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Can machine learning predict resecability of a peritoneal carcinomatosis?

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ABSTRACT

Background: Approximately 20% of initially eligible patients in a HIPEC procedure eventually underwent a simple surgical exploration. These procedures are called 'open & close' (O & C) representing up to 48% of surgery. The objective of this study was to predict the resecability of peritoneal carcinomatosis using a machine-learning model for decision-making support, for eligible patients of HIPEC.

Methods: The study was conducted as an intention to treat based on three databases including a prospective, between January 2000 and December 2015. A propensity score allowed us to obtain two groups of comparable and matched patients. Subsequently, several algorithm models of classification were studied (simple classification, conditional tree, support vector machine, random forest) to determine the model having the best performance and accuracy.

Results: Two groups of 155 patients were obtained: one group without resection and one group with resection. Nine criteria of non-resecability reflecting the organ involvement have been retained. They were coded according to their importance. Five classification algorithms were tested. The training data included 218 patients and 92 test data. The random forest model exhibited the best performance with an accuracy of close to 98%. Only two errors of predictions were observed.

Discussion: The largest number of patients will allow us to improve the precision prediction. Gathering more data such as biologic, radiologic, and even laparoscopic features, should improve the knowledge of the disease and decrease the number of 'O & C' procedures.

1. Introduction

Since the 1990s, numerous studies have been conducted to assess the association of hyperthermic intraperitoneal chemotherapy (HIPEC) to a cytoreductive surgery (CRS) in the therapeutic management of peritoneal carcinomatosis (PC) [1]. It was in 1995 that Sugarbaker [2] described the peritonectomy procedures for the first time.

More recent studies showed a median survival time of 13–63 months [3,4]. The results in terms of morbidity and mortality are high, i.e. 34% (grade 3–4 disease) and 4.1% respectively. However, survival is good, with a rate of 37% survival at 5 years [5,6].

The results of the cytoreduction allowed after the report of the French Surgery Association in 2008, being recognised as a feasible treatment for the peritoneal carcinomatosis of colorectal origin, Pseudomyxoma peritonei (PMP), and mesothelioma [7].

The high morbidity and mortality are explained by the combination of extensive and sometimes major surgical procedures (anastomotic leakage, bleeding, abscesses), associated with the specific toxicity of the HIPEC and the various molecules used (renal failure, neutropenia, and thrombocytopenia).

Thus, the patients eligible for the CRS procedure associated with HIPEC must meet strict criteria. A number of major contraindications exist regarding the general condition (score Balducci than IIa, Performans status (PS) greater than 2, serious history) on the evolution of the disease (extra-abdominal metastases, peritoneal carcinomatosis diffuse or mass). Furthermore, the contraindication for which the addition is equivalent to a major contraindication (obesity, obstruction, malnutrition) [8] exists.

HIPEC is performed only for a complete CRS, and a survival benefit is observed [9,10]. Two prognostic resection factors have been identified, the PCI (Peritoneal Cancer Index) defining the extent of the disease before surgery, calculated intraoperatively, and the quality of surgical debulking, as measured by the surgical completeness cytoreduction score (CCs) [11–14].

Thus, in a number of patients eligible for initial CRS and HIPEC, is finally realised that a simple exploratory laparotomy. These procedures called 'O & C' represent 23%–48% of the procedures [16,17].

The objective of this study was to predict the resectability of PC

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using a model of machine learning (ML) decision support among patients eligible for the CRS procedure associated with HIPEC.

2. Materials and Methods

2.1. Description of the population

This study was performed with the intention to treat from a surgical oncology service database of Nice University Hospital between January 2000 and December 2015. All patients hospitalised in the service for PC for a decision surgical management by CRS and HIPEC were included in this study.

Each patient had a diagnosis of peritoneal tumour, whether primary or secondary. The diagnosis of peritoneal involvement was always performed on histological evidence.

The patient was evaluated by a surgeon and an anaesthetist; the case was subsequently discussed at a multidisciplinary meeting to validate the assumption by the CRS procedure and HIPEC.

