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MODELING THE DECISIONS REGARDING ONCOLOGICAL PRACTICE UNDER RISK CONDITIONS – AN EXAMPLE FOR COLON

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BACKGROUND: *Decisions taken under conditions of risk are very common, in this case the decision-maker knows all the decision-making alternatives, and probabilistic estimates are associated with their consequences. In this case, an alternative can have at least two consequences, the decision-maker having to calculate the probability of each of them occurring based on previous clinical experiences.*

METHOD USED: *The most suitable model for specific decisions in risk conditions in the oncology field is based on the Decision Tree Method, because decision-making situations are complex, and can be broken down into a series of chained decisions and moments in which the unpredictability occurs. The strategy consists in establishing a value of each decision variable, conditioned on its past (clinical history). In the absence of a definite clinical picture of the patient, the values assigned in the first step for testing the decision tree were generated according to the Hurwicz model.*

RESULTS: *A decision tree was created regarding the oncological practice in conditions of risk for colon cancer, based on the latest clinical practice guidelines, evaluating the value of the maximum utility expected until the cure. It was noted that, despite the approximate calculation performed within the decision tree, the survival chances of the three types of tumors (for colon cancer) were very close to those statistically demonstrated in the specialized literature, which makes the methodology approached to be credible, and with chances to be developed further.*

CONCLUSIONS: *The study carried out for the analysis of the way of making decisions under risk conditions is relevant for the synthetic approach of the decision tree in completing the clinical tree resulting from the medical practice guidelines.*

Keywords: Decision modeling, Oncology practice, Risk conditions, Decision trees, Colon cancer

INTRODUCTION

Decisions taken under conditions of risk are very common, with the decision-maker knowing all decision-making alternatives, and with the probabilistic estimates associated to their consequences. An alternative can have at least two consequences, the decision-maker having to calculate the probability of each of them occurring based on previous experiences.

Decision theory and related research focuses on the selection of the best option from a set of solutions containing two or more options. Clinical recommendations are presented in the form of decision trees, with the aim to identify the best option from a predefined option set established based on the considered parameters. When several options are considered, screening is important because it reduces the workload in making the decision, but also the risk of making the wrong choice. Using structured approaches for decision making involving multiple criteria can provide insight into the ultimate goal of decisions. An example for such an approach is the objective consensus methodology. Here, the way in which the criteria are weighed is influenced by the medical assistance framework, the individual training of the doctor, as well as the patient's behavior.

The entity of a tumor and the stage of the tumor play an important role in the decision-making process. Treatment is largely based on the stage/extent of the cancer. Treatments and recommendations for localized tumors are different from those for more advanced diseases or metastasized tumors. The position of a single lymph node can determine operability. Biological characteristics and specific tests may well support decision-making (e.g. methylation of the gene encoding MGMT in glioblastoma predicts survival factor in glioblastoma patients undergoing chemotherapy with alkylating agents; for the elderly subpopulation, phase III studies, it has been shown that overall survival in methylated patients was better if temozolomide treatment was applied, while in unmethylated patients radiotherapy was much more effective). Another example is the use of a DX-type Onco-Test, which has been associated with a significant change in treatment decisions, with an overall reduction in chemotherapy use. Also, the Ki-67 index is a marker used in clinical practice and can independently improve the prediction of treatment response and prognosis in breast cancer patients receiving neoadjuvant treatment.

But, often, deciding on the purpose of a treatment becomes a problem. For colorectal cancer for example, it is not clear whether we want to improve progression-free survival, time-deprivation therapy, or overall survival, even depending on the level of side effects the patient is willing to risk.

The doctor may use some treatments to slow, stop or eliminate the cancer. Palliative and supportive care will also be used to manage symptoms and side effects. For example, if a cancer treatment causes nausea, there are several different ways to avoid or reduce the nausea, such as a prescription of drugs. It is important to correctly understand the goals of each treatment step in the treatment plan. Cancer treatments, also called cancer therapies, have two goals: to cure cancer, or to control cancer, [1].

When therapies are used to eliminate cancer, they are called "curative cancer treatments." A treatment program that is intended to cure cancer will also include palliative and supportive care to manage symptoms and side effects.

