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Response to repeat echoendoscopic celiac plexus neurolysis in pancreatic cancer patients: A machine learning approach

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ABSTRACT

Background: /Objectives: Efficacy of repeat echoendoscopic celiac plexus neurolysis is still unclear. Aim of the study was to assess the efficacy of repeat celiac plexus neurolysis and to build an artificial neural network model able to predict pain response.

Methods: Data regarding 156 patients treated with repeat celiac plexus neurolysis between 2004 and 2019 were reviewed. Artificial neural network and logistic regression models were built to predict pain response after treatment. Performance of the models was expressed in terms of accuracy, positive predictive value, and positive likelihood ratio.

Results: Median age was 62 years (range 39–86) and most patients were male (66%) with pre-procedural visual analogue score 7. Fifty-one patients (32.6%) experienced treatment response, of which 6 (3.8%) complete pain suppression. Median duration of pain relief was 6 (2–8) weeks. Tumoral stage, interval from initial to repeat treatment, response to initial neurolysis, and tumor progression between the two treatments resulted as significant predictors of pain response. The performance of the artificial neural network in predicting treatment response was higher than regression model (area under the curve: 0.94, 0.89–0.97 versus 0.85, 0.78–0.89; $p < 0.001$). Positive predictive value and positive likelihood ratio resulted 90.3% and 19.35, respectively. Classification error rate was 5.7% with the artificial neural network compared to 14.7% of regression model ($p < 0.001$). These findings were confirmed through ten-fold cross validation.

Conclusions: Pain response following repeat neurolysis is generally less pronounced than after initial treatment. Artificial neural network may help to identify those subjects likely to benefit from repeat neurolysis.

Introduction

Severe refractory abdominal pain arising from locally invasive pancreatic cancer (PC) has a considerable negative impact on quality of life [1]. A significant proportion of these patients require opioids but, after the transient initial pain-relief, usually experience systemic drug-related side effects and dependency, which often lead to therapy interruption and pain relapse [2].

In order to overcome the drawbacks of systemic pharmacological therapy, celiac plexus neurolysis (CPN) has been developed [3]. Endoscopic ultrasonography (EUS) guided-CPN (EUS-CPN), consisting in the injection of a neurolytic agent directly into the celiac ganglion by means of a linear echoendoscope, was proven to be a relatively safe procedure able to significantly decrease the daily usage of narcotic analgesia and relieve pain in about 80% of treated patients [4–6].

Unfortunately, the results of EUS-CPN are often suboptimal and transient, probably due to technical failure, disease extension outside of the celiac axis, or the concomitant presence of neuropathic pain. Repeat celiac plexus neurolysis (rCPN) is occasionally performed for refractory PC pain or after response to a previous CPN session; however, there is scant evidence to guide practice. Based on very limited clinical observation derived from two small retrospective series of PC patients treated with percutaneous CPN [7,8], rCPN appears to result in lower and less durable pain relief than initial CPN (iCPN). Although current guidelines do not support

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rCPN [9] due to the aforementioned limitations, it is unclear whether findings of these studies may be applicable to larger series of PC patients treated with EUS-guided CPN.

As patient survival can in times exceed the benefit of CPN as a consequence of recent improvements in diagnosis and therapy of PC, it is important to determine whether EUS-guided CPN should be repeated, and if so, the factors associated with successful rCPN.

Since the interaction among biological factors is frequently complex and non-linear, thus making it difficult to distinguish between classes when using the conventional linear discriminant analysis, machine learning methods have been demonstrated to perform better than conventional discriminant analysis [10]. Among them, artificial neural network (ANN) which consists of a set of highly interconnected processing units (neurons) tied together with weighted connections, can accurately identify patterns or make predictions on several novel datasets [10].

Aim of the present study was to assess the feasibility and efficacy of repeat EUS-guided CPN in PC patients. Furthermore, a novel statistical model based on ANN was built aiming to predict response to rCPN given a set of pre-treatment clinical and oncological variables. We also compared the predictive performance of this ANN model to that of a conventional logistic regression model.

Materials and methods

Patients

From a prospectively collected database, data regarding 156 patients suffering from cancer-related abdominal pain secondary to unresectable pancreatic adenocarcinoma (confirmed by EUS-guided fine needle aspiration and CT-scan) who underwent two repeat EUS-guided pain treatments at our Institution between March 2004 and Jan 2019 were reviewed. All patients had undergone neo-adjuvant gemcitabine-based chemotherapy ± radiotherapy and, as they did not meet the resectability criteria when experienced pain-related symptoms, were offered EUS-guided pain therapy. Institutional Review Board approbation for this retrospective report was obtained.