The first surgical step consisted of an exploratory phase of the abdominal cavity to assess the importance of the disease and the feasibility of the procedure. Following this assessment, the CRS process and HIPEC were either performed or not. It was based on the sole discretion of the surgeon and his experience. Several factors were considered: tumour burden, the extent of the possible resection, primary aetiology, age, and fragility of the patient.

An oncogeriatric assessment was performed for all patients over 70 years of age.

2.2. Engineering and data analysis

We collected data from a group of non-resected patients for which the CRS and HIPEC procedure could not be performed. For each patient, we collected the medical records of epidemiological data: age, sex, BMI (Body Mass index), ASA score, and the primary aetiology of the cancer.

Each operative report was analysed to identify the different surgical factors discovered during surgery that contribute to the non-fulfilment of the CRS and HIPEC. Thus, among these factors, nine were selected: the diffuse involvement of bowel, the involvement of the pancreas, the celiac lymph nodes, the mesenteric lymph nodes, the retroperitoneal lymph nodes, liver damage (liver metastasis), vascular disease (infiltration of the vessel wall), the ureter involvement concerned the upper urinary tract involvement (kidney damage and/or lumbar ureter), and the involvement of pelvis gathering the bladder, ureteral pelvic, rectal, and gynaecological involvement.

The other obvious factors were eliminated (diffused carcinomatosis, impenetrable abdomen).

The same epidemiological data were collected from a prospective database of a patient group who underwent resection. We could obtain all the histological elements of all resections performed. To specify the actual involvement and the level of importance for each organ or tissue resected, factors resulting in organ damage were encoded to clarify the importance of

- no damage (normal),
- resecable microscopic reached,
- unresecable macroscopic reached,
- macroscopic achieving resecability unlikely,
- macroscopic not likely reached.

A Likert scale was used to quantify these variables and to compare them.

To obtain two comparable groups matched on epidemiological variables, we used a propensity score. The two groups of patients were thus distributed between a non-resection group and a resection group for the final analysis.

2.3. Modelling

An ML model predicts a target event from the change data using several algorithms. These algorithms, classification or regression, under supervised analysis, predict a response from the target variable with an error that is dependent on the volume, the quality of the processed data, and the complexity settings of the algorithm. Moreover, the evolution of the accuracy of the answer is by learning due to the implementation of a loop reentry.

In this study, we tested several ML models to predict the resecability of peritoneal carcinomatosis. Regarding the prediction of the variable target unresecability, we used a classification algorithm in a supervised exploration. This type of algorithm enables the study of qualitative data. A supervised analysis is a machine learning technique in which one seeks to predict a target variable from the training data containing 'examples' (generally previously treated cases and validated).

Several classification algorithms models were studied (simple classification, conditional tree, support vector machine (SVM), and random forest) to select the model with the highest precision performance.

Decision tree: This is an aid to decision representing a set of choices in graphic form such as a tree. The possible decisions are at the ends of the branches (the 'leaves' of the tree), and are reached based on the decisions taken at each node. We differentiate a conditional tree from a simple classification tree in that every decision is based on the probabilities of decisions taken upstream. This is an easily understandable algorithm but underperforming and low operational efficiency.

Random forest: This is a particularly efficient algorithm to identify the links between a dependent variable and the explanatory variables. It classifies variables according to their relationship with the dependent variable. Multiple sets of data are generated from the original game (bootstrapping) and several decision trees can be generated. These subsamples are drawn at random in the original dataset. The charts are different from each other by the data subsample in which they are driven.

The end result will be the average of all trees created.

Support vector machine: The machine support vector, often translated as a 'large margin splitter', is a class learning algorithm originally defined for the discrimination of a binary variable. The idea is to obtain a method to classify, or a discrimination function, for the generalisation ability (quality forecast) is the largest.

Unlike decision tree algorithms, random forest algorithms and the SVM are used for research performance, less explicit, and less easily understood.

2.3.1. The implementation of these algorithms

Each model includes two datasets: training data and test data. Building an ML model requires a training dataset to train the classification model (random forest or SVM), and testing data are required to subsequently validate the prediction performance. In our case, 70% of the base will be the training dataset and 30% the test dataset.

Modelling is performed on the training set for each of the algorithms; thus, a first model that must be optimised is obtained. The parameters enable an improvement in the model complexity and optimisation.