Sometimes a cure for cancer is not possible, but this does not necessary mean that cancer cannot be treated and controlled for a period of time. Cancer treatments that

are used to control cancer are called 'palliative cancer treatments', because the treatments help relieve symptoms and side effects as much as possible. The goal of palliative cancer treatment is to help the patient survive as well as possible, for as long as possible.

Colon cancer usually affects adults over 50, although the disease can occur at any age. Usually, it is initially manifested by small clusters of non-cancerous cells called polyps (small, benign growths) that form inside the colon. Over time, some of these polyps can become malignant. Doctors recommend screening tests to help prevent colon cancer by identifying and removing polyps before they turn malignant.

In the early stages, colon cancer is asymptomatic. Along with tumor growth and local evolution, then at a distance, colon cancer generates symptoms, in some cases quite aggressive. The location of the tumor in the intestine is an important factor that influences the symptomatic clinical picture.

Compared to the classic oncological approach, precision oncology is gaining ground in the treatment of colon cancer, as a result of the fact that the therapy is chosen based on the molecular properties of the given tumor, in fact based on a genetic study.

As described above, colorectal cancer is classified into nonmetastatic (stages I-III) and metastatic disease (stage IV, or metachronous metastases). Treatment of patients with non-metastatic disease consists of neoadjuvant treatment for a minority of patients (mainly rectal cancer) and surgery of the primary tumor. A subgroup of patients with colon cancer is eligible for adjuvant chemotherapy, depending on the stage of the tumor (stage II and high-risk stage III). For patients with metastatic cancer, different treatment modalities are integrated, such as systemic therapy (chemotherapy, targeted therapy and immunotherapy for a subset of patients) and local treatment of metastases, depending on the resectability of the metastases, [2-7].

But, as can be seen, only the enumeration of aspects related to stages, localization and management does not provide the optimal solution in the development of an adequate treatment plan, which is why clinical practice guidelines are needed.

Clinical practice guidelines are developed to facilitate the application of medicine based on diagnostic methods, to optimize the quality of care and to reduce variations in therapies, many of which are unjustified in clinical practice. The number, length, and complexity of guidelines available in oncology have grown rapidly over the past two decades, but clearly, disease case history and patient-specific factors influence the application of guideline recommendations. Interpretation of clinical practice guidelines is a time-consuming operation, which complicates their application in clinical practice, [8 – 12]. So that the simplification of the guidelines, in the sense of converting the guidelines into decision trees, which can transform the guideline into an interactive implementation system to facilitate the interpretation of the guideline, can generate decisions for a viable treatment strategy. Decision trees are algorithms structured around decision nodes, which represent data elements, data values (representing different outcomes), and branches leading to (treatment) recommendations, respectively. However, few studies are known about the process of development, validation, implementation and evaluation of decision trees in clinical practice.

For colorectal cancer, one of the most widespread types of cancer, the suboptimal use of the guidelines' recommendations – which are too complex and can lead to confusing decisions, but also the substantial variation of current medical practice – have been demonstrated.

It is obvious that a successful conversion of the guideline into decision trees must correctly quantify the variables necessary for decision-making and thereby increase the credibility of the applicability of the guidelines in clinical practice, which will ultimately contribute to the optimization of the quality of patient care with colon cancer, [13 – 16].

Decision trees should be separated for colon and rectal cancers, and for the metastatic versus non-metastatic setting. In addition, colon cancer care must be subdivided into: diagnosis, staging, primary treatment, adjuvant treatment and follow-up during and after treatment. On the other hand, the decision trees should be quantified only after a cooperation with a multidisciplinary panel made up of specialists in: medical oncology, surgery, pathology, radiology, radiotherapy oncology, and specialists in clinical informatics.

METHOD

If the alternatives of the problem, the states of nature, the estimated results as well as the occurrence probabilities of the states of nature are known, the mathematical hope, the size of the risk and the risk coefficient can be calculated, so that the decision can be adopted in the knowledge of the case. In multistage decision making with imprecise probabilities, one studies problems in which there is a sequence of event-conditioned decisions. The most suitable model for specific decisions in the oncological field is based on the Decision Tree Method. The decision tree method is used when the decision-making situations are complex, and can be broken down into a series of chained decisions and moments when the unpredictability intervenes. With the help of this method, decisions and random events are represented as they are perceived by the decision-makers. For each likely future event, the action that can be adopted by the decision-maker is provided, resulting in a quantifiable tree structure.