The following exclusion criteria were used: presence of an implanted pain-relieving device; direct invasion of the pancreatic cancer to the stomach or other nearby organs; patients under antiaggregant or anticoagulant therapy or presence of diseases impairing normal blood clotting.

All procedures were performed by a board-certified gastroenterologist (NM) who had performed more than 60 EUS-CPNs before the study period.

Indications to rCPN were pain recurrence after successful initial neurolysis or insufficient pain control in spite of adequate opioid treatment after the first CPN session.

Written informed consent was obtained from all patients before the procedure.

Technical procedure

Under sedation with propofol, EUS was conducted with a Pentax FG-36UA ultrasound endoscope (Pentax Europe, Ltd, Hamburg, Germany) using a curved-array transducer. Once into the stomach, the endoscopic ultrasound probe was located in contact with the gastric wall and the aorta was identified in an elongated cross-section and such a finding was confirmed by color Doppler imagery. The scope was then slowly advanced in order to identify the celiac trunk. A 19 G needle (Echotip 19, Cook Medical, Winston-Salem, NC, USA) was introduced though the endoscope's working channel to inject the medication to the celiac region. Once the injection needle was targeted in the desired area, an aspiration syringe was used to confirm that a blood vessel was not punctured. If blood was not aspirated, 10 mL 2.0% lidocaine and 20 mL 95% ethanol were injected into the base of the celiac trunk at its origin from the aorta (central approach) [6,11].

Patients were continuously monitored during the procedure by a board-certified anesthesiologist with an automated noninvasive blood pressure device, electrocardiogram tracing and pulse oximetry.

Follow up and outcomes

All patients undergoing the procedures were hospitalized and were administered pre- and post-procedure questionnaires.

Pain intensity was measured according to the Visual Analogue Scale (VAS), ranging from 0 (no pain) to 10 (maximal pain) [12]. A successful procedure (pain response) was defined as a $\geq$50% pain relief persisting for $\geq$ 1 month after rCPN without an increase in analgesic usage (primary outcome) [8]. Complete pain response was defined as VAS score 0 without increase in pain medication dosage [6,13]. VAS score was recorded at baseline, at 24 h after the procedure (before hospital discharge), during the scheduled ambulatory visits at 7, 14 days, and monthly thereafter.

Adverse event (AE) rates were evaluated during the procedure, before discharge, at 7 and 14 days by means of ambulatory visits and were classified according to Common Terminology Criteria for Adverse Events 4.0[6].

Statistical analysis

Categorical variables were described as frequencies and percentages and continuous variables as medians and ranges. Comparison of baseline parameters between responders and non-responders were performed by means of Kruskal-Wallis test in the case of continuous variables and Chi-square test in cases of categorical ones. Time to event data were estimated in terms of medians (95% CI) and compared by means of log-rank test.

Univariate and multivariate logistic regression models were applied to identify the independent predictors of pain response after rCPN and the results were expressed as odds ratio (OR) and 95% confidence intervals (CI).

Two statistical predictive models then were built based on variables found to be significantly related to pain response at the univariate analysis. First, a forward conditional logistic regression model was computed. Logistic regression generates the coefficients of a formula to predict a logit transformation of the probability of presence of the characteristic of interest: $logit(p) = b_0 + b_1x_1 + b_2x_2 + \ldots + b_kx_k$. The probability of presence of the characteristic of interest was obtained by the formula $p = 1/(1 + e^{-logit(p)})$ in which 0 = pain response absent, and 1 = pain response present [14].

The second model was based on artificial neural network. ANN uses computer technology to model a biological neural system both structurally and functionally. Like its biological counterpart, an artificial neural network consists of a set of highly interconnected processing units (neurons) tied together with weighted connections [10]. The network itself consists of an input layer, an output layer, and one or more hidden layers. The input layer comprises the data available for the analysis (baseline variables) and the output layer comprises the outcome (pain response). One of the basic characteristics of the ANN is that it learns through examples: learning is achieved through exposure of paired input–output data (training). An ANN learns to associate each input with the corresponding output, by modifying the weight of the connections between neurons. Once an input has been applied as a stimulus to the first layer of neurons it is propagated through each upper layer until an output is generated. This output pattern is then compared to the

desired output and an error signal is generated: the error signal is then transmitted backwards across the net and the connection weight between neurons is updated in order to decrease the overall error of the network. As learning proceeds, the error between ANN output and the desired output decreases until a minimum is reached. Based on the knowledge accumulated during training, the ANN can assign outputs to new input data not used in the learning process. Thus, after training, the ANN can identify patterns or make predictions on datasets never seen before [10].