This model is subsequently validated on the set of test data to verify its predictions, and infer its performance and generalizability. Moreover, the evolution of the accuracy of the answer is by learning due to the implementation of a reentry loop.

Such learning and evolution of precision will allow the application in real conditions.

The difficulty of modelling is in obtaining a sufficiently high complex and flexible model to obtain an error as small as possible while having a prediction model generalizable to the application in real conditions.

Each non-resecable variable was analysed according to its importance; this model allows a better consideration of the complexity of situations.

The performance of the prediction is assessed by a confusion matrix between prediction and reality. The performance curve is obtained by an ROC curve, and the performance comparison of the models tested was conducted by measuring the area under curve (AUC).

2.4. Statistical analysis

Statistical analysis was performed using the R software, version 3.4, and the programming interface used was rstudio 1.0.143 release.

The population was described using medians and the continuous variables and the statistical student's *t*-test were described using standard deviations.

For the descriptive qualitative data, the chi-square or Fisher was tested.

A threshold value $p \leq 0.05$ was defined as statistically significant.

3. Results

3.1. Global and quantitative

Between November 2000 and December 2015, 763 patients were hospitalised for the surgical treatment of PC.

From November 2000 to December 2015, 557 patients underwent a CRS and HIPEC procedure in the service.

Between November 2006 and December 2015, 206 patients have undergone CRS and HIPEC proceedings before the extent of the injuries noted in intraoperative. After analysing the operative reports, nine of the criteria involved in unresecability were determined (Table 1). Bowel involvement was the most represented (43.20%), followed by pelvis involvement (21.36%).

Combining the two databases with the descriptive variables, we obtained a 763-patient base. To obtain two comparable groups, we performed a match using a propensity score. Two groups of 155 patients were obtained, a non-resection group and a resection group, for the realisation of the final analysis and ML modelling.

The epidemiological characteristics are described in Table 2. No significant epidemiological differences were observed between the two groups in terms of age and BMI; however, a difference was noted on the sex and ASA score ($p = 0.013$ and $p = 0.032$, respectively).

The different aetiologies were divided into groups. The gynaecological group represents ovarian, uterine tumours, and primary peritoneal serous papillary carcinoma. Mesothelioma and primary peritoneal serous carcinoma were in the peritoneal primitive group. The aetiologies were distributed primarily between the colorectal and gynaecological groups for the non-resection group (44.5% and 44%). For the resection group, the majority aetiology group was the gynaecological group (55%) followed by colorectal (18%).

The division between the two groups of different organ involvements is described in Table 3. A significant difference typically expected between the two groups was observed for each of the criteria.

Table 1
Criteria involved in unresecability.

	Total	
	n = 206	(%)
Bowel involvement, (n)	89	43,20
Pancreas involvement, (n)	3	1,46
Celiac lymph node, (n)	16	7,77
Mesenteric lymph node, (n)	15	7,28
Retroperitoneal lymph node, (n)	21	10,19
Liver involvement, (n)	19	9,22
Vascular involvement, (n)	26	12,62
Ureter involvement, (n)	12	5,83
Pelvis involvement, (n)	44	21,36

Table 2
Epidemiological characteristics in non-resection and resection group.

	Non-resection group	Resection group	p Value
	N = 155	N = 155	
	(%)	(%)	
Sexe (n)			0.013
M	49 (32)	29 (19)	
F	106 (68)	126 (81)	
Age, (médiane [min-max])	61 [26–77]	59 [21–78]	0,143
BMI, Kg/m^2 (median [min-max])	23,8 [7–15,15–39]	23 [16–41]	0,938
ASA score (n)			0.032
1	7 (4)	19 (12)	
2	130 (84)	124 (80)	
3	18 (12)	12 (8)	
Aetiology, (n)			
Colo-rectal	69 (44,5)	28 (18)	
Gynaecological	68 (44)	85 (55)	
Stomach	11 (7)	5 (3)	
Pseudomyxoma peritonei	4 (2,5)	12 (8)	
Peritoneal primitive origin	2 (1,4)	11 (7)	
Sarcoma - Others	1 (0,6)	14 (9)	

3.2. Modelling

After randomisation, our database was separated into two datasets. We obtained a group of 218 patients constituting the training base, and a group of 92 patients constituting the test database.