The strategy consists in establishing a value of each decision variable, conditioned on its past. In clinical research, the clinical history is decisive in making a subsequent decision, which makes the method particularly useful especially in the field of oncology or chronic / neurodegenerative diseases, etc. The formalism of decision trees provides a simple and explicit representation of a sequential decision problem under risk. A tree can be created with two types of nodes: decision/action nodes (represented by squares) and transition/event definition nodes at the base – the states of nature (represented by circles). A decision node (or chance node) can be seen as a decision variable (or random variable), whose domain corresponds to the labels of the branches starting from that node. Branches that represent the possible variants or alternatives depart →

from these nodes. The decision nodes are the points where the choice of decision between alternatives must be made, based on the estimates and the calculation of the anticipated effect of the treatment. Probabilities of occurrence of events are known on the branches that leave from the crossing nodes. In these nodes, the expected values of the results are calculated, based on the chosen mathematical model, [17].

A decision node can consist of a clinical (e.g. comorbidity), topographic (e.g. colon or rectum), pathological (e.g. degree of tumor differentiation), or molecular characteristic. A branch from a decision node could lead to a subsequent decision node, a recommendation, or a recommendation in combination with a link to another decision tree (eg, recommendation: perform a total mesorectal excision and a link to the next decision tree: pathological staging after primary tumor resection).

By analyzing the decision tree, the decision-maker can quantitatively evaluate the risk associated with each decision, especially in conditions of uncertainty, and thus conceptually accumulate the analysis of medical strategies that are simultaneously affected by risk and uncertainty in a way that increases their clinical relevance.

In the case mentioned above, taking an action based on a future event may involve adopting one or more paths to follow. Solving a decision tree means finding an optimal strategy according to a given decision criterion (here Hurwicz was preferred). Unfortunately, the number of potential strategies can grow exponentially with the size of the decision tree, in fact with the number of decision nodes.

Decision trees can support medical decisions and are coherent representations of decisions and their consequences. By connecting several elements from a starting point a decision tree can be built by adding possible options as branches. Recommendations (or actions) are located at the end of branches, with nodes representing predefined parameters (diagnostic nodes). For example, the parameter 'gender' can be represented by two branches: 'male' or 'female' and 'age' e.g. by "<60 years" or ">60 years". Simple random criteria can be defined for exploration (e.g. colonoscopy, imaging tests, histology). Numeric values with a range (age: 0–100 years), boolean (imaging visibility: true/false), or categorical (histology: benign/ malignant) can be generated to include different types and ranges of data. These parameters can be randomly combined to create different decision trees of varying complexity. To provide recommendations for changing treatment e.g.: 'radiotherapy', 'surgery', 'drug-x' etc. random decisions can be distributed in the nodes of the decision tree. For any given combination of parameters, each tree can be traced from the starting node (left side in the figures) to the final recommendation. Even if no common parameters are used, any combination of parameters can be tested. For example, when using the situation "Visible = yes and Histology = malignant", the tree can recommend for example either "Surgery" or "Radiotherapy". Analogously to this procedure, the recommendations can be evaluated by considering every possible combination of parameters of each branch of the decision tree.

The decision trees can then be analyzed to determine the most common recommendations for each possible combination of parameters, and based on these, the best overall medical recommendation can be determined. This decision tree can then be iteratively checked against clinical scenarios, and with any possible combination of parameters. The parameters must be clearly defined and agreed upon by all parties involved, at least through the doctor-patient relationship. Implementation of all parameters within a recommendation tree is not mandatory. In clinical routine, they may be parameters of little utility, which can be ignored. Due to the inherent structure of a decision tree, the order of parameters is also irrelevant as long as combinations of parameters lead to the same recommendation. This shows the necessity of applying the criterion related to uncertainty. Areas of controversy and consensus may be equally represented. The completeness of the decision tree can provide guidance to users where traditional clinical methodologies or guidelines remain inconclusive.