For both models, optimal cut-offs found through receiver operating characteristic (ROC) curve with the best relationship between sensitivity and specificity were used for classification.

To avoid overoptimistic results due to overfitting, we tested the performance of both models by means of 10-fold cross validation. Ten-fold cross-validation refers to the process of dividing the original patient sample into 10 equal groups, then removing 1 group, used as validation sample, and reconstructing the model using the reduced sample set. The new model is then tested for predictive accuracy against the excluded fraction, the process is repeated 10 times (each time with a different excluded subset). Finally, ten-fold cross-validation is repeated 250 times by means of bootstrapping to reduce the effect of random splits, and an overall error rate is calculated [14–16].

The performances of both ANN and logistic regression models in predicting pain response were expressed and compared in terms of overall accuracy (sum of correct predictions divided by total predictions), positive predictive value (PPV), and positive likelihood ratio (PLR).

Statistical analysis and ROC analysis were computed using MedCalc 7.2.1.0 (MedCalc software, Mariakerke, Belgium) and the neural network was developed using NeuroSolution version 5 (Neurodimension Inc., Gainesville, FL, USA).

Results

Patients

Baseline characteristics of the whole study population of 156 patients who underwent repeat EUS-guided celiac plexus neurolysis are reported in Table 1. Treatment was successful in 51 patients whereas 105 subjects were classified as non-responders.

No significant differences in terms of most baseline patient characteristics were reported. Median age was 62 (range 39–86) and most patients were male (66%) without differences between groups.

Pre-procedural VAS score was 7 in both groups ($p = 0.8$) and the majority of patients had already been administered opioids (88.2% and 84.7% in the two groups, respectively; $p = 0.55$).

Non-responders were more frequently in stage IV (presence of metastases; $p < 0.001$) and experienced tumor progression between iCPN and rCPN ($p < 0.001$). Response to iCPN was experienced by 136 patients (87%), of which only 49 responded to rCPN while 87 remained refractory to repeat treatment (96% versus 82.8%, $p = 0.02$).

Treatment outcomes

Treatment outcomes after iCPN and rCPN are reported in Table 2.

After iCPN, 136 (87%) patients achieved a condition of pain relief, of which 20 (13%) obtained a complete pain response. On the other hand, only 51 patients (32.6%) experienced treatment response, of which 6 (3.8%) complete pain suppression. Likewise, median duration of pain relief was 13 (8–15) and 6 (2–8) weeks after iCPN and rCPN, respectively. After the procedure, reduction in opioid use was registered in 67 (43%) patients after iCPN and in 11 (7%) patients after rCPN.

Median overall survival was 2.3 months (95% CI: 1.2–3.3) in responders to rCPN and 1.9 (1.1–2.8) in non-responders ($p = 0.32$).

No severe treatment-related adverse events were reported. Mild diarrhea was observed in 15 patients (9.6%) after iCPN and 20 (12.8%) after rCPN, while hypotension (responding to intravenous fluids) in 7 (4.4%) after iCPN and 13 (8.3%) after rCPN. These adverse events were minor and self-limited (usually lasted <48 h).

Machine learning models

At univariate logistic regression, tumoral stage, interval from first to repeat CPN, response to iCPN, and tumor progression between the two treatments resulted as being significantly associated with pain relief (Table 3). All of these features were confirmed as significant predictors of response to CPN in multivariate analysis (Table 3).

These variables were used to build the two models. The calculated regression coefficients (b coefficients; Table 3) were entered

Table 1
Baseline patients' characteristics of study population at the time of repeat celiac plexus neurolysis.

