure 8: Mesenterial fibrosis is caused by a small-bowel carcinoid tumor, excluding the appendix. It may lead to obstruction and ischaemia, which are characterized by abdominal pain. Although the release of substances such as serotonin are thought to play a role in the development of mesenterial fibrosis, the exact mechanism is not clear.

The variable mesfib^t has parent variables $\mathsf{primloc}^t$, $\mathsf{release}^{t-1}$, mesfib^{t-1}, and $\mathsf{survival}^{t-1}$. Although mesenterial fibrosis is a continuous process, we interpret the presence of mesenterial fibrosis as that degree of fibrosis that may cause obstruction and/or ischaemia. For mesenterial fibrosis, we require that the primary tumor is located in the small-bowel, and we assume that if mesenterial fibrosis was already present, then mesenterial fibrosis remains present. The remaining estimates are given by

$$\begin{aligned}
&P(\mathsf{mesfib}^t = \mathit{present} \mid \mathsf{release}^{t-1} = \mathit{normal}, \mathbf{x}) = 2.5 \cdot 10^{-3} \\
&P(\mathsf{mesfib}^t = \mathit{present} \mid \mathsf{release}^{t-1} = \mathit{elevated}, \mathbf{x}) = 0.03 \\
&P(\mathsf{mesfib}^t = \mathit{present} \mid \mathsf{release}^{t-1} = \mathit{extreme}, \mathbf{x}) = 0.05
\end{aligned}$$

where $\mathbf{x}$ stands for $\mathsf{mesfib}^{t-1} = \mathit{absent} \wedge \mathsf{primloc}^t = \mathit{small\text{-}bowel} \wedge \mathsf{survival}^{t-1} = \mathit{yes}$.

The distribution for $\mathsf{tumor.primloc}^t$ is given by $P(\mathsf{primloc}^t = x \mid \mathsf{primloc}^{t-1} = x') = 1_{x=x'}$, since primary localization does not change. For the prior distribution, we estimate $P(\mathsf{primloc}^0 = \mathit{small\text{-}bowel}) = 0.778$ and $P(\mathsf{primloc}^0 = \mathit{appendix}) = 0.222$. Note that this prior estimate is specific to the NKI, and not in accordance with findings reported in [31] for the general patient population.

The variable $\mathsf{bowel.ischaemia}^t$ has parent variables mesfib^t, $\mathsf{ischaemia}^{t-1}$, and $\mathsf{survival}^{t-1}$. If mesenterial fibrosis is absent then we assume that ischaemia is absent, and if ischaemia was present at a previous point in time then we assume that it is present now. We estimate that

$$P(\mathsf{ischaemia}^t = \mathit{present} \mid \mathsf{mesfib}^t = \mathit{present}, \mathsf{ischaemia}^{t-1} = \mathit{absent}, \mathsf{survival}^{t-1} = \mathit{yes})$$

is equal to 0.10.

The variable $\mathsf{bowel.obstruction}^t$ has parent variables mesfib^t, $\mathsf{obstruction}^{t-1}$, and $\mathsf{survival}^{t-1}$. Since there is a small probability of obstruction in the absence of mesenterial fibrosis, we estimate

$$\begin{aligned}
&P(\mathsf{obstruction}^t = \mathit{present} \mid \mathsf{mesfib}^t = \mathit{present}, \mathsf{obstruction}^{t-1} = \mathit{absent}, \mathsf{survival}^{t-1} = \mathit{yes}) = 0.05 \\
&P(\mathsf{obstruction}^t = \mathit{present} \mid \mathsf{mesfib}^t = \mathit{present}, \mathsf{obstruction}^{t-1} = \mathit{absent}, \mathsf{survival}^{t-1} = \mathit{yes}) = 0.01
\end{aligned}$$

The variable $\mathsf{bowel.abdpain}^t$ has parent variables $\mathsf{bowel.motility}^t$, $\mathsf{bowel.ischaemia}^t$, $\mathsf{bowel.obstruction}^t$ and $\mathsf{tumor.other.ext}^t$. We assume that the presence of abdominal pain represents abdominal pain to a degree that morphine-like medication is required. Assuming that these causes act independently, we assume that the distribution can be specified by a leaky noisy-max model:

$$P(\mathsf{abdpain}^t = e \mid \mathbf{C}) = \sum_{\mathbf{z}:\ max(\mathbf{z}) = e} \prod_{C_i \in \mathbf{C}} P(z_i \mid C_i)$$

with $\mathbf{C} = \{\mathsf{bowel.motility}, \mathsf{bowel.ischaemia}, \mathsf{bowel.obstruction}, \mathsf{tumor.other.ext}, \mathsf{leak}\}$. Contrary to the noisy-max model for bowel motility, we have chosen not to represent intermediate variables explicitly. Using $Z(C)$ to temporarily denote an intermediate variable of a cause C, the model is determined by the following eight parameters:

$$\begin{aligned}
P(Z(\mathsf{leak.cause}^t) = \mathit{present} \mid \mathsf{leak.cause}^t = \mathit{present}) &= 0.10 \\
P(Z(\mathsf{bowel.motility}^t) = \mathit{present} \mid \mathsf{bowel.motility}^t = \mathit{increased}) &= 0.10 \\
P(Z(\mathsf{bowel.motility}^t) = \mathit{present} \mid \mathsf{bowel.motility}^t = \mathit{extreme}) &= 0.20 \\
P(Z(\mathsf{ischaemia}^t) = \mathit{present} \mid \mathsf{ischaemia}^t = \mathit{present}) &= 0.1 \\
P(Z(\mathsf{obstruction}^t) = \mathit{present} \mid \mathsf{obstruction}^t = \mathit{present}) &= 0.2 \\
P(Z(\mathsf{other.ext}^t) = \mathit{present} \mid \mathsf{other.ext}^t = 1) &= 0.01 \\
P(Z(\mathsf{other.ext}^t) = \mathit{present} \mid \mathsf{other.ext}^t = 2) &= 0.02 \\
P(Z(\mathsf{other.ext}^t) = \mathit{present} \mid \mathsf{other.ext}^t = 3) &= 0.03
\end{aligned}$$

The variable mesfib^0 has parent variables $\mathsf{primloc}^0$ and $\mathsf{release}^0$. Since appendiceal tumors do not cause mesenterial fibrosis, we may complete the distribution as follows:

$$\begin{aligned}
P(\mathsf{mesfib}^0 = \mathit{present} \mid \mathsf{primloc}^0 = \mathit{small\text{-}bowel}, \mathsf{release}^0 = \mathit{normal}) &= 0.10 \\
P(\mathsf{mesfib}^0 = \mathit{present} \mid \mathsf{primloc}^0 = \mathit{small\text{-}bowel}, \mathsf{release}^0 = \mathit{elevated}) &= 0.30 \\
P(\mathsf{mesfib}^0 = \mathit{present} \mid \mathsf{primloc}^0 = \mathit{small\text{-}bowel}, \mathsf{release}^0 = \mathit{extreme}) &= 0.50
\end{aligned}$$

The variables ischaemia^0 and obstruction^0 have parent variable mesfib^0. We estimate that the probability of complication given mesenterial fibrosis equals 0.054 and 0.10 respectively, and we assume that 5% of patients suffer from bowel obstruction in the absence of mesenterial fibrosis.

2.6 General Health Status

Prognosis in carcinoid tumors is rather favorable compared to that of other cancers. The five-year survival rate is high but depends on several prognostic factors. Our main interest with regard to making a prognosis for low-grade carcinoids, is in tracking the general health status (health.ghs) of the patient over time. In oncology, one way to estimate the general health status is by means of the *performance status*, as shown in Table 11 [23].

Table 11: The WHO performance status (PS) and its associated impairments.

PS	Impairments
0	Normal, no complaints
1	Mild complaints for physical activities, but patient needs no assistance and can do easy work
2	Ambulatory, patient cares for self, but age-appropriate activity severely impaired
3	Confined to bed more than 50% of time, needs nursing care
4	Confined to bed or prostrated on chair, needs intensive care
5	Death

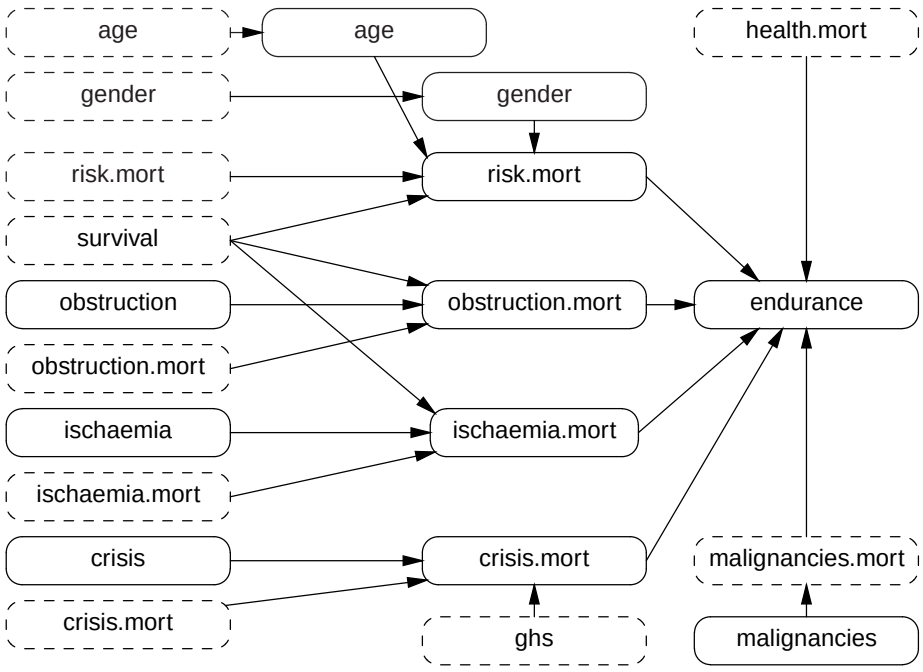

Figure 9: Patient survival as it is influenced by various causes.

We distinguish two different ways in which ghs may be influenced. Either, a variable has a positive or negative influence on ghs that causes a change in ghs over time, or a variable is one of the factors that determines the causes immediate patient death, such that ghs $= 5$. Immediate patient death is captured by the variable health.endurance, and factors are depicted in Fig. 9, where it is assumed that the probabilities of mortality is zero at time zero. We use survival, with distributions given by $P(\text{survival}^t = yes \mid \text{ghs} \neq 5) = 1$ and $P(\text{survival}^t = no \mid \text{ghs} = 5) = 1$, to model if a patient survived at time-slice t. Mortality due to some cause at time t may then only occur

given that the patient was alive (survival$=yes$) at time $t-1$. Mesenterial fibrosis and a carcinoid crisis can both cause immediate patient death, where a crisis is more dangerous to people of poor general health status, as is indicated by the dependency between ghs and crisis.mort. The past general health status itself also conditions survival, to represent the death of patients at an earlier point in time. We use health.mort, to represent this influence.

It is important to realize that patients may also die from causes other than carcinoid disease. The variable malignancies.other represents whether or not a patient has malignancies other than the carcinoid tumor. We use $P(\text{malignancies.other}^t = yes \mid \text{malignancies.other}^{t-1} = no) = 10^{-4}$, $P(\text{malignancies.other}^0 = yes \mid \text{hep.ext}^0 \neq none) = 10^{-3}$ an $P(\text{malignancies.other}^0 = yes \mid \text{hep.ext}^0 = none) = 0.30$, where the latter probability is high since patients without hepatic metastases must have been admitted due to some other cause. We estimate that $P(\text{malignancies.other.mort}^t = yes \mid \text{malignancies.other}^t = yes) = 0.07$. We condition lung.ext^0, rep.ext^0, and other.ext^0 on hep.ext^0 and malignancies.other^0, with the probability of presence of these metastases being 0.33 and 0.07 for lung.ext^0 and rep.ext^0 respectively if hep.ext$^0 \neq none$ and malignancies.other$^0 = no$. For other.ext^0 we have probabilities of 0.35, 0.10, and 0.05 for 1,2 and three or more localizations in case hep.ext$^0 \neq$ *none* and malignancies.other$^0 = no$.