The difficulty in implementing this methodology may result from the effort required to produce a medical recommendation tree that covers all clinical contingencies. In clinical practice, the selected permutations (contingencies) may be very rare, and physicians may never have to decide on such issues. When recommendations are collected in a decision tree format, users must either provide a recommendation for all these situations (since all permutations should be covered), or consciously decide that they cannot reach a conclusion. For example, if a decision tree includes the recommendation "surgery" and then additional recommendations based on how this treatment worked, like: "follow-up" after "total resection", or "adjuvant radiotherapy" after "subtotal resection", inconsistencies may occur. Depending on the complexity, a potential approach could be to define one decision tree up to the recommendation (e.g. "operation") and another with this recommendation as the starting point. If the implemented decision criteria are identical to the criteria used in published clinical guidelines, a comparison of a decision tree with these guidelines would be possible. If this is the goal, parameters should be defined prospectively, as it is possible that additional criteria to be used in individual trees, that are not considered in published guidelines.

It should be noted that clinical guidelines and decision trees based on them are standardized and limit the application of personal decisions in the development of treatment schemes. On the other hand, due to the major heterogeneity in the analysis and management of the symptoms of cancer patients, there cannot be a unitary model of good practice in the management of symptoms in oncology based exclusively on decision trees, and therefore it is absolutely necessary to develop models for specific clinical decision-making processes based on symptoms, patient personal history and risk factors, with customization of decision trees and inclusion of patient-specific therapy.

Such an example of a decision tree, which is only partially based on medical guidelines, in fact very simplistic and made only for didactic purposes, appears in the recent literature [18], and unfortunately only generically analyzes the relationship “without treatment” – “with treatment”, which in the concrete case of the clinical approach is useless and inopportune (because for example a cancer cannot be left without treatment). The inclusion of the resulting difference between the two cases is

Figure 1. Example of a decision tree [18]