Variable	All patients (n = 156)	Responders (n = 51)	Non-responders (n = 105)	p value
Age (years)	62 (39–86)	59 (39–83)	65 (41–86)	0.7
Gender M	103 (66%)	32 (62.7%)	71 (67.6%)	0.54
BMI	18.5 (16–27)	19 (16–27)	18 (17–26)	0.6
ASA score	2 (1–3)	2 (1–3)	2 (1–3)	0.9
VAS score	7 (5–10)	7 (6–10)	7 (5–10)	0.8
Concomitant opioid use	134 (85.8%)	45 (88.2%)	89 (84.7%)	0.55
Tumor max diameter (mm)	40 (22–59)	38 (25–59)	43 (22–59)	0.4
Pancreatic cancer location Head	86 (55.1%)	31 (60%)	55 (52.3%)	0.32
Body/Tail	70 (44.9%)	20 (40%)	50 (47.7%)	
Tumoral stage III	43 (27.6%)	27 (52.9%)	16 (15.2%)	**< 0.001**
IV	113 (72.4%)	24 (47.1%)	89 (84.8%)	
CT ± RT at the time of intervention	136 (87%)	45 (88.2%)	91 (86.6%)	0.78
Median duration of CT (months)*	7.2 (4.8–8.5)	7.8 (4.8–8.5)	7.1 (4.8–7.8)	0.13
Interval from diagnosis to first treatment (months)*	6.8 (2.7–7.6)	5.1 (4.8–8.6)	6.9 (4.7–8.5)	0.08
Interval from first to repeat treatment (months)*	3.5 (2.7–4.3)	4.2 (2.9–5.1)	2.1 (1.5–3)	**0.001**
Response after first treatment	136 (87%)	49 (96%)	87 (82.8%)	**0.02**
Disease progression between the two treatments	129 (82.6%)	31 (60%)	98 (93.3%)	**< 0.001**

Continuous variables are reported as median values and range. Comparisons were performed by Kruskall-Wallis test for continuous variables and Chi-square test for categorical ones.
*Compared by means of log-rank test.
Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiology; CT, Chemotherapy; RT, Radiotherapy.

Table 2
Pain control outcomes after the first and second session of celiac plexus neurolysis.

Variable	First treatment (n = 156)	Second treatment (n = 156)
Pain relief yes no	136 (87%) 20 (13%)	51 (32.6%) 105 (67.4%)
Onset of pain relief (days)	3 (2–6)	4 (2–8)
Duration of pain relief (weeks)	13 (8–15)	6 (2–8)
Complete pain response yes no	20 (13%) 136 (87%)	6 (3.8%) 149 (96.2%)
VAS score reduction (%)	62.4 (41.8–73)	28.1 (11.3–42.5)
Reduction in opioid use yes no	67 (43%) 89 (57%)	11 (7%) 148 (93%)
Reduction in opioid dosage (%)	42.1 (31.3–52.2)	28.2 (14.3–41.2)

Variables expressed as absolute number (percentage) and median (95% confidence interval) when appropriate.

Table 3
Logistic regression analysis of predictors for pain relief.

Variables	Univariate Analysis		Multivariate Analysis		
	Odds Ratio (CI 95%)	p-value	Odds Ratio (CI 95%)	p-value	b coefficient
Age (reference ≤ 60 years)	1.05 (0.95–1.09)	0.32			
Gender (reference F)	1.08 (0.61–1.86)	0.89			
BMI (reference ≤ 20)	1.02 (0.95–1.12)	0.48			
ASA (reference 1)	1.12 (0.79–1.65)	0.44			
VAS score (reference ≤ 7)	0.89 (0.67–1.14)	0.35			
Opioid use (reference no)	0.85 (0.57–1.16)	0.41			
Tumor diameter (reference ≤ 40 mm)	0.87 (0.68–1.23)	0.54			
Cancer location (reference head)	0.88 (0.71–1.12)	0.36			
Tumoral stage (reference III)	0.15 (0.07–0.34)	**<0.001**	0.23 (0.11–0.43)	**0.001**	−1.40
Interval from diagnosis to first treatment (reference ≤ 3 months)	0.43 (0.37–1.06)	0.08			
Interval from first to repeat treatment (reference ≤ 3 months)	3.38 (1.17–5.75)	**0.001**	4.41 (2.18–8.81)	**0.001**	1.50
Response after first treatment (reference no)	5.06 (1.12–22.7)	**0.03**	8.03 (2.21–31.4)	**0.02**	2.1
Disease progression between the two treatments (reference no)	0.11 (0.04–0.28)	**< 0.001**	0.23 (0.10–0.76)	**0.008**	−1.40

Abbreviations: CI 95%, confidence interval 95%; BMI, Body Mass Index; ASA, American Society of Anesthesiology; VAS, Visual Analogue Scale; EUS-CPN, Endoscopic Ultrasound-guided Celiac Plexus Neurolysis.

into the regression formula in order to calculate a prediction score for pain response.