Secondly, young patients have higher chances of survival than old patients, and female patients have higher chances of survival than male patients. We use the patient mortality (risk.mort) to represent death due to risk factors such as patient age and gender. Since only adults are admitted to the clinic, we will restrict ourselves to patients over twenty years of age. The distribution for patient mortality due to general patient characteristics is estimated from data collected by the *Central Bureau of Statistics* (CBS), for the period 2000–2004 [33]. We define $\Omega_{\text{risk.mort}} = \{no, yes\}$, $\Omega_{\text{risk.gender}} = \{male, female\}$ and $\Omega_{\text{risk.age}} = \{20-30, \ldots, 80-90, >90\}$ since only adults are treated at the NKI, and approximate the distribution $P(\text{risk.mort}^t \mid \text{age}^t, \text{gender}^t, \text{risk.mort}^{t-1} = no)$ for male and female mortality quotients by means of logistic regression, as shown in Table 12.

Table 12: Estimates of patient mortality due to general patient properties, where p_1 stands for $P(\text{risk.mort}^t = yes \mid \text{age}^t, \text{gender}^t = male, \text{risk.mort}^{t-1} = no, \text{ghs} \neq 5)$, and p_2 stands for $P(\text{risk.mort}^t = yes \mid \text{age}^t, \text{gender}^t = female, \text{risk.mort} = no, \text{ghs} \neq 5)$.

	p_1	p_2
age^t=20-30	$1.03 \cdot 10^{-4}$	$3.41 \cdot 10^{-5}$
age^t=30-40	$2.68 \cdot 10^{-4}$	$1.01 \cdot 10^{-4}$
age^t=40-50	$6.98 \cdot 10^{-4}$	$2.99 \cdot 10^{-4}$
age^t=50-60	$1.82 \cdot 10^{-3}$	$8.87 \cdot 10^{-4}$
age^t=60-70	$4.73 \cdot 10^{-3}$	$2.62 \cdot 10^{-3}$
age^t=70-80	$1.23 \cdot 10^{-2}$	$7.72 \cdot 10^{-3}$
age^t=80-90	$3.14 \cdot 10^{-2}$	$2.25 \cdot 10^{-2}$
age^t=>90	$7.79 \cdot 10^{-2}$	$6.40 \cdot 10^{-2}$

The distribution for age^t is approximated by $P(\text{age}^t = x \mid \text{age}^{t-1} = y) = 0.025$ with $x, y \in \Omega_{\text{age}}$, such that there is no $z \in \Omega_{\text{age}}$ for which $x < z < y$. To estimate the prior distribution for age, dependencies between primloc^0 and age^0, and gender^0 and age^0 were introduced, since patient age is dependent on both of these variables. We used the data given in [31], in order to complete the distribution. For male patients with small-bowel tumors the odds for the first seven age groups are approximately $0.25 : 0.6 : 1.0 : 2.65 : 4.9 : 7.2 : 5$ and for female patients with small-bowel tumors the odds for the different age groups are approximately $0.35 : 0.75 : 1.0 : 2.1 : 3.5 : 5.6 : 3.8$. For male patients with appendiceal tumors the odds for the different age groups are approximately $0.57 : 0.40 : 0.32 : 0.32 : 0.40 : 0.61 : 0.59$ and for female patients with appendiceal tumors the odds for the different age groups are approximately $1.15 : 0.70 : 0.53 : 0.4 : 0.53 : 0.54 : 0.55$. We also assume a small probability of $P(\text{age}^0 = >90 \mid \cdot) = 0.01$ since no patients were present in the last age group. We obtain the distribution shown in Table 13.

For gender we have $P(\text{gender}^t = x \mid \text{gender}^{t-1} = x') = 1_{x=x'}$. Note that, in general, evidence is

Table 13: The CPT for $P(\mathsf{age}^0 \mid \mathsf{primloc}^0, \mathsf{gender}^0)$.

$\mathsf{primloc}^0$	*small-bowel*		*appendix*	
gender^0	*male*	*female*	*male*	*female*
$\mathsf{age}^0 = $20-30	0.0114	0.0203	0.1758	0.2586
$\mathsf{age}^0 = $30-40	0.0275	0.0434	0.1234	0.1575
$\mathsf{age}^0 = $40-50	0.0458	0.0579	0.0987	0.1193
$\mathsf{age}^0 = $50-60	0.1215	0.1216	0.0987	0.09
$\mathsf{age}^0 = $60-70	0.2246	0.2026	0.1234	0.1193
$\mathsf{age}^0 = $70-80	0.33	0.3242	0.1881	0.1215
$\mathsf{age}^0 = $80-90	0.2292	0.22	0.1819	0.1238
$\mathsf{age}^0 = > 90$	0.01	0.01	0.01	0.01

instantiated at each time-slice for these observable variables. The variable gender^0 has no parent variables. A large-scale study on carcinoid tumors was used, where the female to male ratio is estimated to be 1.04 for the period 1992–1999 [16], in order to estimate $P(\mathsf{gender}^0 = female) = 0.49$ and $P(\mathsf{gender}^0 = male) = 0.51$.

ghs is a conditioning variable for crisis.mort, and the actual probability of death increases as general health status deteriorates. This variable represents the mortality associated with a carcinoid crisis; a potentially life-threatening condition that is evoked by a carcinoid tumor. The approach taken to model the influence of the conditioning variable ghs^{t-1} on other domain variables such as crisis.mort (excluding ghs^t), is to estimate the distributions that are conditioned on ghs only for the average general health status g_1 ($\mathsf{ghs} = 1$), and to infer the probabilities for the other states of ghs from this estimated probability. We accomplish this by assuming that the influence of GHS on these distributions can be written as

$$\frac{P(y_1 \mid \mathbf{u}, \mathrm{g})}{P(y_0 \mid \mathbf{u}, \mathrm{g})} \quad = \quad \frac{P(y_1 \mid \mathbf{u}, \mathrm{g}_1)}{P(y_0 \mid \mathbf{u}, \mathrm{g}_1)} \cdot \theta_{\mathsf{ghs}}(g) \tag{3}$$

where $\theta_{\mathsf{ghs}}(g) = \frac{P(y_1|\mathbf{u},\mathrm{g})}{P(y_1|\mathbf{u},\mathrm{g}_1)}$ represents the change in the odds for y_1 given a change in GHS. The impact of GHS is estimated by the physician as

$$\theta_{\mathsf{ghs}} = \{(0, 0.99), (1, 1), (2, 1.75), (3, 10), (4, 100), (5, 0)\},$$

where the choice of 0 for $\mathsf{ghs} = 5$ represents the fact that there is no patient mortality due to some cause Y, whenever the general health status already implies patient death. This use of default influences of GHS leads to a six-fold decrease in the number of probabilities that need to be specified for variables that are conditioned on ghs, since we can use Eq. (3) to compute the probabilities for $\mathsf{ghs} \neq 1$.

If $\mathsf{crisis.mort}^{t-1} = yes$ then also $\mathsf{crisis.mort}^t = yes$, which reflects the notion that the patient has died from a crisis somewhere in the past. If $\mathsf{crisis}^t = no$ and $\mathsf{crisis.mort}^{t-1} = no$ then also $\mathsf{crisis.mort}^t = no$, since an absent crisis will not induce this type of mortality. It is estimated that $P(\mathsf{crisis.mort}^t \mid \mathsf{crisis}^t = yes, \mathsf{ghs}^{t-1} = 1, \mathsf{crisis.mort} = no) = 0.03$, and other probabilities can be easily computed using Eq. (3). For example,

$$\frac{P(\mathsf{crisis.mort}^t = yes \mid \mathsf{crisis}^t = yes, \mathsf{ghs}^{t-1} = 1, \mathsf{crisis.mort}^{t-1} = no)}{P(\mathsf{crisis.mort}^t = no \mid \mathsf{crisis}^t = yes, \mathsf{ghs}^{t-1} = 1, \mathsf{crisis.mort} = no)} \theta_{\mathsf{ghs}}(0) \approx 0.0306,$$

such that $P(\mathsf{crisis.mort}^t = yes \mid \mathsf{crisis}^t = yes, \mathsf{ghs}^{t-1} = 0, \mathsf{crisis.mort} = no) = \frac{0.0306}{1+0.0306}$. In this way, we obtain the distribution given in Table 14. Note that at $t = 0$, $P(\mathsf{crisis}^0.\mathsf{mort} = yes \mid \mathsf{crisis}^0) = 0$.

In order to die of mesenterial fibrosis, either ischaemia or bowel obstruction must be present, where both causes act independently given their common cause of mesenterial fibrosis. The physician assessed

$$P(\mathsf{x.mort}^t = yes \mid \mathsf{x}^t = yes, \mathsf{x.mort}^{t-1} = no, \mathsf{survival}^{t-1} = yes) = \begin{cases} 0.05 \text{ if } \mathsf{x} = \mathsf{obstruction} \\ 0.10 \text{ if } \mathsf{x} = \mathsf{ischaemia} \end{cases}$$

Table 14: The probability of death due to a crisis for the different general health statuses.

$\mathsf{crisis.mort}^{t-1}$	*no*					
crisis^{t}	*yes*					
ghs^{t-1}	0	1	2	3	4	5
$\mathsf{crisis.mort}^{t} = no$	0.9703	0.97	0.9487	0.7638	0.2443	1
$\mathsf{crisis.mort}^{t} = yes$	0.0297	0.03	0.0513	0.2362	0.7557	0

Let $\mathbf{C}$ be the parents of endurance. If a patient has died from any of the causes $C \in \mathbf{C}$, then the patient will not have survived. Therefore, endurance is functionally dependent on its parents, and naturally modeled by a logical *and*: $P(\mathsf{endurance}^{t} = alive \mid \mathbf{C}) = 1_{\bigwedge_{C \in \mathbf{C}} (C = no)}$.

The current general health status is influenced by the past general health status, by the immediate result, by the negative effect of carcinoid heart disease, by the tumor load on the patient, and by possible severe bone-marrow depression as depicted in Fig. 10.

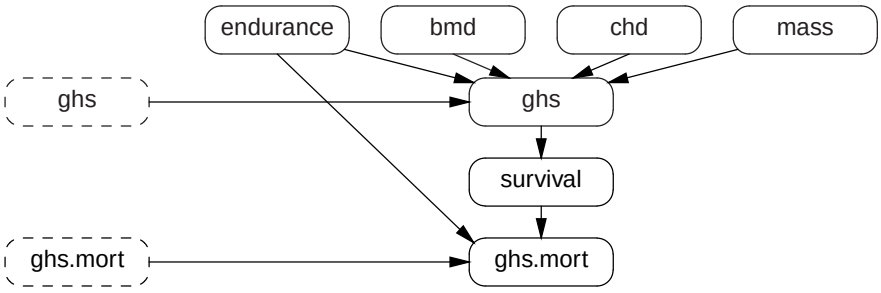

Figure 10: The factors that influence ghs.

We use bmd with $\Omega_{\mathsf{bmd}} = \{no, yes\}$ such that $\mathsf{bmd} = yes$ denotes grade 3-4 bone-marrow depression, according to the Common Toxicity Criteria. Since bmd occurs in case particular treatments are administered, we may ignore its effect for the moment. The variable ghs.mort indicates if patients have died due to health related problems, and has the following distribution:

$$P(\mathsf{ghs.mort}^{t} = yes \mid \mathsf{ghs.mort}^{t-1} = x, \mathsf{endurance}^{t} = y, \mathsf{survival}^{t} = z) = 1_{x = yes \vee (y = yes \wedge z = no)}.$$

We proceed by examining how ghs^{t} is influenced by its conditioning variables. Since $\mathsf{ghs}^{t} = 5$ given that $\mathsf{endurance}^{t} = no$, we assume in the following that endurance $= yes$. The variables chd^{t}, bmd, and mass^{t} can be regarded as the risk factors that lead to a poorer general health status. The variable ghs^{0} has parent variables mass^{0} and chd^{0}. Note that since it is assumed that $\mathsf{endurance}^{0} = yes$ and $\mathsf{bmd} = no$ during admission, the estimates in Table 15 suffice.

Table 15: The probability estimates for ghs^{0}.

chd^{0}	*no*					*yes*				
mass^{0}	*no*	*mi*	*mo*	*se*	*ex*	*no*	*mi*	*mo*	*se*	*ex*
$\mathsf{ghs}^{t} = 0$	0.80	0.70	0.50	0.20	0.08	0.50	0.40	0.35	0.15	0.05
$\mathsf{ghs}^{t} = 1$	0.15	0.20	0.40	0.65	0.53	0.389	0.40	0.45	0.60	0.50
$\mathsf{ghs}^{t} = 2$	0.05	0.09	0.09	0.10	0.23	0.10	0.189	0.18	0.20	0.40
$\mathsf{ghs}^{t} = 3$	0	0.01	0.01	0.05	0.13	0.01	0.01	0.019	0.04	0.03
$\mathsf{ghs}^{t} = 4$	0	0	0	0	0.03	0.001	0.001	0.001	0.01	0.02

Tables 16–20 show the CPTs for the transition model, given different tumor masses.