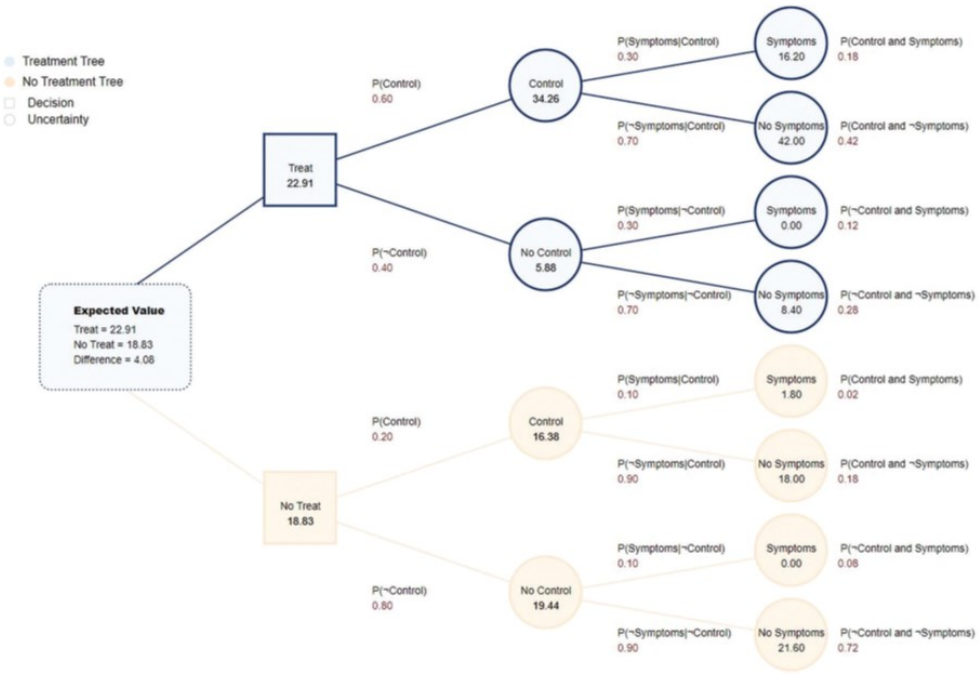


Figure 2. Examples of decision trees in the treatment of colon cancer

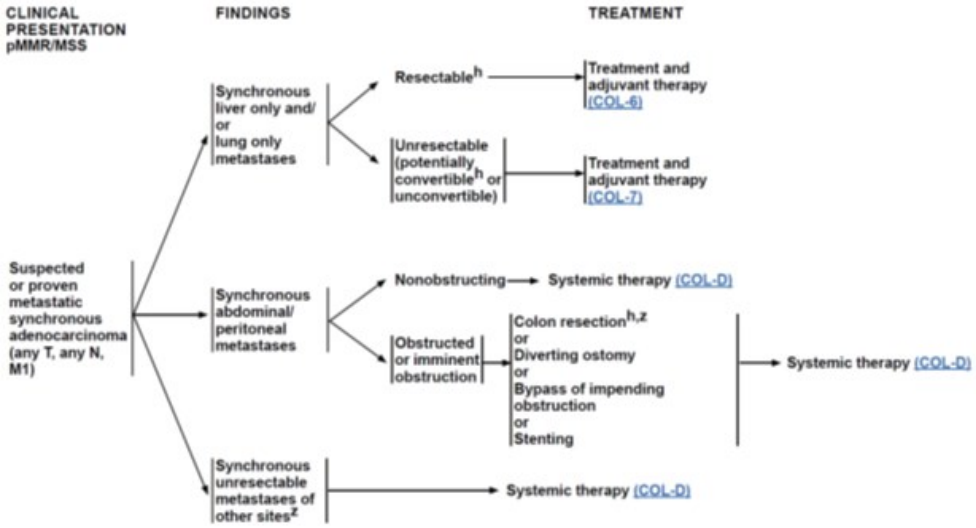


Table 1. Hurwicz correction coefficients

Criteria	Factor p_i
Disease-related symptoms	0.95
Biomarkers, laboratory values Morphological/histological characteristics of cancer	0.90
Tumor stage	0.95
Treatment compliance	**1**
Treatment toxicity	0.90
Time margin	0.95

totally questionable in our opinion, especially in the context of the uncertainty of the decision, analyzed above, and the high mortality in certain cancer cases, or in certain stages of the disease. (Figure 1)

It is obvious that the approach to decision trees in the oncological field must be carried out professionally, under conditions of analysis of both uncertainty and risk, a risk that is related to the type of cancer, the stages of the disease, comorbidities and treatment options.

RESULTS AND DISCUSSION

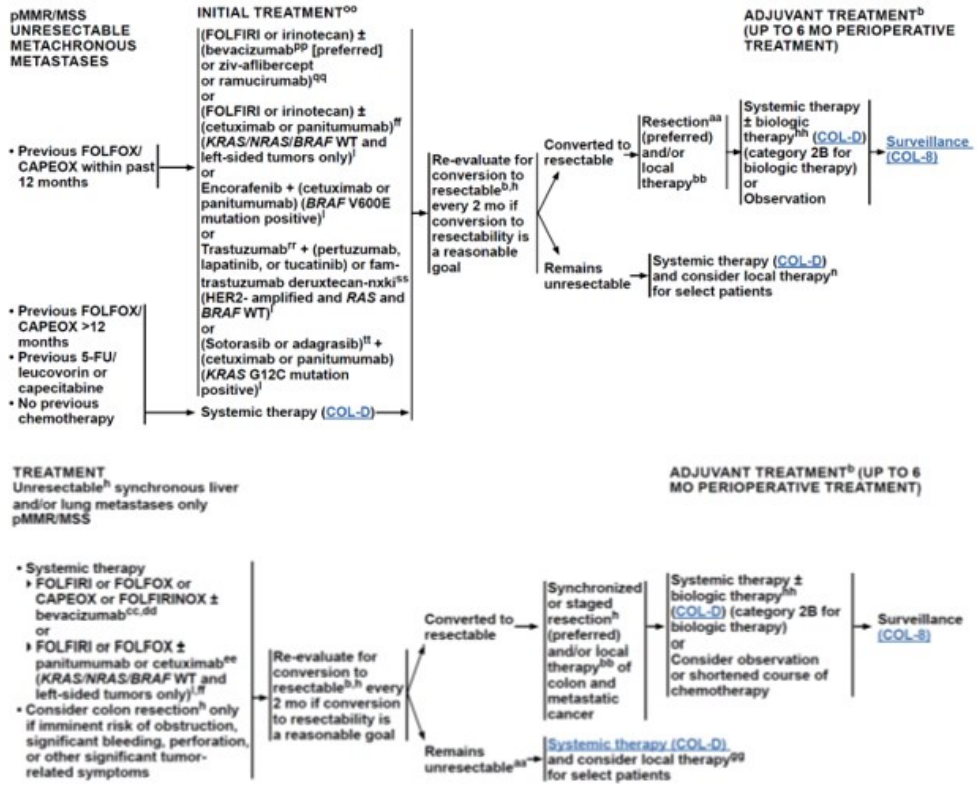
The formalism of decision trees provides a simple and explicit representation of a sequential decision under risk conditions. A tree can be created with two types of nodes: decision/action nodes (represented by squares) and transition/event definition nodes at the base – states of nature (represented by circles). A decision node (or random node) can be seen as a decision variable (or random variable), whose domain corresponds to the labels of the branches starting from that node. The branches that represent the possible variants or alternatives start from these nodes. Decision nodes are the points where the decision choice between alternatives must be made, based on estimates and calculation of the anticipated effect of the treatment. The probabilities of occurrence of the events are known on the branches leaving the transition nodes. In these nodes, the expected values of the results are calculated, based on the chosen mathematical model, [17].