The first model tested was a simple classification tree and the accuracy was 90.22%. Of the 92 patients in the database test, nine prediction errors were found for this model. The second model was a conditional tree, with an accuracy of 85.86% and 13 prediction errors.

The random forest model exhibited the highest precision with 97.82%, and only two prediction errors were observed. This means that in almost 98% of the cases, the model yielded the same answer on unresecability with the test basis.

Each variable used was analysed according to its importance. The two variables having the greatest importance were first bowel involvement, followed by the pelvis involvement. Ureter involvement was the least important (Fig. 1).

The latest model tested was an SVM. After adjusting the complexity, the accuracy reached 97.11% and was within eight prediction errors.

The set of ROC curves is compared in Fig. 2, and the matrix performances for all tested algorithms are described in Fig. 3.

4. Discussion

4.1. The PCI tool and its boundaries within the resecability

As mentioned in the introduction, the HIPEC procedure is only possible when a complete CRS is performed. Subsequently, a survival benefit is observed [15,16].

The first index used was the PCI. It defines the macroscopic

Table 3
Repartition of criteria involved in unresecability between the two groups with a Likert scale.

	Non-resection group	Resection group	p Value
	N = 155	N = 155	
Bowel involvement			< 0,05
Normal	53	114	
Micro	0	1	
Macro resecable	0	32	
Macro less resecable	34	8	
Macro no resecable	68	0	
Pancreas involvement			< 0,05
Normal	130	120	
Micro	0	25	
Macro resecable	0	3	
Macro less resecable	22	7	
Macro no resecable	3	0	
Celiac lymph node			< 0,05
Normal	136	122	
Micro	0	10	
Macro resecable	0	14	
Macro less resecable	6	9	
Macro no resecable	13	0	
Mesenteric lymph node			< 0,05
Normal	124	120	
Micro	0	9	
Macro resecable	0	19	
Macro less resecable	17	7	
Macro no resecable	14	0	
Retroperitoneal lymph node			< 0,05
Normal	122	116	
Micro	0	5	
Macro resecable	0	24	
Macro less resecable	16	10	
Macro no resecable	17	0	
Liver involvement			< 0,05
Normal	132	138	
Micro	0	3	
Macro resecable	0	5	
Macro less resecable	6	9	
Macro no resecable	17	0	
Vascular involvement			< 0,05
Normal	127	140	
Micro	0	5	
Macro resecable	0	0	
Macro less resecable	4	10	
Macro no resecable	24	0	
Ureter involvement			< 0,05
Normal	131	143	
Micro	0	1	
Macro resecable	0	1	
Macro less resecable	13	10	
Macro no resecable	11	0	
Pelvis involvement			< 0,05
Normal	84	41	
Micro	0	12	
Macro resecable	0	94	
Macro less resecable	38	8	
Macro no resecable	33	0	

carcinomatous involvement of all peritoneal cavities and expresses a prognostic value. This method is the Sugarbaker procedure that was used for the first time in 1998 [19,24]. This score ranges from 1 to 39, and 13 intraperitoneal areas were defined with a score from 0 to 3 for each zone.

The PCI was known as the standard in the evaluation of PC at the 5th International Workshop on Peritoneal Surface Malignancy Held in Milan in December 2006, and later by an international expert group [11,25].

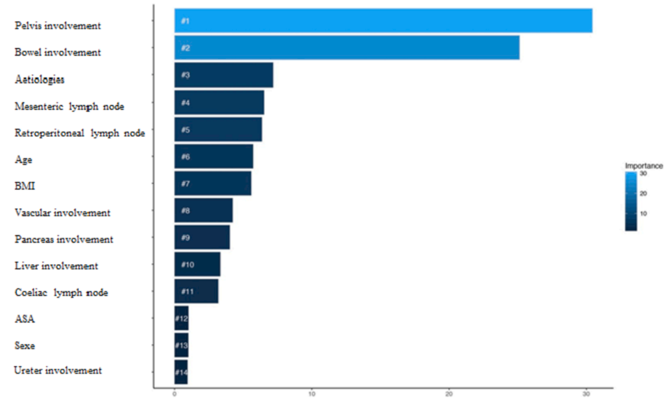

Fig. 1. Variables classification according to its importance in Random Forest algorithm.