Table 16: The probability estimates with respect to $\mathsf{mass}^t = none$.

chd^t	*no*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.99	0.02	0	0	0	0.97	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.01	0.96	0.02	0	0	0.01	0.95	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.02	0.96	0.10	0	0	0.02	0.95	0.05	0
$\mathsf{ghs}^t = 3$	0	0	0.02	0.85	0.25	0	0	0.02	0.75	0.05
$\mathsf{ghs}^t = 4$	0	0	0	0.05	0.55	0	0	0	0.10	0.45
$\mathsf{ghs}^t = 5$	0	0	0	0	0.20	0.02	0.02	0.02	0.10	0.50
chd^t	*yes*									
bmd^t	*no*					*yes*				
$\mathsf{ghs}^t = 0$	0.99	0.01	0	0	0	0.97	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.01	0.97	0.01	0	0	0.01	0.95	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.02	0.95	0.01	0	0	0.02	0.95	0.01	0
$\mathsf{ghs}^t = 3$	0	0	0.04	0.89	0.01	0	0	0.02	0.79	0.01
$\mathsf{ghs}^t = 4$	0	0	0	0.10	0.19	0	0	0	0.10	0.19
$\mathsf{ghs}^t = 5$	0	0	0	0	0.80	0.02	0.02	0.02	0.10	0.8

Table 17: The probability estimates with respect to $\mathsf{mass}^t = mild$.

chd^t	*no*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.98	0.01	0	0	0	0.97	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.02	0.96	0.01	0	0	0.01	0.95	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.03	0.96	0.10	0	0	0.02	0.95	0.05	0
$\mathsf{ghs}^t = 3$	0	0	0.03	0.84	0.05	0	0	0.02	0.75	0.05
$\mathsf{ghs}^t = 4$	0	0	0	0.06	0.45	0	0	0	0.10	0.45
$\mathsf{ghs}^t = 5$	0	0	0	0	0.50	0.02	0.02	0.02	0.10	0.50
chd^t	*yes*									
bmd^t	*no*					*yes*				
$\mathsf{ghs}^t = 0$	0.98	0.01	0	0	0	0.97	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.02	0.96	0.01	0	0	0.01	0.95	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.03	0.95	0.01	0	0	0.02	0.95	0.01	0
$\mathsf{ghs}^t = 3$	0	0	0.04	0.89	0.01	0	0	0.02	0.79	0.01
$\mathsf{ghs}^t = 4$	0	0	0	0.10	0.19	0	0	0	0.10	0.19
$\mathsf{ghs}^t = 5$	0	0	0	0	0.80	0.02	0.02	0.02	0.10	0.8

Table 18: The probability estimates with respect to $\mathsf{mass}^t = \textit{moderate}$.

chd^t	*no*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.95	0.01	0	0	0	0.95	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.05	0.94	0.01	0	0	0.03	0.94	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.05	0.94	0.06	0	0	0.03	0.94	0.05	0
$\mathsf{ghs}^t = 3$	0	0	0.05	0.84	0.05	0	0	0.03	0.75	0.05
$\mathsf{ghs}^t = 4$	0	0	0	0.10	0.35	0	0	0	0.10	0.35
$\mathsf{ghs}^t = 5$	0	0	0	0	0.60	0.02	0.02	0.02	0.10	0.60
chd^t	*yes*									
bmd^t	*no*					*yes*				
$\mathsf{ghs}^t = 0$	0.95	0.01	0	0	0	0.95	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.05	0.94	0.01	0	0	0.03	0.94	0.01	0	0
$\mathsf{ghs}^t = 2$	0	0.05	0.94	0.01	0	0	0.03	0.94	0.01	0
$\mathsf{ghs}^t = 3$	0	0	0.05	0.89	0.01	0	0	0.03	0.79	0.01
$\mathsf{ghs}^t = 4$	0	0	0	0.10	0.19	0	0	0	0.10	0.19
$\mathsf{ghs}^t = 5$	0	0	0	0	0.80	0.02	0.02	0.02	0.10	0.80

Table 19: The probability estimates with respect to $\mathsf{mass}^t = \textit{severe}$.

chd^t	*no*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.80	0.01	0	0	0	0.80	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.10	0.80	0.01	0	0	0.10	0.80	0.01	0	0
$\mathsf{ghs}^t = 2$	0.08	0.10	0.80	0.05	0	0.08	0.10	0.80	0.05	0
$\mathsf{ghs}^t = 3$	0.01	0.08	0.10	0.80	0.01	0	0.07	0.10	0.75	0.01
$\mathsf{ghs}^t = 4$	0.009	0.009	0.089	0.10	0.29	0	0	0.07	0.10	0.29
$\mathsf{ghs}^t = 5$	0.001	0.001	0.001	0.05	0.70	0.02	0.02	0.02	0.10	0.70
chd^t	*yes*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.80	0.01	0	0	0	0.80	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.10	0.80	0.01	0	0	0.10	0.80	0.01	0	0
$\mathsf{ghs}^t = 2$	0.08	0.10	0.80	0.05	0	0.08	0.10	0.80	0.01	0
$\mathsf{ghs}^t = 3$	0.01	0.08	0.10	0.80	0.01	0	0.07	0.10	0.79	0.01
$\mathsf{ghs}^t = 4$	0.009	0.009	0.089	0.10	0.19	0	0	0.07	0.10	0.19
$\mathsf{ghs}^t = 5$	0.001	0.001	0.001	0.05	0.80	0.02	0.02	0.02	0.10	0.80

Table 20: The probability estimates with respect to $\mathsf{mass}^t = \textit{extreme}$.

chd^t	*no*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.70	0.01	0	0	0	0.70	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.15	0.70	0.01	0	0	0.15	0.70	0.01	0	0
$\mathsf{ghs}^t = 2$	0.13	0.15	0.70	0.01	0	0.13	0.15	0.70	0.01	0
$\mathsf{ghs}^t = 3$	0.01	0.13	0.15	0.65	0.01	0	0.12	0.15	0.65	0.01
$\mathsf{ghs}^t = 4$	0.009	0.009	0.139	0.24	0.19	0	0	0.12	0.24	0.19
$\mathsf{ghs}^t = 5$	0.001	0.001	0.001	0.10	0.80	0.02	0.02	0.02	0.10	0.80
chd^t	*yes*									
bmd^t	*no*					*yes*				
ghs^{t-1}	0	1	2	3	4	0	1	2	3	4
$\mathsf{ghs}^t = 0$	0.70	0.01	0	0	0	0.70	0.01	0	0	0
$\mathsf{ghs}^t = 1$	0.15	0.70	0.01	0	0	0.15	0.70	0.01	0	0
$\mathsf{ghs}^t = 2$	0.13	0.15	0.70	0.01	0	0.13	0.15	0.70	0.01	0
$\mathsf{ghs}^t = 3$	0.01	0.13	0.15	0.65	0.01	0	0.12	0.15	0.65	0.01
$\mathsf{ghs}^t = 4$	0.009	0.009	0.139	0.24	0.19	0	0	0.12	0.24	0.19
$\mathsf{ghs}^t = 5$	0.001	0.001	0.001	0.10	0.80	0.02	0.02	0.02	0.10	0.80

3 The Treatment Model

We proceed by modeling how the decision-maker influences the natural course of events by means of various treatments. Although curative surgical removal of the primary tumor is the treatment of choice for small and localized tumors, it is almost impossible in the presence of intra-abdominal or hepatic metastases. We assume that curative surgery is not possible, and we distinguish other (non-symptomatic) treatments into *surgical interventions*, *hepatic treatment*, and *systemic treatment*.

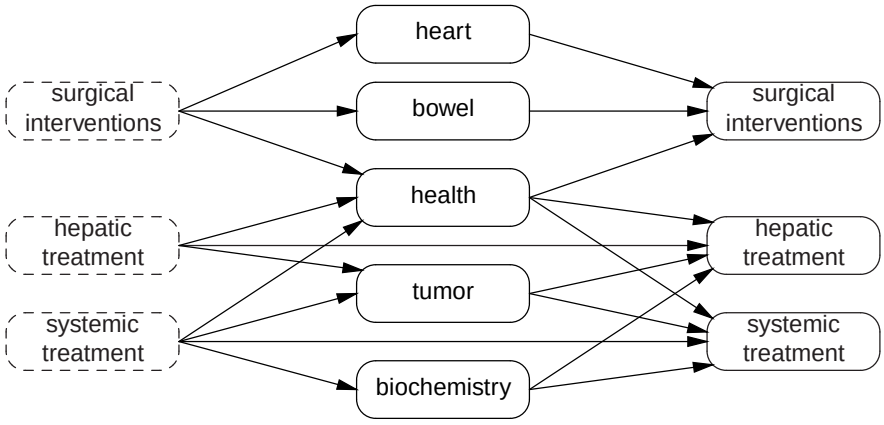

Figure 11: Architecture of the transition model of the treatment component, where dashed objects represent the situation at time $t-1$ and solid objects represent the situation at time t. Not all variables and influences are shown.

Figure 1 depicts the transition model for the treatment component of the carcinoid model. We assume that interventions and treatments influence the pathophysiological state at the next time-slice since, although a treatment decision is made at each time-slice, its execution can be done anywhere in between two subsequent time-slices. Therefore, a decision has an observable effect only at the next follow-up time.[2] In the following we implement the various treatments.

[2]Decisions such as laboratory tests or symptomatic treatment can give an immediate result. However, we have

3.1 Surgical Interventions

We distinguish the interventions *bowel resection* in order to treat mesenterial fibrosis, and *cardiac surgery* in order to treat carcinoid heart disease.

3.1.1 Bowel Resection

In general, the primary tumor itself seldom leads to complaints. Only when the primary tumor leads to mesenterial fibrosis, treatment in the form of *bowel resection* becomes necessary [26]. However, this also presents a risk to the patient (Fig. 12).

Figure 12: Complications due to mesenterial fibrosis may be reduced by means of bowel resection.

For the variable $\mathsf{bowres.mort}^t$, we need to estimate the mortality rates for bowel resection, conditional on the states of the parent variables ghs^{t-1} and $\mathsf{bowres.treat}^{t-1}$. Given an average general health status, we estimate

$$P(\mathsf{bowres.mort}^t = yes \mid \mathsf{bowres.treat}^{t-1} = yes, \mathsf{ghs}^{t-1}, \mathsf{bowres.mort}^{t-1} = no) = 0.02.$$

Under the assumption that bowel resection is a prerequisite for bowel resection mortality, and using the default θ_{ghs}, this completes the distribution, as shown in Table 21.

Table 21: The probability of death due to bowel resection for the different general health statuses.

$\mathsf{bowres.treat}^{t-1}$	*yes*					
ghs^{t-1}	0	1	2	3	4	5
$\mathsf{bowres.mort}^t = no$	0.9802	0.98	0.9656	0.8305	0.3289	1
$\mathsf{bowres.mort}^t = yes$	0.0198	0.02	0.0344	0.1695	0.6711	0

The variable mesfib^t has $\mathsf{bowres.treat}^{t-1}$ as a parent variable. Bowel resection is a preventive palliative treatment that is performed whenever the patient experiences mesenterial fibrosis, or obstruction in the absence of mesenterial fibrosis, given an acceptable general health status and given that the fibrosis is curable. We use $P(\mathsf{health.accept}^t = yes \mid \mathsf{ghs}^t = x) = 1_{x \leq 2}$. to represent an acceptable and unacceptable general health status respectively. We use the variable bowel.curable to represent whether or not the fibrosis can be cured. Incurable fibrosis may occur in up to 20% of cases, and it is persistent. If the conditions are fulfilled, then the treatment is performed with a probability of 0.95, which leads to the absence of mesenterial fibrosis, bowel obstruction, and ischaemia. Figure 13 depicts this treatment strategy for bowel resection.

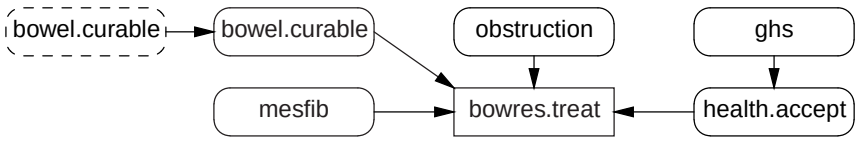

Figure 13: The treatment strategy for bowel resection.

chosen not to model tests since they are performed routinely and can therefore be regarded as observable variables. We have chosen to disregard symptomatic treatment since it doesn't influence disease progression.