An operational procedure is proposed to determine an optimal strategy according to the Hurwicz criterion in a decision tree, by calculating an upper bound on the value of a strategy with the determination of the maximum expected utility, see Table 1.

We start from the clinical tree of stage III-IV metastatic adenocarcinoma, and evaluate the patient according to the subsequent evolution and treatment method. The examples of decision trees that are presented below are in accordance with the latest international guidelines, for example: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) - Colon Cancer, Version 4.2023 - November 16, 2023, [19]. (Figure 2)

In the absence of a definite clinical picture of the patient, subjective values will be assigned in the first step to the Hurwicz coefficients for testing the decision tree, starting from the hypothesis that we are dealing with a

Figure 3. Decision tree regarding oncology practice under risk conditions



previously demonstrated compliant treatment with probability 1. The importance of the applied Hurwicz coefficients, for example, related to the probabilities of metastases occurrence, is relevant in assessing the patient's chances of treatment because, for example, treatment toxicity lowers the chances, as do worsening laboratory test values (the probability is multiplied by a lower value). In this context, the probability elements for: Tumor stage – is applicable to unresectable tumors; Time margin – is applicable in case of conversion to resectable treatment; Treatment toxicity - is applicable depending on the dosage restrictions of a cytostatic, etc. Based on the presented methodology, the decision tree regarding the oncological practice under risk conditions is made, Figure 3.

Decision tree analysis:

- the occurrence of metastases (AM) in the liver/lung has a probability of 35% (M P/F), and they are not directly resectable - even if they can be differentiated as resectable - 80% (R) or unresectable - 20% (NR). That is why the additional evaluation and subjection of the patient to a stage of preparatory treatment (T TA) is compulsory, first to the treatment with cytostatics (C), or without cytostatics (FC) but systemic (TS), as the clinical case may require. The toxicity of 0.9 is applied to the cytostatic branch. In both cases, re-evaluation is carried out for resection (Ev). The branch for resection, with a percentage of 80%, is analyzed clinically - tumor stage - with probability 0.95, then follows the surgical phase (Rez) and reevaluation (Ev). In a proportion of 80%, the cancer is treatable and enters the treatment line (T TA) - with toxicity 0.9 and then in the surveillance stage (S). The partial resection, in a proportion of 20%, re-enters the circuit of preparation for a new operation (return to the T TA loop).

- the occurrence of abdominal metastases has a probability of 60% (M Abd), and they can be resected immediately if they obstruct (O) - a coefficient of 0.95 is applied for the complexity of the tumor. After the resection (Rez), the morphological/histological characteristics are evaluated with the coefficient 0.9. In both cases (post-operative resectable and non-resectable), systemic therapy (TS) is necessary, followed by the reevaluation stage (Ev). After the reevaluation, the operative cycle is resumed if there is a recurrence, if not - it is moved to the treatment and supervision phase. Basically, it re-enters the previously discussed circuit for liver/lung metastases if there is a relapse.