For several years, a PCI threshold value has been sought. A score above 20 is not a good indication for CRS and the HIPEC procedure. This would entail a high surgical stress and would directly impact the quality of resection. In 2010, in a multicentre French study, the survival rate at 5 years was only 7% for a PCI greater than or equal to 20 against 44% for a PCI between 1 and 6 [26].

In the last year, new studies have set the PCI to yet another threshold value ranging from 15 to 17 [27,28]. Conversely, this new threshold does not affect resecability but affects survival.

The PCI is a reliable tool to measure the extent of PC but remains only a prognostic score.

4.2. Other scores

To reduce the number of surgical explorations for unresecable diseases, data from preoperative imaging were also studied including CT scan. However, no imaging technique has reflected the same assessment of PC as the PCI [29,30].

A PET scan was also studied but its performance is not superior to that of CT [31,32]. Several researchers have attempted to evaluate the PC imagery, but the detection rate was low especially when the peritoneal implants were less than 6–8 mm [32–35].

The CCs score, which we described earlier, is a score after resection. A score greater than 1 does not allow for HIPEC [21]. It is therefore not a predictor, but a real resecability variable.

The PSDSS, defined in 2009, is a score assessing the severity of disease at diagnosis. It allows for the stratification of patients into prognostic groups and thus improves patient selection for the appropriate therapy. It has been shown as an important prognostic indicator [36–38].

This score has also been studied as a preoperative assessment tool to predict the resecability of PC [39].

4.3. Proposal of a strategy

For over 20 years, ML has been used in the diagnosis of cancer [40–42]. Its use varies according to cancer diagnosis, from imaging to genetic analysis [43,44]. Currently, ML is increasingly tested on cancer prediction models and in the study of the prognosis [45,46]. The appearance of much larger volume databases, computerisation of medicine, the development of computer storage capacity and computing capacity, and the speed of information transmission through broadband enabled the development and use of ML.

The treatment of PC requires special knowledge and specific care. Many scores were created to assess the damage, severity, or prognosis