3.1.2 Cardiac Surgery

If a patient suffers from carcinoid heart disease, then we may perform cardiac surgery. This normally amounts to tricuspid valve replacement, thus reducing tricuspid valve thickening, and consequently regurgitation. Cardiac surgery has however also a high associated mortality rate (Fig. 14).

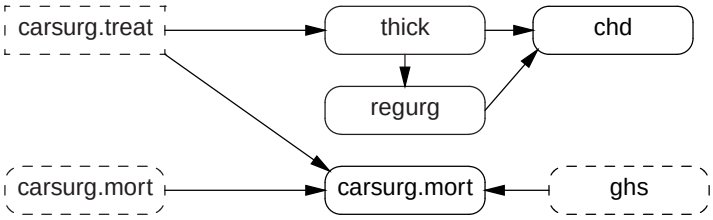

Figure 14: Cardiac surgery reduces cardiac valve thickening but also has an associated mortality.

The variable $\mathsf{carsurg.mort}^t$ has parent variables ghs^{t-1}, $\mathsf{carsurg.treat}^{t-1}$, and $\mathsf{carsurg.mort}^{t-1}$.We require the estimation of the mortality rate, conditional on $\mathsf{carsurg.treat}^{t-1} = yes$ and $\mathsf{carsurg.mort}^{t-1} = no$. In one clinical study, 12 out of 71 patients died of cardiac surgery [4]. Under the assumption that this holds for the average patient, we have

$$P(\mathsf{carsurg.mort}^t \mid \mathsf{carsurg.treat}^{t-1} = yes, \mathsf{ghs}^{t-1} = 1, \mathsf{carsurg.mort}^{t-1} = no) = 0.169$$

which, using the default θ_{ghs}, completes the distribution, as shown in Table 22.

Table 22: The probability of death due to cardiac surgery for the different general health statuses.

$\mathsf{carsurg.treat}^{t-1}$	yes					
ghs^{t-1}	0	1	2	3	4	5
$\mathsf{carsurg.mort}^t = no$	0.832	0.831	0.738	0.33	0.047	1
$\mathsf{carsurg.mort}^t = yes$	0.168	0.169	0.262	0.67	0.953	0

Cardiac surgery is performed in case the patient has carcinoid heart disease and an acceptable general health status; however, the patient should be sufficiently stable for this type of surgery and therefore we use $P(\mathsf{carsurg.treat}^t = yes \mid \mathsf{chd}^t = yes, \mathsf{health.accept}^t = yes) = 0.90$ in order to represent a stochastic policy. It is assumed that if a patient survives cardiac surgery then surgery will be successful. The treatment strategy is depicted in Fig. 15.

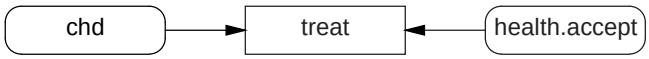

Figure 15: The treatment strategy for cardiac surgery.

3.2 Hepatic Treatment

In case of hepatic metastases one may opt for *partial liver resection* (plr), but few patients are amenable to complete resection of their hepatic metastases. More commonly used treatments with regard to hepatic metastases are *radiofrequency ablation* (rfa) and *hepatic artery embolization* (embo) [15]. Hepatic treatment has a positive effect due to reductions in tumor mass (Fig. 16) and a negative effect due to treatment related mortality (Fig. 17). The positive effect of treatment can be represented by means of the tumor response, as depicted in Table 23.

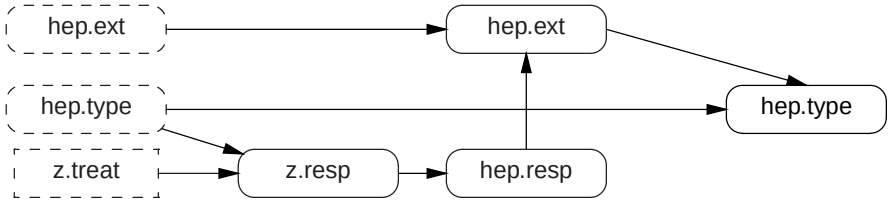

Figure 16: Positive effects of the treatment of hepatic metastases.

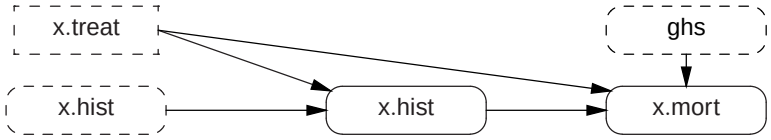

Figure 17: Negative effects of the treatment of hepatic metastases.

Table 23: The criteria for tumor response.

Tumor Response	**Criteria**
Complete remission (*cr*)	Disappearance of all lesions.
Partial remission (*pr*)	$> 50\%$ decrease in tumor mass.
Progressive disease (*pd*)	$> 25\%$ increase in lesions, or appearance of a new lesion.
Stable disease (*sd*)	Neither *pr* nor *pd*.
No treatment (*nt*)	No treatment given.

We combine the responses of hepatic treatments using the variable hep.resp and the following *max* model:

$$P(\mathsf{hep.resp}^t = e \mid \mathbf{z}) = 1 \Leftrightarrow max(\mathbf{z}) = e,$$

with $\mathbf{Z} = \{\mathsf{plr.resp}^t, \mathsf{rfa.resp}^t, \mathsf{embo.resp}^t, \mathsf{tumresp}^t\}$, assuming a total order $pd < sd < pr < cr$.[3]

The influence of hep.resp on the hepatic metastases proceeds as follows. If $\mathsf{hep.resp} \in \{nt, pd\}$ then tumor growth follows the specification in Section 2.1. If $\mathsf{hep.resp} = cr$ then hep.ext returns to 0. For $\mathsf{hep.resp} = pr$, we have a decrease of more than 50% in tumor mass. We therefore use the following specification:

$$P(\mathsf{hep.ext}^t = y \mid \mathsf{hep.ext}^{t-1} = x, \mathsf{hep.resp}^t = pr) = \begin{cases} 1 & \text{if } y = x \text{ and } \frac{1}{2}x < 1 \\ \frac{1}{\lfloor \frac{1}{2}x \rfloor} & \text{if } y \in [1, \frac{1}{2}x] \\ 0 & \text{otherwise.} \end{cases}$$

We use a similar approach for the effect of stable disease. For $\mathsf{hep.resp} = sd$, we have a decrease of less than 50%, or an increase of less than 25% in tumor mass. We therefore use the following specification:

$$P(\mathsf{hep.ext}^t = y \mid \mathsf{hep.ext}^{t-1} = x, \mathsf{hep.resp}^t = sd) = \frac{0.9}{\lfloor \frac{1}{2}x \rfloor} \text{ if } y \in [\frac{1}{2}x, x].$$

If $y \notin [\frac{1}{2}x, x]$, then it is assumed that $P(\mathsf{hep.ext}^t = y \mid \mathsf{hep.ext}^{t-1} = x, \mathsf{hep.resp}^t = sd)$ equals $P(\mathsf{hep.ext}^t = y \mid \mathsf{hep.ext}^{t-1} = x, \mathsf{hep.resp}^t = nt)$. Hepatic treatments have an associated mortality which increases with repeated treatment, as captured by the respective treatment histories (Fig. 17).

[3]The variable tumresp models the effect of systemic treatment.

3.2.1 Partial Liver Resection

Hepatic metastases are operable only if there are no more than three localized metastatic regions. If plr is performed, then there is either a complete response (successful surgery), or progressive disease (surgery was unsuccessful). It was estimated that

$$\begin{aligned} P(\mathsf{plr.resp}^t = cr \mid \mathsf{hep.type}^{t-1} = \mathit{localized}, \mathsf{plr.treat}^{t-1} = \mathit{yes}) &= 0.98 \\ P(\mathsf{plr.resp}^t = pd \mid \mathsf{hep.type}^{t-1} = \mathit{localized}, \mathsf{plr.treat}^{t-1} = \mathit{yes}) &= 0.02 \end{aligned}$$

According to the physician, plr can be administered at most two times, such that we obtain

$$P(\mathsf{plr.hist}^t = x+1 \mid \mathsf{plr.hist}^{t-1} = x, \mathsf{plr.treat}^{t-1} = \mathit{yes}) = 1_{x \in \{0,\ldots,2\}}.$$

Treatment mortality depends on the administration of treatment, the treatment history and the patient's general health status. In [7], the mortality of plr and rfa are said to be comparable at $< 0.8\%$. In our experience, mortality is somewhat higher, and we assume a probability of 0.01. We assume that this assessment is conditional on an average general health status, and use the default θ_{ghs} to complete the distribution. If $\mathsf{plr.hist} = 3$ then we assume that the probability of patient death equals 1. We then obtain the distribution as given in Table 24.

Table 24: The probability of death due to plr, for the different general health statuses.

$\mathsf{plr.hist}^t$	≤ 2					
ghs^{t-1}	0	1	2	3	4	5
$\mathsf{plr.mort}^t = no$	0.9901	0.990	0.983	0.908	0.497	1
$\mathsf{plr.mort}^t = yes$	0.0099	0.010	0.017	0.092	0.503	0

plr is performed with a probability of 0.95, in case of localized hepatic metastases with $\mathsf{plr.hist} < 2$, $\mathsf{hep.degree} = \mathit{present}$, and an acceptable general health status, Figure 18 depicts this treatment strategy.

Figure 18: The treatment strategy for plr.

3.2.2 Radiofrequency Ablation

Hepatic metastases may be treated by radiofrequency ablation (rfa) when there are no more than six metastatic localizations, each region being less than 4 cm in diameter. rfa heats tumors to over 100 degrees Celsius and thereby kills the cancer cells. The procedure has a low complication rate, can be performed without major open surgery and only involves overnight hospitalization. In the study of [7], fourteen out of nineteen patients that were treated with rfa showed a response, of which six had a complete response, seven a partial response and one stable disease:

$$\begin{aligned} P(\mathsf{rfa.resp}^t = cr \mid \mathsf{hep.type}^{t-1} = \mathit{multiple}, \mathsf{rfa.treat}^{t-1} = \mathit{yes}) &= 0.32 \\ P(\mathsf{rfa.resp}^t = pr \mid \mathsf{hep.type}^{t-1} = \mathit{multiple}, \mathsf{rfa.treat}^{t-1} = \mathit{yes}) &= 0.37 \\ P(\mathsf{rfa.resp}^t = sd \mid \mathsf{hep.type}^{t-1} = \mathit{multiple}, \mathsf{rfa.treat}^{t-1} = \mathit{yes}) &= 0.05 \\ P(\mathsf{rfa.resp}^t = pd \mid \mathsf{hep.type}^{t-1} = \mathit{multiple}, \mathsf{rfa.treat}^{t-1} = \mathit{yes}) &= 0.26 \end{aligned}$$

According to the physician, rfa can be administered at most three times, such that we obtain

$$P(\mathsf{rfa.hist}^t = y+1 \mid \mathsf{rfa.hist}^{t-1} = y, \mathsf{rfa.treat}^{t-1} = \mathit{yes}) = 1_{y \in \{0,\ldots,3\}}.$$

Treatment mortality depends on the administration of treatment, the treatment history and the patient's general health status. In case rfa.hist$=4$, then we assume that the probability of patient death equals 1. The mortality rate for rfa is assumed to be equal to that of plr, such that we obtain the distribution as given in Table 25.

Table 25: The probability of death due to rfa, for the different general health statuses.

rfa.hist^t	≤ 3					
ghs^{t-1}	0	1	2	3	4	5
rfa.mort$^t = no$	0.9901	0.990	0.983	0.908	0.497	1
rfa.mort$^t = yes$	0.0099	0.010	0.017	0.092	0.503	0

rfa is performed with a probability of 0.95, in case of multiple hepatic metastases with rfa.hist $<$ 3, hep.degree$=$*present*, and an acceptable general health status. Figure 19 depicts this treatment strategy.

Figure 19: The treatment strategy for rfa.