- the occurrence of metastases located in other areas has a lower probability, of 5% (M Nz), and is affected by the coefficient of 0.9 - the stage of the tumor. They follow the systemic treatment circuit before the reevaluation stage (Ev). After re-evaluation, it is possible that the tumor can be resected (R), and the surgical stage is moved on. The subsequent approach follows the course previously described in the liver/lung metastases branch (resection with or without recurrence). In the unresectable case (NR) with a probability of 0.2, a new stage is required that implies the resumption of systemic therapy (TS) and a new reassessment (return loop from below), with a departure coefficient of 0.95 given by the time margin.

Determining the maximum expected utility until healing

- liver/lung metastases branch

$UMA_1 = 0.35*(0.8+0.2*0.95)[(0.9*0.8*0.95*0.8*0.9)+(0.9*0.8 *0.95)2*0.2*0.9] = 0.198$

- branch of abdominal metastases

$UMA_2 = 0.60*(0.2*0.95*0.9*0.8*0.95*0.8*0.9+0.8*0.95*0.9*0.9 *0.8*0.95*0.8*0.9+ 0.2*0.95*0.9*0.2*0.95*0.9) = 0.276$

- branch of delocalized metastases

$UMA_3 = 0.05*(0.9*0.9*0.8*0.95*0.8*0.9+0.9*0.9*0.2*0.95*0.9 *0.8*0.95*0.8*0.9) = 0.026$

$UMA = 0.500$

A first observation would be that the usefulness of the treatment based on the scheme proposed by the guide, affected by risk, for a patient with metastatic adenocarcinoma - stage III-IV, to which the uncertainties calculated based on the Hurwicz coefficients are added, is 50%.

If we were to interpret the decision tree from the point of view of the chance of survival, in the

sense that the type of tumors is already determined, then the proportion of occurrence of the three tumor patterns could be ignored, and the chances are calculated separately for each one.

- liver/lung metastases:

$SS_1 = UMA_1 / 0.35 = 0.566$ - approx. 57%

- abdominal metastases:

$SS_2 = UMA_2 / 0.6 = 0.926$ - approx. 93%

- delocalized metastases:

$SS_3 = UMA_3 / 0.05 = 0.52$ - approx. 52%

It should be noted that, despite the approximate calculation performed within the decision tree exemplified above, the survival chances of the three types of tumors resulted in values very close to those statistically demonstrated in the specialized literature [20, 21], which makes the methodology approached credible, and with chances of being developed further.

CONCLUSIONS

The study carried out for the analysis of the way of making decisions in conditions of risk is relevant for the synthetic approach of the decision trees in completing the clinical trees resulting from the medical practice guidelines. Thus, a real link is ensured with several successive clinical trees and the decision approach is integrated, including coefficients according to the Hurwicz criterion (for example, recommendation: perform a total excision, and a link with the following decision trees: pathologic staging after tumor resection primary, with systemic or adjuvant therapy).

The limitations of the study, which will be the subject of future research, are related to the impossibility of validating the model for now. The future objective is to customize the coefficients according to the Hurwicz criterion in relation to the case history of a particular patient, because at the moment no concrete data have been entered regarding the analyzes and the tests performed regarding the different phases of the patients' disease, respectively the course of the disease before of primary treatment after diagnosis, outcome of adjuvant treatment, disease recurrence/ progression after surgical and/or systemic treatment, or treatment options for metastatic disease. On the other hand, patient data such as gender, age, comorbidities, etc. and disease characteristics, i.e. previous treatment conclusions and recommendations, were not taken into account. Such a study will require elements of artificial intelligence to develop a data-sensitive algorithm, based of course on the tree structure presented previously, and to validate the model with preliminary data in certain clinical conditions, based on clinical decisions already made, basically a validation in the context a pre-validated clinical database. After that, it will be possible to directly enter the new patient's data, and the model will issue decisions based on the data library, which can be operated by the oncologist. However, this will require approvals from the Ethics Committee of the Oncology Institute, patient consent, access to classified data, etc., which requires more time, and such aspects will be addressed in the next step.

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