The same variables were then used to build the ANN, which resulted in a three layer feedforward neural network with 4 input nodes, 3 neurons in the hidden layer, and two output neurons (Fig. 1).

Based on data of all recruited patients, we plotted relevant results in two ROC curves in order to select the more accurate cut-off points able to stratify the study population according to treatment response (Fig. 2). ROC analysis showed a score point of 2.0 with the regression model and 0.5 with the ANN as the values at higher

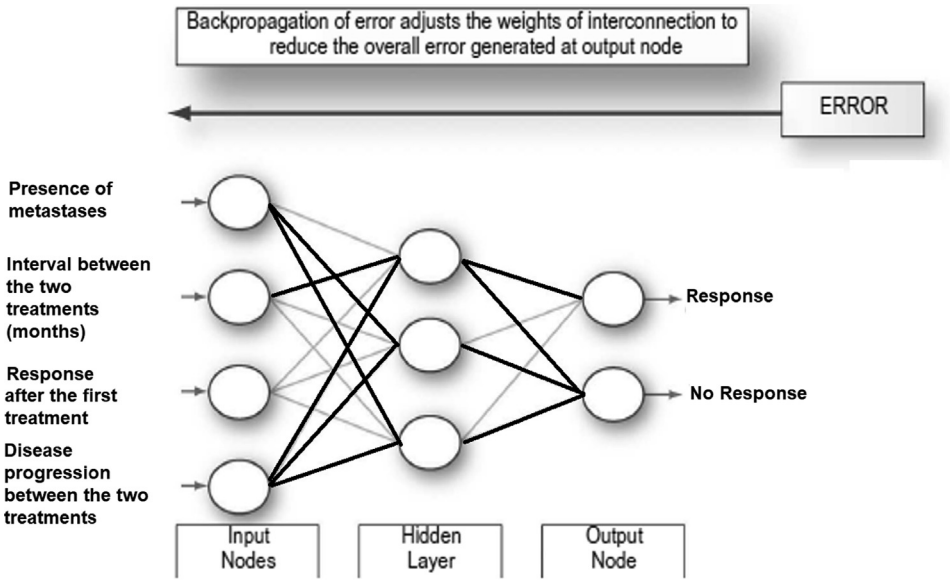

Fig. 1. Schematic representation of the artificial neural network (ANN) developed to predict pain response after endoscopic ultrasound celiac plexus neurolysis. Significant variables in logistic regression analysis were used to build the ANN, which resulted as a three layer feedforward neural network with 4 input nodes, 3 neurons in the hidden layer, and two output neurons. The weight of each particular interconnection between neurons is represented by the thickness of the line.

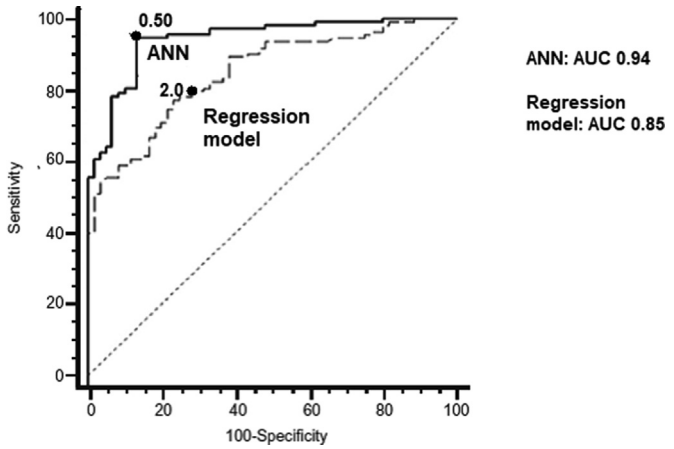

Fig. 2. ROC analysis displaying the ability of artificial neural network (ANN: continuous line) and logistic regression model (dotted line) to predict pain response to treatment. ROC analysis showed a score point of 2.0 with the regression model and 0.5 with the ANN as the values at higher specificity and sensitivity for predicting pain response. The performance of the ANN was higher than that of regression model, with an area under the ROC curve (AUC) of 0.94 (95% confidence interval = 0.89–0.97) versus 0.85 (0.78–0.89) of regression model ($p < 0.001$).

specificity and sensitivity for predicting pain response (Fig. 2).