3.2.3 Embolization

Embolization (embo) is a method to treat diffuse carcinoid localizations in the liver. Central embolization leads to occlusion of the liver artery, cutting off blood supply to the tumor, depriving it of oxygen and nutrients. Embolization of the liver arteries may lead to the post-embolization syndrome, which is characterized by fever and pain, and may cause life-threatening complications [6, 15]. For embo, we base ourselves on [6], where, eight out of twenty-one patients showed a complete or partial response, and six out of twenty-one patients showed stable disease:

$$\begin{aligned}
P(\text{embo.resp}^t = cr \mid \text{hep.type}^{t-1} = \textit{diffuse}, \text{embo.treat}^{t-1} = yes) &= 0 \\
P(\text{embo.resp}^t = pr \mid \text{hep.type}^{t-1} = \textit{diffuse}, \text{embo.treat}^{t-1} = yes) &= 0.38 \\
P(\text{embo.resp}^t = sd \mid \text{hep.type}^{t-1} = \textit{diffuse}, \text{embo.treat}^{t-1} = yes) &= 0.52 \\
P(\text{embo.resp}^t = pd \mid \text{hep.type}^{t-1} = \textit{diffuse}, \text{embo.treat}^{t-1} = yes) &= 0.10
\end{aligned}$$

According to the physician, embo can be administered at most two times, such that

$$P(\text{embo.hist}^t = z+1 \mid \text{embo.hist}^{t-1} = z, \text{embo.treat}^{t-1} = yes) = 1_{z \in \{0,\ldots,3\}}.$$

Treatment mortality depends on the administration of treatment, the treatment history and the patient's general health status. The mortality rate for embolization is high due to post-embolization syndrome. We follow the results of [8], who found 7 patient deaths due to embolization in a group of 184 patients that presented with a tumor. We assume that these assessments are conditional on an average general health status, and use the default θ_{ghs} to complete the distribution. In case embo.hist$=3$, then we assume that the probability of patient death equals 1. We then obtain the distribution as given in Table 26.

Since embolization is an invasive procedure, it is performed with a 0.95 probability, only in case of diffuse hepatic metastases when the systemic treatments r-mibg and r-soma have failed, with embo.hist < 2, hep.degree $\neq$ *untreatable*, and an acceptable general health status. Figure 20 depicts this treatment strategy.

Table 26: The probability of death due to embo, for the different general health statuses.

embo.hist^t	≤ 2					
ghs^{t-1}	0	1	2	3	4	5
embo.mort$^t = no$	0.9624	0.962	0.935	0.717	0.202	1
embo.mort$^t = yes$	0.0376	0.038	0.065	0.283	0.798	0

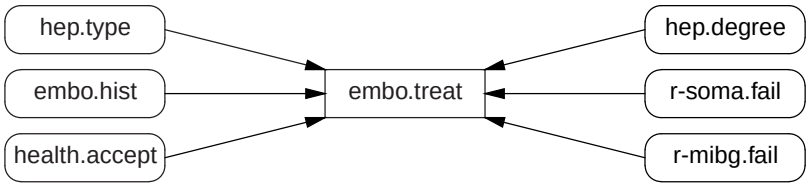

Figure 20: The treatment strategy for embo, which requires that the two systemic treatments r-mibg, and r-soma have failed.

3.3 Systemic Treatment

Systemic treatment focuses on reducing the overall tumor activity and on reducing tumor growth. In general, one can say that a treatment is characterized by positive effects (such as tumor reduction and reduction of biological activity) and possible side-effects, such as bone-marrow depression. We assume that the individual tumor responses and biochemical responses are combined using a max model.

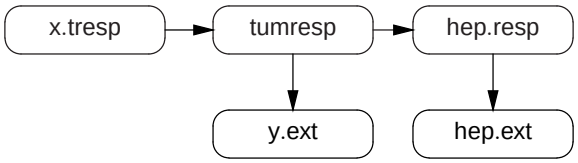

Figure 21: The combined effect of tumor response on tumor extensiveness with x $\in$ {ifn, f-soma, r-soma, f-mibg, r-mibg} and y $\in$ {rep, lung, other}.

The structure of this combination for tumor response is shown in Fig. 21. For tumresp, we specify $P(\text{tumresp}^t = e \mid \mathbf{z}) = 1_{\max(\mathbf{z})=e}$, with $\mathbf{Z} = \{\text{x.tumresp}^t \mid \text{x} \in \{\text{ifn, f-soma, r-soma, r-mibg}\}\}$, assuming a total order $pd < sd < pr < cr$. The influence of tumor response on hepatic metastases was already discussed in Section 3.2. Specification of the influence on the other metastases proceeds as follows. If systemic.tumresp$^t \in \{nt, pd\}$ then tumor growth follows the specification in Section 2.1. If systemic.tumresp$^t = cr$ then x.ext^t with x $\in$ {rep, lung, other} returns to 0. For tumresp$^t = pr$, we have a decrease of more than 50% in tumor mass. For rep.ext^t and lung.ext^t we can only speak of the presence or absence of metastases. Therefore, we specify the effect of partial regression as follows:

$$\begin{aligned} P(\text{rep.ext}^t = 0 \mid \text{rep.ext}^{t-1} = 1, \text{systemic.tumresp}^t = pr) &= 0.75 \\ P(\text{rep.ext}^t = 0 \mid \text{rep.ext}^{t-1} = 0, \text{systemic.tumresp}^t = pr) &= 1, \end{aligned}$$

and likewise for lung.ext^t. other.ext^t can be viewed as 0–3 of these metastatic regions. Here, we use the specification:

$$P(\text{other.ext}^t = m \mid \text{other.ext}^{t-1} = n, \text{systemic.tumresp}^t = pr) = \binom{n}{m} \left(\frac{1}{4}\right)^m \left(\frac{3}{4}\right)^{n-m}$$

with $m \leq n$. We use a similar approach for the effect of stable disease. For systemic.tumresp$^t = sd$, we have a decrease of less than 50%, or an increase of less than 25% in tumor mass. For rep.ext^t

and lung.ext^t, we obtain

$$\begin{aligned} P(\text{rep.ext}^t = 0 \mid \text{rep.ext}^{t-1} = 1, \text{systemic.tumresp}^t = sd) &= 0.25 \\ P(\text{rep.ext}^t = 0 \mid \text{rep.ext}^{t-1} = 0, \text{systemic.tumresp}^t = pr) &= 1, \end{aligned}$$

and likewise for lung.ext^t. For other.ext^t, we use the specification:

$$P(\text{other.ext}^t = m \mid \text{other.ext}^{t-1} = n, \text{systemic.tumresp}^t = sd) = \binom{n}{m} \left(\frac{3}{4}\right)^m \left(\frac{1}{4}\right)^{n-m}$$

with $m \leq n$.

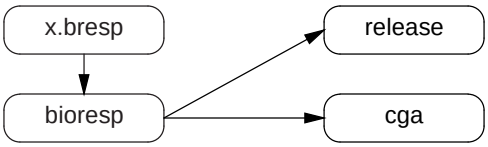

Figure 22: The combined effect of biochemical response on release with x $\in$ {ifn, f-soma, r-soma, r-mibg, f-mibg}.

Likewise, the structural representation of this combination for biochemical response is shown in Fig. 22. For bioresp, we specify $P(\text{bioresp}^t = e \mid \mathbf{z}) = 1_{max(\mathbf{z})=e}$, with $\mathbf{Z} = \{\text{x.bioresp}^t \mid \text{x} \in \{\text{ifn, f-soma, r-soma, r-mibg, f-mibg}\}\}$, assuming a total order $pd < sd < pr < cr$. For bioresp $\in \{nt, pd\}$, we use the specifications for cga and release, given in Section 2.2. For the other states of bioresp, we use the following specification with respect to cga:

$$\begin{aligned} &P(\text{cga}^t = \textit{elevated} \mid \text{mass}^t, \text{bioresp}^t = cr) = P(\text{cga}^t = \textit{extreme} \mid \text{mass}^t, \text{bioresp}^t = cr) = 0 \\ &P(\text{cga}^t = x \mid \text{mass}^t, \text{bioresp}^t = pr) = 0.25 \cdot P(\text{cga}^t = x \mid \text{mass}^t, \text{bioresp}^t = nt) \\ &P(\text{cga}^t = x \mid \text{mass}^t, \text{bioresp}^t = sd) = 0.88 \cdot P(\text{cga}^t = x \mid \text{mass}^t, \text{bioresp}^t = nt) \end{aligned}$$

for $x \in \{\textit{elevated}, \textit{extreme}\}$. An analogous specification is used for release.

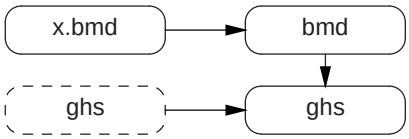

Figure 23: Negative effects on general health status due to severe bone-marrow depression with x $\in$ {ifn, r-soma, r-mibg}.

The negative effect of systemic treatment is modeled by the associated severe bone-marrow depression (Fig. 23). ifn, r-soma and r-mibg can all cause severe bone-marrow depression. We combine their effects by means of a logical *or*, such that

$$P(\text{health.bmd}^t = yes \mid \text{ifn.bmd}^t = x_1, \text{r-soma.bmd}^t = x_2, \text{r-mibg.bmd}^t = x_3) = 1_{x_1 \vee x_2 \vee x_3}.$$

3.3.1 Farmacological Somatostatin

Somatostatin is a peptide that has widespread inhibitory effects and leads to a reduction in the release and production of serotonin and vasoactive substances by the tumor. It binds to the somatostatin receptors which are expressed on more than 80% of the carcinoid tumors. Native somatostatin has limited use by its short half life, but a number of longer acting somatostatin analogues have been developed. Octreotide [13] is a somatostatin analogue, that often induces symptomatic improvement, although this is not always accompanied by a reduction in 5-hiaa excretion. Somatostatin analogues have been reported to inhibit tumor growth, but a reduction

in tumor volume is seldom observed [40]. We refer to this form of medication as *farmacological somatostatin* (f-soma). Farmacological somatostatin may induce increased bowel motility and over time, farmacological somatostatin efficacy decreases due to somatostatin receptor down-regulation. A tracer dose of radiolabeled octreotide may be used to detect somatostatin receptors by means of a so-called octreoscan. The structure is shown in Fig. 24.

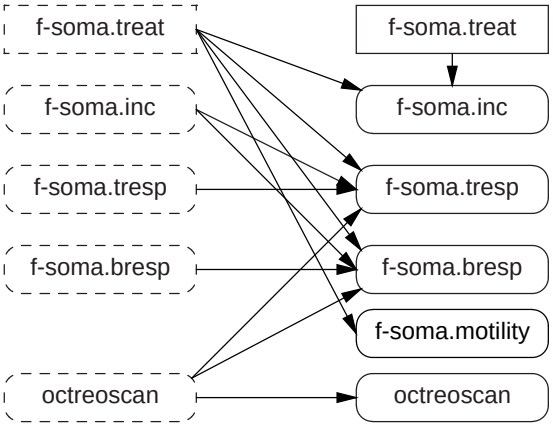

Figure 24: The network structure for farmacological somatostatin treatment.

f-soma can be administered in different dosages, and we assume that the influence that the lower dosages exert on the tumor as a percentage of the influence for f-soma.treat$^{t-1} = high$. We express the influence of f-soma.treat$^{t-1} = low$ as 83% and the influence of f-soma.treat$^{t-1} = medium$ as 95% of the influence exerted by f-soma.treat$^{t-1} = high$. A prerequisite for a treatment effect is a positive octreoscan. The prior distribution is estimated as $P(\text{octreoscan}^0 = positive) = 0.85$ and transition distribution is given by $P(\text{octreoscan}^t = x \mid \text{octreoscan}^{t-1} = y) = 1_{x=y}$.

The estimate of the tumor response for f-soma is based on [20]. It is estimated that due to receptor down-regulation, there is a decrease in treatment effectiveness of about 50% in response, after two years. We represent this decrease by assuming that the probability of change from stable disease to progressive disease is 0.30 in three-months time, given a fixed dosage. The distribution, given a fixed dosage is shown in Table 27.

Table 27: Tumor response due to f-soma treatment, given a fixed dosage.

octreoscan^{t-1}	*positive*							
f-soma.inc^{t-1}	*no*							
f-soma.treat^{t-1}	*none*				*low/medium/high*			
f-soma.tresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*
f-soma.tresp$^t = nt$	1	1	1	1	-	0	0	0
f-soma.tresp$^t = pd$	0	0	0	0	-	1	0.30	0
f-soma.tresp$^t = sd$	0	0	0	0	-	0	0.70	1
f-soma.tresp$^t = pr$	0	0	0	0	-	0	0	0

We assume that given an increase in dosage (f-soma.inc), 60% of the patients with progressive disease will respond. It holds that f-soma.inc $= yes$ if and only if there is a change in dosage from *none* to *mild*, from *mild* to *moderate*, or from *moderate* to *severe*. The distribution, given an increase in dosage, is shown in Table 28 In terms of biochemical response[4], results of Ref. [20] showed a complete regression in 3% of the patients, a partial regression in 64% of the patients, stable disease in 18% of the patients, and progressive disease in 15% of the patients. The distributions,

[4]Note that the biochemical response can be explained in part by the tumor response, since reductions in tumor mass will lead to reductions in the release of neuroendocrine substances. For now, this effect is ignored.

given an increase in dosage and a fixed dosage, are shown in Tables 29 and 30 respectively.