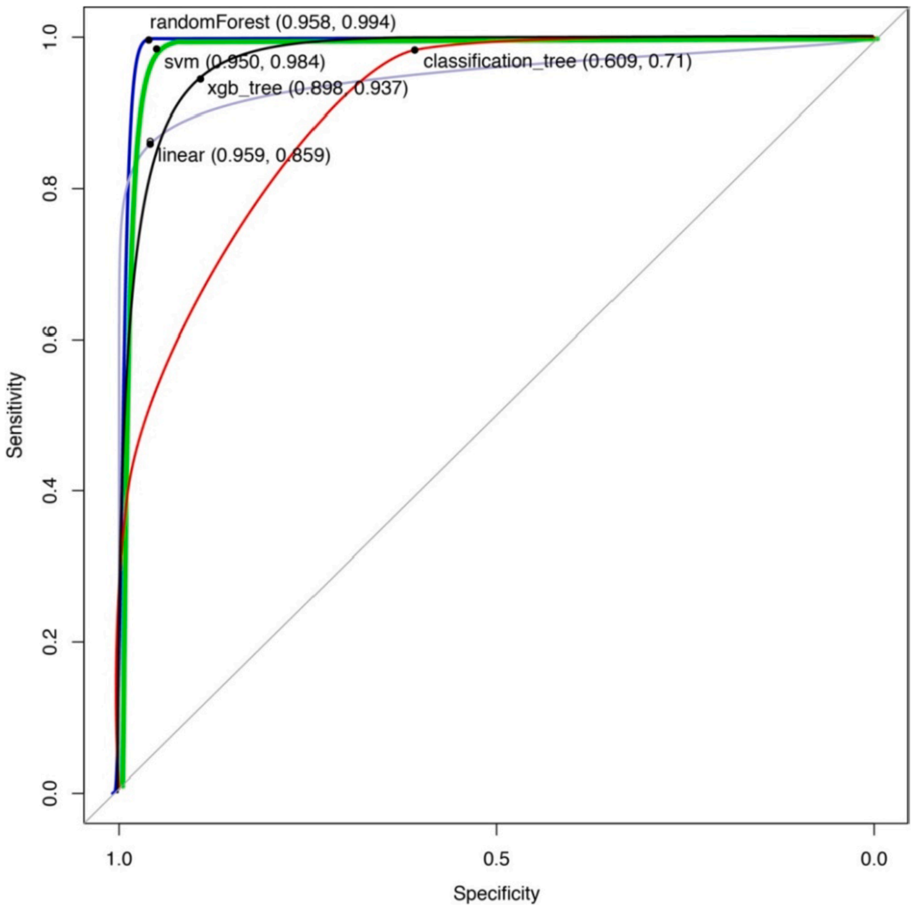

Fig. 2. ROC curves for all tested algorithms with confidence intervals.

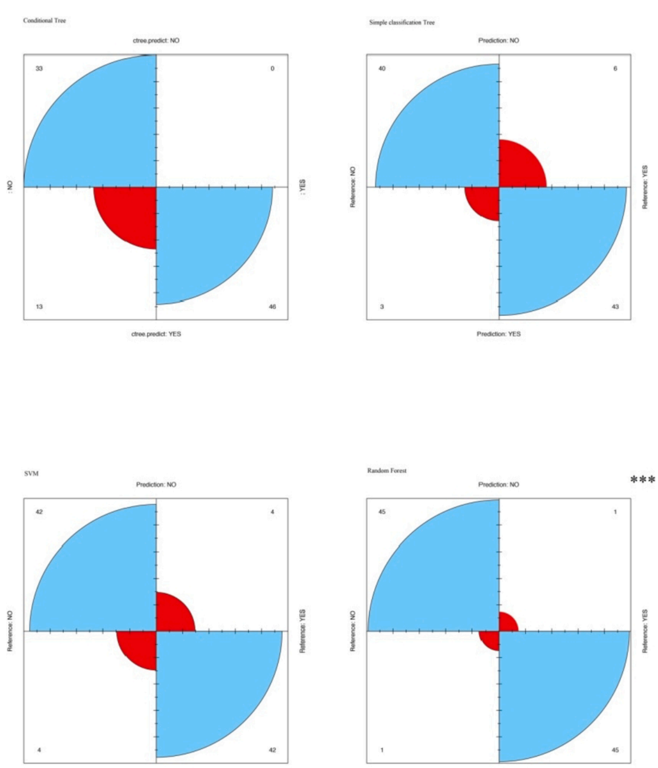

Fig. 3. Matrix performances for all tested algorithms. Blue represents true answer and errors in red. (*** Performed model).

of the disease. However, none has reported the possibility to predict the resecability of the disease.

This problem is related to the complexity and a number of factors that must be considered simultaneously.

The use of ML helped us to realise this prediction.

Hence, we established a strong and robust repository to define the concept of resecability/unresecability. Therefore, we used exploratory surgical variables expressing the probability of non-resection, as well as epidemiological variables. In addition, the removal of obvious unresecability variables (carcinomatosis diffuse, impenetrable abdomen) allowed us to improve the signal quality by removing the obvious factors.

As explained previously, the ML model operates by continuous machine learning.

From this study, and in the future, the implementation of new variables, considered as a weak signal, could supplement the strong signal. These are biological and demographic variables of imaging tests, or even of laparoscopic data.

Laparoscopy and/or imaging data (CTscan, PET-CTscan, MRI) may facilitate in the determination of those suffering from organ variables.

The goal is to eventually reduce the number of laparotomies because they represent 23%–48% of the procedures [22,23].

5. Conclusion

Through this study, we implemented and verified the possibility of using an ML model classification algorithm to predict the resecability of PC.

The analysis of our purported 'O & C′ has allowed us to highlight the criteria of non-resecability to define our organ damage variables. The addition of epidemiological variables defined our target variable.

Several models were tested to obtain the most efficient model. The random forest model yielded the highest accuracy (97.82%).

Finally, to further improve the accuracy of the model, the implementation of a continuous patient flow is necessary. A computer tool is essential owing to the structured databases.

The implementation of additional variables called 'weak signal' with a high volume, could afford to replace our variable called 'strong signal' and help us to reduce or stop 'O & C′ procedures.

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