The performance of the ANN in predicting treatment response was very high, with an area under the ROC curve (AUC) of 0.94 (95% C.I. = 0.89–0.97) significantly higher ($p < 0.001$) compared to that of the logistic regression model (AUC: 0.85, 0.78–0.89; Fig. 2).

Performance details of the ANN and logistic regression models are outlined in Table 4. Applying the aforementioned cut-off of 0.50 for ANN, PPV and PLR for pain response resulted 90.3% and 19.35, respectively. Classification error rate with the ANN model was 5.7% with a κ concordance with actual treatment response as high as 0.81.

For the logistic regression model (cut-off: 2.0), PPV and PLR for pain response resulted significantly lower (76.9% and 6.86, respectively) than those above reported, with a classification error rate of 14.7% and a κ concordance with actual response of 0.58.

Both the ANN and the logistic regression model were finally tested by means of ten-fold cross validation. This validation method resulted in an AUC of 0.91 (95% CI: 0.82–0.93) and in an overall error rate of 0.06 for the ANN model, and AUC of 0.79 (95% CI: 0.67–0.84) and error rate of 0.17 for the regression model (Fig. 3).

Discussion

Given the retroperitoneal growth of the neoplasia and invasion of celiac plexus, approximately 75% of all patients with unresectable pancreatic cancer experience severe abdominal pain [1,2]. In order to ameliorate quality of life of these patients and to decrease the need of narcotic drugs, EUS-guided CPN and celiac plexus block have been developed and are now considered as first-line option for the treatment of severe refractory pain in PC patients [3–5,17].

Given the recent improvements of PC survival outcomes, mainly due to earlier diagnosis and more effective treatments, patient survival can in times exceed the benefit of EUS-guided CPN, therefore occasionally repeat CPN may be considered at the time of pain relapse. Furthermore, recent evidence speaks in favor of an earlier use of CPN at the time of EUS diagnosis in patients with PC-related pain [13], thus determining a higher need of repeat treatment.

In a retrospective study including 24 patients with PC-related pain in which repeat percutaneous neurolysis was performed, the success rate decreased from 67% after initial CPN to 29% following repeat CPN with an associated decrease in mean duration of pain relief from 3.4 months for initial CPN to 1.6 months of repeat CPN [8].

Although these disappointing results have discouraged the broad use of repeat CPN so far, the findings of the aforementioned study should be interpreted with great caution due to the small sample size. Moreover, there is no evidence on effectiveness of repeat EUS-guided CPN.

To the best of our knowledge, this is the first report on outcomes of repeat EUS-guided CPN in PC patients.

Pain response to treatment dropped from 87% after iCPN to 32.6% after rCPN, thus confirming the significantly lower response rate with repeat treatment reported in the above cited study [8]. Consequently, also complete pain response was considerably lower after rCPN (3.8% versus 13%) while median duration of pain relief was only 6 weeks after repeat treatment.

Therefore the current study demonstrates that both the magnitude and duration of pain relief following rCPN were significantly less than after the initial procedure.

Although these findings tend to discourage the use of rCPN, a small subset of patients could still benefit from repeat treatment; therefore, given the broad sample size of our series, we performed a complex and robust statistical analysis aiming to determine the predictors of pain response and the characteristics of those subjects who are likely to benefit from rCPN.

In fact, simple logistic regression analysis may result inadequate to capture the complex interplay of the different baseline variables determining pain response. On the other hand, recent studies have demonstrated that neural network analysis is potentially more useful than traditional statistical techniques when the importance of a given prognostic variable is expressed as a complex unknown function of the value of the variable or when the prognostic impact of a variable is influenced by other prognostic variables in a complex multidimensional non-linear function [18,19]. This condition is found in a complex biological system such as PC biology.

Variables resulted to be significantly associated to pain response after rCPN, namely presence of metastases, interval from first to repeat CPN, response to iCPN, and tumor progression between the two treatments were entered into two different statistical models. The performance of the ANN in predicting treatment response was significantly higher than the regression model (AUC: 0.94 versus 0.85; $p < 0.001$).

Applying the cut-off values of 0.50 for ANN and 2.0 for the regression model (computed through an ROC analysis), PPV and PLR for prediction of pain response resulted significantly higher with the ANN model.