Table 28: Tumor response due to f-soma treatment, given an increase in dosage.

octreoscan^{t-1}	*positive*							
f-soma.inc^{t-1}	*yes*							
f-soma.treat^{t-1}	*none*				*low*			
f-soma.tresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*
f-soma.tresp$^{t} = nt$	-	-	-	-	0	-	-	-
f-soma.tresp$^{t} = pd$	-	-	-	-	0.3194	-	-	-
f-soma.tresp$^{t} = sd$	-	-	-	-	0.6557	-	-	-
f-soma.tresp$^{t} = pr$	-	-	-	-	0.0249	-	-	-
f-soma.treat^{t-1}	*medium*				*high*			
f-soma.tresp$^{t} = nt$	0	0	0	0	0	0	0	0
f-soma.tresp$^{t} = pd$	0.2210	0.4	0	0	0.18	0.4	0	0
f-soma.tresp$^{t} = sd$	0.7505	0.5780	1	1	0.79	0.5780	1	1
f-soma.tresp$^{t} = pr$	0.0285	0.0220	0	0	0.03	0.0220	0	0

Table 29: Biochemical response due to f-soma treatment, given a fixed dosage.

octreoscan^{t-1}	*positive*									
f-soma.inc^{t-1}	*no*									
f-soma.treat^{t-1}	*none*					*low/medium/high*				
f-soma.bresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*cr*	*nt*	*pd*	*sd*	*pr*	*cr*
f-soma.bresp$^{t} = nt$	1	1	1	1	1	-	0	0	0	0
f-soma.bresp$^{t} = pd$	0	0	0	0	0	-	1	0.30	0	0
f-soma.bresp$^{t} = sd$	0	0	0	0	0	-	0	0.70	1	1
f-soma.bresp$^{t} = pr$	0	0	0	0	0	-	0	0	0	0
f-soma.bresp$^{t} = cr$	0	0	0	0	0	-	0	0	0	0

Table 30: Biochemical response due to f-soma treatment, given an increase in dosage.

octreoscan^{t-1}	*positive*									
f-soma.inc^{t-1}	*yes*									
f-soma.treat^{t-1}	*none*					*low*				
f-soma.bresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*cr*	*nt*	*pd*	*sd*	*pr*	*cr*
f-soma.bresp$^{t} = nt$	-	-	-	-	-	0	-	-	-	-
f-soma.bresp$^{t} = pd$	-	-	-	-	-	0.2945	-	-	-	-
f-soma.bresp$^{t} = sd$	-	-	-	-	-	0.1494	-	-	-	-
f-soma.bresp$^{t} = pr$	-	-	-	-	-	0.5312	-	-	-	-
f-soma.bresp$^{t} = cr$	-	-	-	-	-	0.0249	-	-	-	-
f-soma.treat^{t-1}	*medium*					*high*				
f-soma.bresp$^{t} = nt$	0	0	0	0	0	0	0	0	0	0
f-soma.bresp$^{t} = pd$	0.1925	0.4	0	0	0	0.15	0.4	0	0	0
f-soma.bresp$^{t} = sd$	0.171	0.1271	1	1	1	0.18	0.1271	1	1	1
f-soma.bresp$^{t} = pr$	0.608	0.4518	0	0	0	0.64	0.4518	0	0	0
f-soma.bresp$^{t} = cr$	0.0285	0.0211	0	0	0	0.03	0.0211	0	0	0

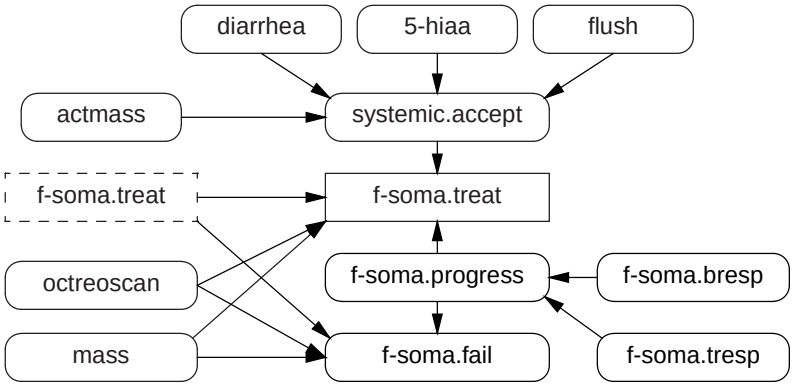

Figure 25: The treatment strategy for f-soma.

The probability of bowel motility due to f-soma administration is given by

$$
\begin{array}{lcl}
P(\text{f-soma.motility}^{t-1} = \textit{elevated} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{low}) & = & 0.0415 \\
P(\text{f-soma.motility}^{t-1} = \textit{extreme} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{low}) & = & 0.0083 \\
P(\text{f-soma.motility}^{t-1} = \textit{elevated} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{medium}) & = & 0.0475 \\
P(\text{f-soma.motility}^{t-1} = \textit{extreme} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{medium}) & = & 0.0095 \\
P(\text{f-soma.motility}^{t-1} = \textit{elevated} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{high}) & = & 0.05 \\
P(\text{f-soma.motility}^{t-1} = \textit{extreme} \mid \text{f-soma}^{t-1}.\text{treat} = \textit{high}) & = & 0.01
\end{array}
$$

through Eq. (2). The treatment strategy for f-soma is depicted in Fig. 25. In order to treat with f-soma, the octreoscan must be positive, and biochemically active metastases must be present in conjunction with either extreme 5-hiaa levels and/or both diarrhea $=$ *severe* and flush $=$ *severe*. We summarize this condition by means of the variable systemic.accept with $\Omega_{\text{systemic.accept}} = \{no, yes\}$. When the disease becomes progressive, we increase the dosage, until the highest dosage is reached. Progression is represented by f-soma.progress $=$ *yes* $\Leftrightarrow$ f-soma.tumresp $=$ *pd* $\wedge$ f-soma.bresp $=$ *pd*. This treatment is never discontinued but it may fail, which is captured by f-soma.fail and defined as a negative octreotide scan and/or f-soma.progress $=$ *yes* in conjunction with f-soma.treat $=$ *high*. Finally, if the tumor mass is severe or extreme, then we treat with the highest dosage and immediately try to start another systemic treatment.

3.3.2 Interferon-α

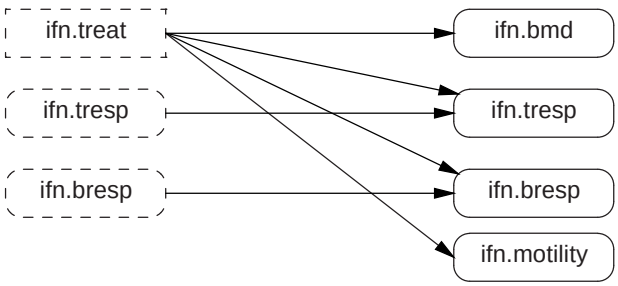

Figure 26: The network structure for interferon treatment which induces a biochemical response (ifn.bresp) by reducing the cellular biochemical activity and a tumor response (ifn.tresp) by reducing the total amount of tumor mass.

Interferon-α (ifn) is a synthetic copy of a substance that is produced naturally by monocyte/ macrophages. Due to binding of ifn to interferon receptors a complex series of signal transduction events takes place, resulting in the production of a multitude of proteins with different actions. ifn works directly on cancer cells by interfering with how the cells grow and multiply and it stimulates the immune system by encouraging killer T cells and other cells that attack cancer cells [21]. Due to these side-effects, such as bone-marrow depression, ifn is only administered for at most a year (Fig. 26). In terms of three month follow-up time, we therefore can only continue administration for four consecutive time-slices. We represent this notion of a series of treatments by defining $\Omega_{\text{ifn.treat}} = \{0, 1, 2, 3, 4, 5\}$ where 5 is included to represent prolonged treatment with serious adverse effects. The estimate of the tumor response is shown in Table 31.

Table 31: Tumor response due to ifn treatment.

ifn.treat^{t-1}	*no*				*yes*			
ifn.tresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*
ifn.tresp$^{t} = nt$	1	0.4	0.4	0.4	0	0	0	0
ifn.tresp$^{t} = pd$	0	0.6	0	0	0.06	1	0	0
ifn.tresp$^{t} = sd$	0	0	0.6	0.6	0.75	0	1	1
ifn.tresp$^{t} = pr$	0	0	0	0	0.19	0	0	0

In [21], there was an objective biochemical response (either complete or partial remission) in 42% of the patients and no objective biochemical response (either stable disease or progressive disease) in 58% of the patients. We use the distribution depicted in Table 32 as an estimate, and assume that complete remission only occurs in a minority of patients.

Table 32: Biochemical response due to ifn treatment.

ifn.treat^{t-1}	*no*					*yes*				
ifn.bresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*cr*	*nt*	*pd*	*sd*	*pr*	*cr*
ifn.bresp$^{t} = nt$	1	0.4	0.4	0.4	0.4	0	0	0	0	0
ifn.bresp$^{t} = pd$	0	0.6	0	0	0	0.29	1	0	0	0
ifn.bresp$^{t} = sd$	0	0	0.6	0.6	0.6	0.29	0	1	1	1
ifn.bresp$^{t} = pr$	0	0	0	0	0	0.40	0	0	0	0
ifn.bresp$^{t} = cr$	0	0	0	0	0	0.02	0	0	0	0

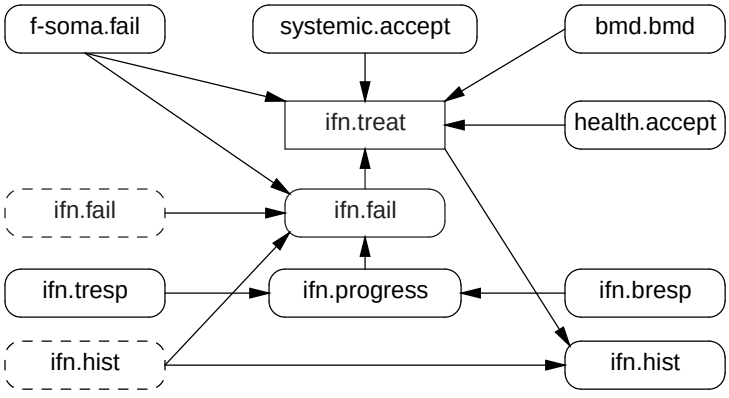

Figure 27: The treatment strategy for ifn.

For bowel motility, we estimate $P(\text{ifn.motility}^t = \textit{elevated} \mid \text{ifn.treat}^{t-1} = \textit{yes}) = 10^{-3}$ and $P(\text{ifn.motility}^t = \textit{extreme} \mid \text{ifn.treat}^{t-1} = \textit{yes}) = 10^{-4}$ through Eq. 2. There are also negative

effects on ghs due to severe bone-marrow depression. Although bone-marrow depression due to ifn treatment is common [34], the probability of severe bone-marrow depression due to ifn treatment (ifn.bmd) is estimated to be as low as 10^{-3}. The treatment strategy for ifn is depicted in Fig. 27, where ghs should be acceptable, and bmd should be absent, and due to long-term negative effects, interferon may be administered at most four times, and is discontinued when there is progression.

3.3.3 Radiolabeled Somatostatin

^{177}Lu labeled Octreotide (Lutetium) may be used to invoke autoradiation (Fig. 28). We refer to this treatment as *radiolabeled somatostatin* (r-soma). The estimate of the tumor response for r-soma is based on [35, 12]. r-soma is only administered once in a series of four treatments with two month intervals. In terms of our three month follow-up time, we therefore can only continue administration for three consecutive time-slices. We represent this notion of a series of treatments by defining $\Omega_{\text{r-soma.treat}} = \{0, 1, 2, 3, 4\}$. Here r-soma.treat$=0$ represents no treatment and r-soma.treat$=4$ represents prolonged treatment with serious adverse effects.

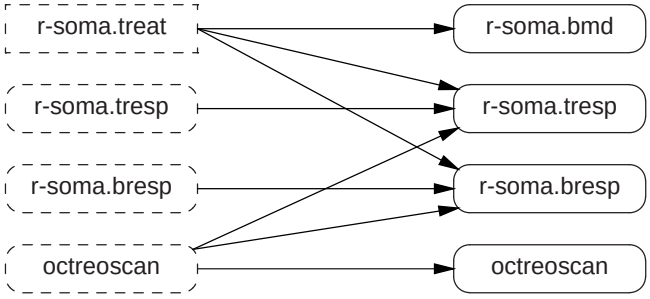

Figure 28: The network structure for radiolabeled somatostatin treatment.