The lack of an external validation cohort may push to argue that the absence of data originating from other centers may lead to a wrong prediction of pain response; however, we strongly feel that this should not be considered a limitation since the distinctive characteristic of the artificial neural networks is that they can learn

Table 4
Predictive accuracy of response to treatment based on artificial neural network and regression model.

Model Prediction	Actual Response		Cut-off	Accuracy	PPV	PLR
Artificial Neural Network						
	Response	No response	0.5	94.2%	90.3%	19.35
Response	47	5				
No response	4	100				
Regression Model						
	Response	No response	2.0	85.2%	76.9%	6.86
Response	40	12				
No response	11	93				

Abbreviations: PLR, Positive Likelihood Ratio; PPV, Positive Predictive Ratio.

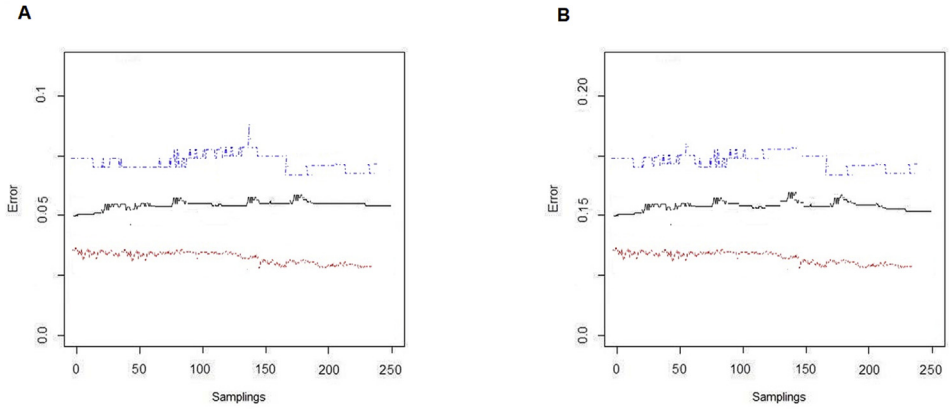

Fig. 3. Ten-fold cross validation error rate. The overall error rate was 0.06 with the artificial neural network model, and 0.17 with the regression model. Red line indicates error rate for pain response prediction, blue line indicates error rate for non-response prediction, black line the average error rate.

through examples making the prediction of histological features feasible on datasets never seen before. Moreover, an internal cross-validation by means of 250 bootstrap samplings randomly drawn with replacement from the original population was performed. This way, both the model building process and its performance were simultaneously validated in a broad range of random samples, thus obviating the lack of an external cohort, as recently confirmed by simulation studies [10,20].

Similar to previous research demonstrating the importance of tumor location and tumor burden [7,8], our study confirms that oncological factors such as disease progression and metastases play an important role in determining outcomes following rCPN. This observation can explain at least partially why those subjects who failed to obtain relief from rCPN tended to experience a longer time interval between procedures. Another possible contributing factor is that as the adverse effects of disease progression are realized and expectations decline, the placebo effect may be weaker [21].

The current manuscript has some limitations. First, the retrospective nature of the study which could have led to selection or outcome report biases. It should be noted that this retrospective analysis on rCPN procedures automatically selected patients at higher survival and better response to iCPN as these are the subjects who actually needed to perform the repeat treatment. Second, this series reported no objective documentation of functional improvement or quality of life. Third, as above mentioned, the single-center nature of the study did not allow to externally validate our results, although a robust internal cross-validation was performed.

Conclusions

Despite the aforementioned limitations of our report, the results of this study show that pain response following rCPN is generally less pronounced and more transient than after initial CPN. However, a small subset of patients may benefit from rCPN and an ANN model based on significant predictors of response, such as absence of metastases, longer interval from first to repeat CPN, response to iCPN, and stable disease between the two treatments may help to identify accurately those subjects likely to benefit from rCPN.

Prospective studies are necessary to confirm our results and to identify the best candidates for rCPN.

Author disclosures

Drs Antonio Facciorusso, Valentina Del Prete, Matteo Antonino, Vincenzo Rosario Buccino, and Nicola Muscatiello have no conflicts of interest or financial ties to disclose.

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None.

Specific author contributions

Antonio Facciorusso, MD, PhD designed the study and performed the statistical analysis; Valentina Del Prete, MD, and Matteo Antonino, MD collected the data; Nicola Muscatiello, MD performed the procedures; Vincenzo Rosario Buccino, MD revised the manuscript. All the authors approved the final draft submitted.

Guarantor

Nicola Muscatiello, MD.

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