Table 33: Tumor response due to r-soma treatment.

octreoscan^{t-1}	*positive*									
r-soma.treat^{t-1}	0					>0				
r-soma.tresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*cr*	*nt*	*pd*	*sd*	*pr*	*cr*
r-soma.tresp$^{t}=nt$	1	0.3	0.3	0.3	0.3	0	0	0	0	0
r-soma.tresp$^{t}=pd$	0	0.7	0	0	0	0.18	1	0	0	0
r-soma.tresp$^{t}=sd$	0	0	0.7	0.7	0.7	0.54	0	1	1	1
r-soma.tresp$^{t}=pr$	0	0	0	0	0	0.26	0	0	0	0
r-soma.tresp$^{t}=cr$	0	0	0	0	0	0.02	0	0	0	0

Table 34: Biochemical response due to r-soma treatment.

octreoscan^{t-1}	*positive*									
r-soma.treat^{t-1}	0					>0				
r-soma.bresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*cr*	*nt*	*pd*	*sd*	*pr*	*cr*
r-soma.bresp$^{t}=nt$	1	0.3	0.3	0.3	0.3	0	0	0	0	0
r-soma.bresp$^{t}=pd$	0	0.7	0	0	0	0.18	1	0	0	0
r-soma.bresp$^{t}=sd$	0	0	0.7	0.7	0.7	0.54	0	1	1	1
r-soma.bresp$^{t}=pr$	0	0	0	0	0	0.26	0	0	0	0
r-soma.bresp$^{t}=cr$	0	0	0	0	0	0.02	0	0	0	0

Tumor response is depicted in Table 33. The biochemical response has not yet been described in the literature, but an informed guess is given in Table 34. The treatment strategy for r-soma is complex. As for all systemic treatments, the general condition systemic.accept should hold, given that we have not yet treated. r-soma treatment is only considered when ifn treatment has failed. However, at this point we may choose between either r-soma treatment or r-mibg treatment; which we discuss in a later section. We use the variable choice with $\Omega_{\text{choice}} = \{none, r\text{-}soma, r\text{-}mibg\}$ to represent this choice (Table 35).

Table 35: Choosing between r-soma and r-mibg in case ifn treatment has failed.

ifn.fail^t	*yes*											
choice^{t-1}	*none*				*r-soma*				*r-mibg*			
r-soma.fail^t	no		yes		no		yes		no		yes	
r-mibg.fail^t	no	yes	no	yes	no	yes	no	yes	no	yes	no	yes
choice^t = *none*	0	0	0	0	0	0	0	1	0	0	0	1
choice^t = *r-soma*	0.5	0.5	0.5	0.5	1	1	0	0	0	1	0	0
choice^t = *r-mibg*	0.5	0.5	0.5	0.5	0	0	1	0	1	0	1	0

Figure 29 depicts this representation, where we administer r-soma if choice = *r-soma*.

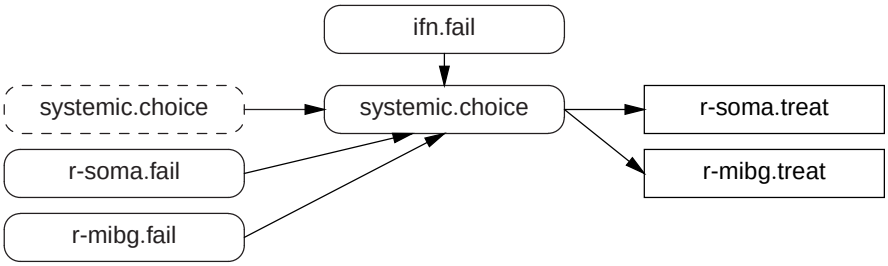

Figure 29: Representing the choice between two treatments.

The treatment strategy for r-soma is depicted in Fig. 30.

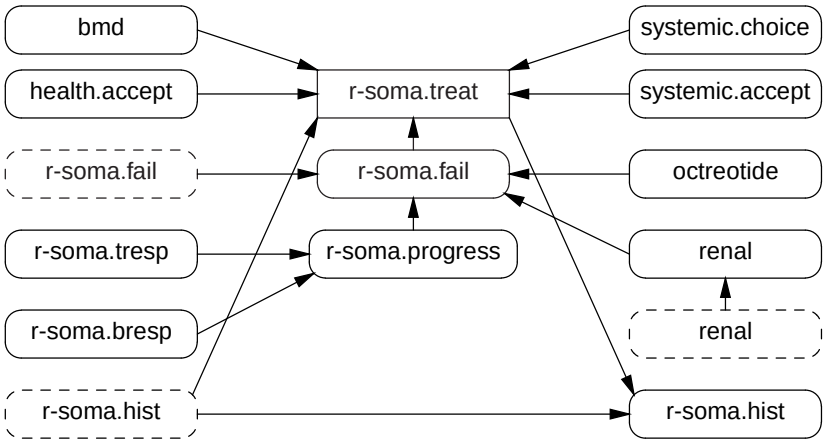

Figure 30: The treatment strategy for r-soma.

Observed toxicities of autoradiation therapy are nausea and vomiting, haematological toxicity and renal function impairment [40]. Therefore, a good renal function is required for treatment, and bone-marrow may not be severely depressed. In [11], 2% of patients were reported to have severe bone-marrow depression after treatment with radiolabeled octreotide, and therefore we estimate

$P(\text{r-soma.bmd}^t \mid \text{r-soma.treat}^{t-1} \in \{1,2,3\}) = 0.02$. The adverse effect of prolonged treatment is represented by $P(\text{r-soma.bmd}^t \mid \text{r-soma.treat}^{t-1}=4) = 1$. Failure of r-soma treatment is represented by r-soma.fail. It is persistent, as indicated by its dependence on the previous state, and occurs when $\text{ifn.fail}^t = \textit{yes}$ and either the octreoscan is negative ($\text{octreoscan}^t = \textit{negative}$), there is severe bone-marrow depression ($\text{bmd}^t = \textit{yes}$), the general health status is not acceptable ($\text{health.accept}^t > 2$), we have given the maximal amount of treatment ($\text{r-soma.treatment}^{t-1} = 3$), we have progressive disease despite treatment ($\text{r-soma.progress}^t = \textit{yes}$), or there is renal failure ($\text{renal}^t = \textit{bad}$), which is the case if the renal creatinine clearance is lower than 60 mL/minute. This occurs in about 5% of the patient population. Renal failure may arise due to various causes such as medication, vascular obstruction or hypertension, and it is estimated that there is a probability of 0.021 (8% of patients per year) that renal failure develops.

3.3.4 Radiolabeled MIBG

Hot (radiolabeled) MIBG can be used for scanning purposes (mibgscan), and in high dosages for its selective local effect by internal radiation (r-mibg). A positive mibgscan is a prerequisite for radiolabeled MIBG treatment (Fig. 31).

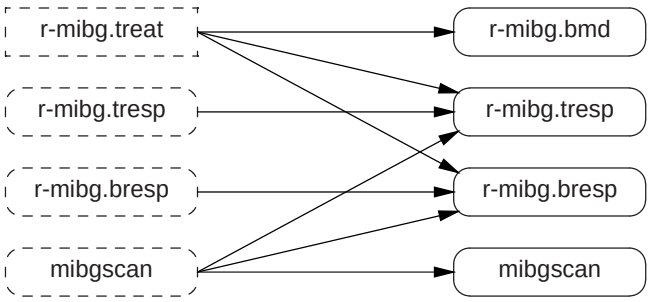

Figure 31: The network structure for radiolabeled MIBG treatment.

Predosing with f-mibg leads to improved tumor targeting of r-mibg since f-mibg has the capacity to render a negative mibgscan positive. We have chosen not to model this interaction within the model, but instead assume that an MIBG scan that is found to be negative can become positive due to proper f-mibg predosing. We estimate that with possible predosing, $P(\text{mibgscan}^0 = \textit{positive}) = 0.62$.

Table 36: Tumor response due to r-mibg treatment.

mibgscan^{t-1}	*positive*							
$\text{r-mibg.treat}^{t-1}$	*no*				*yes*			
$\text{r-mibg.tresp}^{t-1}$	*nt*	*pd*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*
$\text{r-mibg.tresp}^t = nt$	1	0.3	0.3	0.3	0	0	0	0
$\text{r-mibg.tresp}^t = pd$	0	0.7	0	0	0.20	1	0	0
$\text{r-mibg.tresp}^t = sd$	0	0	0.7	0.7	0.60	0	1	1
$\text{r-mibg.tresp}^t = pr$	0	0	0	0	0.20	0	0	0

Radiolabeled MIBG treatment consists of two 200 mCi dosages within a six to eight week interval. This treatment can be administered at most twice due to radiation damage, such that $\Omega_{\text{r-mibg}} = \{0,1,2,3\}$, where r-mibg=3 represents prolonged treatment with severe adverse effects. The estimate of the tumor response for r-mibg is also based on [29], and is depicted in Table 36. We require that mibgscan=*positive* and again assume that there is a residual treatment effect.

In terms of biochemical response, in [29], 7% of the patients experienced partial regression, and 47% of patients experienced stable disease. We use the distribution depicted in Table 37 as an estimate.

Table 37: Biochemical response due to r-mibg treatment.

mibgscan^{t-1}	*positive*									
r-mibg.treat^{t-1}	*no*					*yes*				
r-mibg.bresp^{t-1}	*nt*	*pd*	*cr*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*	*cr*
r-mibg.bresp$^t = nt$	1	0.3	0.3	0.3	0.3	0	0	0	0	0
r-mibg.bresp$^t = pd$	0	0.7	0	0	0	0.20	1	0	0	0
r-mibg.bresp$^t = sd$	0	0	0.7	0.7	0.7	0.38	0	1	1	1
r-mibg.bresp$^t = pr$	0	0	0	0	0	0.40	0	0	0	0
r-mibg.bresp$^t = cr$	0	0	0	0	0	0.02	0	0	0	0

For r-mibg treatment, bone-marrow depression is present but mild. We use $P(\text{bmd}^t = yes \mid \text{r-mibg.treat}^{t-1} = x) = 10^{-4}$ for $x \in \{1, 2\}$. If $x = 3$ then we assume that severe bone-marrow depression is present. The treatment strategy for r-mibg is shown in Fig. 32.

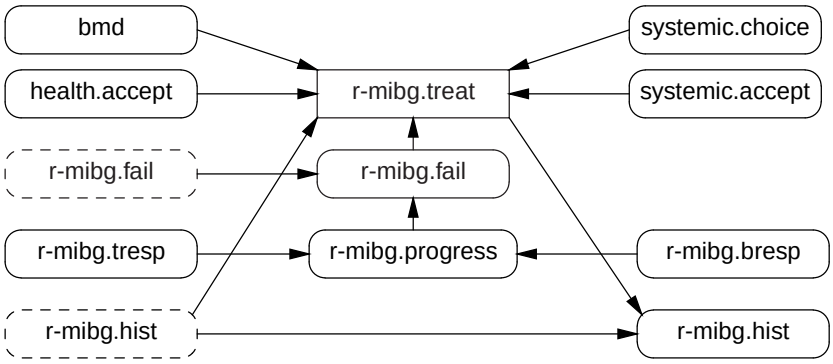

Figure 32: The treatment strategy for r-mibg.

3.3.5 Farmacological MIBG

Meta-Iodobenzylguanidin (MIBG) resembles noradrenalin and serotonin. It is taken up in the carcinoid tumor cells and stored in the neurosecretory granules. The cytotoxic effect of MIBG is related to inhibition of mitochondrial respiration, and is dependent on anaerobic glycolysis, resulting in enhanced glucose consumption, increased lactic acid production, inhibition of oxygen consumption and decreased adenosine triphosphate levels [39]. Cold (unlabeled) MIBG has a cytotoxic effect, which is depicted in Fig. 33.

The estimate of the tumor response for f-mibg is based on [29] and depicted in Table 38. We again assume that there is a residual effect if treatment is discontinued.

Table 38: Tumor response due to f-mibg treatment.

f-mibg.treat^{t-1}	*no*			*yes*		
f-mibg.tresp^{t-1}	*nt*	*pd*	*sd*	*nt*	*pd*	*sd*
f-mibg.tresp$^t = nt$	1	0.5	0.5	0	0	0
f-mibg.tresp$^t = pd$	0	0.5	0	0.35	1	0
f-mibg.tresp$^t = sd$	0	0	0.5	0.65	0	1

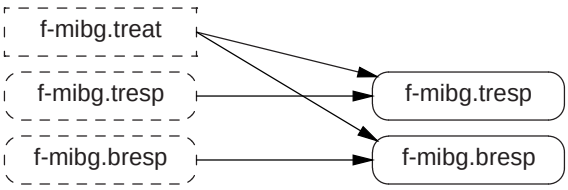

Figure 33: The network structure for farmacological MIBG treatment.

In terms of biochemical response, in [29], 5% of the patients experienced partial regression, and 40% of patients experienced stable disease. We use the distribution depicted in Table 39 as an estimate.

Table 39: Biochemical response due to f-mibg treatment.

f-mibg.treat^{t-1}	*no*				*yes*			
f-mibg.bresp^{t-1}	*nt*	*pd*	*sd*	*pr*	*nt*	*pd*	*sd*	*pr*
f-mibg.bresp$^{t} = nt$	1	0.5	0.5	0.5	0	0	0	0
f-mibg.bresp$^{t} = pd$	0	0.5	0	0	0.55	1	0	0
f-mibg.bresp$^{t} = sd$	0	0	0.5	0.5	0.40	0	1	1
f-mibg.bresp$^{t} = pr$	0	0	0	0	0.05	0	0	0

Farmacological MIBG is administered when other treatments have failed and systemic treatment is accepted (systemic.accept = *yes*). It requires a normal blood pressure since f-mibg induces changes in blood pressure [39]. We define pressure in terms of *normal* and *high*, where pressure = *high* denotes a diastolic blood pressure of more than 100 mm Hg. We estimate that initially 5% of patients has an abnormal blood pressure, and 10% of patients will experience a change to abnormal blood pressure in a year. This amounts to a probability of 0.026 per three months. The treatment strategy for f-mibg is to treat for three months, to stop for six months and then to repeat treatment if possible. This strategy is shown in Fig. 34. The variable f-mibg.hist with $\Omega_{\text{f-mibg.accept}} = \{0, 1, 2\}$ is set to 2 when treatment is given. It deterministically reduces to 0 in six months, at which point we may treat again.

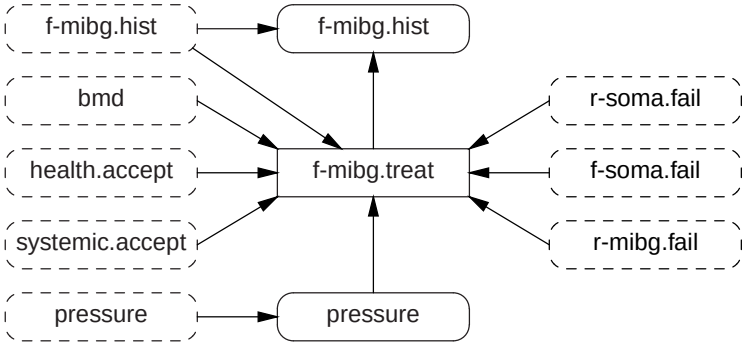

Figure 34: The treatment strategy for f-mibg.

References

[1] R.C. Bast-Jr., D.W. Kufe, R.E. Pollock, R.R. Weichselbaum, J.F. Holland, E. Frei III, and T.S. Gansler. *Cancer Medicine e.5.* B.C. Decker Inc., 2000.

[2] C. Capella, P.U. Heitz, H. Hofler, E. Solcia, and G. Kloppel. Revised classification of neuroendocrine tumours of the lung, pancreas and gut. *Virchows Archiv*, 425(6):547–560, 1995.

[3] J.-F. Chatal and C.A. Hoefnagel. Radionuclide therapy. *The Lancet*, 354:931–935, 1999.

[4] H.M. Connolly, H.V. Schaff, C.J. Mullany, M.D. Abel, and P.A. Pellikka. Surgery for valvular heart disease carcinoid heart disease: Impact of pulmonary valve replacement in right ventricular function and remodeling. *Circulation*, 106:1–51, 2002.

[5] M. D'Herbomez and V. Gouze. Chromogranin: A marker of neuroendocrine tumours. *Annales de Biologie Clinique*, 60:641–646, 2002.

[6] B.K. Eriksson, E.G. Larsson, B.M. Skogseid, A.M. Löfberg, L.E. Lörelius, and K.E. Öberg. Liver embolizations of patients with malignant neuroendocrine gastrointestinal tumors. *Cancer*, 83:2293–2301, 1998.

[7] A.R. Gillams. The use of radiofrequency in cancer. *British Journal of Cancer*, 92:1825–1829, 2005.

[8] A.P. Hemingway and D.J. Allison. Complications of embolization: Analysis of 410 procedures. *Radiology*, 166(3):669–672, March 1988.

[9] E.M.T. Janson and K. Öberg. Carcinoid tumours. *Journal of Clinical Gastroenterology*, 10:589–601, 1996.

[10] K.M. Kuntz and M.C. Weinstein. Modelling in economic evaluation. In M. Drummond and A. McGuire, editors, *Economic Evaluation in Health Care: Merging theory with practice*, pages 141–171. Oxford University Press, 2001.

[11] D.J. Kwekkeboom, J. Mueller-Brand, G. Paganelli, L.B. Anthony, S. Pauwels, L.K. Kvols, T.M. O'Dorisio, R. Valkema, L.Bodei, M. Chinol, H.R. Maecke, and E.P. Krenning. Overview of results of peptide receptor radionuclide therapy with 3 radiolabeled somatostatin analogs. *The Journal of Nuclear Medicine*, 46(1):62S–66S, January 2005.

[12] D.J. Kwekkeboom, J.J. Teunissen, W.H. Bakker, P.P. Kooij, W.W. de Herder, R.A. Feelders, C.H. van Eijck, J.-P. Esser, B.L. Kam, and E.P. Krenning. Radiolabeled somatostatin analog [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with endocrine gastroenteropancreatic tumors. *J. Clin. Oncol.*, 23:2754–2762, 2005.

[13] S.W. Lamberts, A.J. van der Lely, W.W. de Herder, and L.J. Hofland. Octreotide. *N. Engl. J. Med.*, 334(4):246–254, 1996.

[14] C. Makridis, J. Rastad, K. Öberg, and G. Akerstrom. Progression of metastases and symptom improvement from laparotomy in midgut carcinoid tumors. *World J. Surg.*, 20(7):900–906, 1996.

[15] V. Meij, J.M. Zuetenhorst, R. van Hillegersberg, R. Kroger, W. Prevoo, F. van Coevorden, and B.G. Taal. Local treatment in unresectable hepatic metastases of carcinoid tumors: Experiences with hepatic artery embolization and radiofrequency ablation. *World Journal of Surgical Oncology*, 3(75), 2005.

[16] I.M. Modlin, K.D. Lye, and M. Kidd. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*, 97(4):934–959, 2003.

[17] I.M. Modlin, M.D. Shapiro, and M. Kidd. Carcinoid tumors and fibrosis: An association with no explanation. *American Journal of Gastroenterology*, 99:2466–2478, 2004.

[18] D. Nehar, C. Lombard-Bohas, S. Olivieri, B. Claustrat, J-A. Chayvialle, M-C. Penes, G. Sassolas, and F. Borson-Chazot. Interest of chromogranin a for diagnosis and follow-up of endocrine tumours. *Clinical Endocrinology*, 60:644–652, 2004.

[19] F.R.E. Nobels, D.J. Kwekkeboom, R. Bouillon, and S.W.J. Lamberts. Chromogranin A: Its clinical values as marker of endocrine tumours. *European Journal of Clinical Investigation*, 28:431–440, 1998.

[20] K. Öberg. Diagnosis and treatment of carcinoid tumors. *Expert Rev. Anticancer Ther.*, 3(6):863–877, 2003.

[21] K. Öberg and B. Eriksson. The role of interferon in the management of carcinoid tumors. *Acta Oncol.*, 30:519–522, 1991.

[22] K. Öberg, E. Theodorsson-Norheim, and I. Norheim. Motilin in plasma and tumor tissues from patients with the carcinoid syndrome. possible involvement in the increased frequency of bowel movements. *Scandinavian Journal of Gastroenterology*, 22:1041–1048, 1987.

[23] M.M. Oken, R.H. Creech, D.C. Tormey, J. Horton, T.E. Davis, E.T. McFadden, and P.P. Carbone. Toxicity and response criteria of the eastern cooperative oncology group. *American Journal of Clinical Oncology*, 5:649–655, 1982.

[24] Otto Rorstad. Prognostic indicators for carcinoid neuroendocrine tumors of the gastrointestinal tract. *J. Surg. Oncol.*, 89:151–160, 2005.

[25] F. Skinazi, M. Zins, Y. Menu, P. Bernades, and P. Ruszniewski. Liver metastases of digestive endocrine tumors. natural history and response to medical treatment. *European Journal of Gastroenterology and Hepatology*, 8:673–678, 1996.

[26] R. Sutton, H.E. Doran, E.M.I. Williams, J. Vora, S. Vinjamuri, J. Evans, F. Campbell, M.G.T. Raraty, P. Ghaneh andM. Hartley, G.J. Poston, and J.P. Neoptolemos. Surgery for midgut carcinoids. *Endocrine-Related Cancer*, 10:469–481, 2003.

[27] B.G. Taal, C. Hoefnagel, H. Boot, D. De Jong, and M. Rutgers. Carcinoide tumoren van de darm: ontwikkelingen binnen Nederland in diagnostiek en palliatieve behandeling. *Ned. Tijdschr. Geneeskd.*, 143(9):445–451, 1999.

[28] B.G. Taal, C. Hoefnagel, H. Boot, R. Valdés Olmos, and M. Rutgers. Improved effect of ^{131}i-mibg treatment by predosing with non-radiolabeled mibg in carcinoid patients, and studies in xenografted mice. *Annals of Oncology*, 11:1437–1443, 2000.

[29] B.G. Taal, C.A. Hoefnagel, R.A. Valdés Olmos, H. Boot, and J.H. Beijnen. Palliative effect of metaiodobenzylguanidine in metastatic carcinoid tumors. *Journal of Clinical Oncology*, 14(6):1829–1838, 1996.

[30] B.G. Taal and M. Smits. Developments in diagnosis and treatment of metastatic midgut carcinoid tumours. *Minerva gastroenterologica e dietologica*, 51:335–344, 2005.

[31] B.G. Taal and O. Visser. Epidemiology of neuroendocrine tumours. *Neuro-endocrinology*, 80:3–7, 2004.

[32] S. van Eeden, P. F. H. J. Quaedvlieg, B. Taal, G. J. A. Offerhaus, C. B. H. W. Lamers, and M. F. van Velthuysen. Classification of low-grade neuroendocrine tumors of midgut and unknown origin. *Human Pathology*, 33(11):1126–1132, 2002.

[33] Centraal Bureau voor Statistiek. Overlevingstafels naar geslacht. *C.B.S. Periodiek*, 2005.

[34] College voor Zorgverzekeringen. Farmacotherapeutisch kompas.

[35] C. Waldherr, M. Pless, H.R. Maecke, A. Haldemann, and J. Mueller-Brand. The clinical value of [90Y-DOTA]-D-Phe1-Tyr3-octreotide (90Y-DOTATOC) in the treatment of neuroendocrine tumours: a clinical phase II study. *Annals of Oncology*, 12(7):941–945, 2001.

[36] J.M. Zuetenhorst, J.M.G. Bonfrer, C.M. Korse, R.H. Bakker, H. van Tinteren, and B. G Taal. Carcinoid heart disease; the role of urinary 5-HIAA excretion and plasma levels of TGF-β and FGF. *Cancer*, 97:1609–1615, 2003.

[37] J.M. Zuetenhorst, C.M. Korse, J.M.G. Bonfrer, R.H. Bakker, and B.G. Taal. The role of natriuretic peptides in the diagnosis and treatment of patients with carcinoid heart disease. *British Journal of Cancer*, 90:2073–2079, 2004.

[38] J.M. Zuetenhorst, C.M. Korse, J.M.G. Bonfrer, E. Peter, C.B.H.W. Lamers, and B.G. Taal. Daily cyclic changes in the urinary excretion of 5-HIAA in patients with carcinoid tumors. *Clinical Chemistry*, 50:1634–1639, 2004.

[39] J.M. Zuetenhorst, B. G. Taal, H. Boot, R. Valdés Olmos, and C. Hoefnagel. Long-term palliation in metastatic carcinoid tumours with various applications of meta-iodobenzylguanidin (MIBG): Pharmacological MIBG, ^{131}I-labelled MIBG and the combination. *European Journal of Gastroenterology & Hepatology*, 11:1157–1164, 1999.

[40] J.M. Zuetenhorst and B.G. Taal. Metastatic carcinoid tumors: A clinical review. *The Oncologist*, 10(2):123–131, 2005.