JBUON 2021; 26(6): 2631-2638
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Radioactive iodine treatment planning for differentiated thyroid carcinoma: Comparison of different machine learning classification models

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Summary

Purpose: *Radioactive iodine therapy (RAIT) is important when treating patients who have been diagnosed with differentiated thyroid carcinoma and have gone through initial surgery. However, deciding whether a patient should undergo such therapy as well as the proper iodine dose is a complex task, especially for those with a lack of experience. Therein, this paper aimed to develop and compare classifier systems to aid inexperienced physicians in decision making on radioactive iodine therapy for thyroid cancer patients.*

Methods: *The study cohort consisted of 210 thyroid cancer patients who had undergone a total thyroidectomy. We developed and evaluated the performance of three machine learning (ML) algorithms that suggest whether these patients should undergo RAIT and propose an administrable I-131 dose. These algorithms were Artificial Neural Network (ANN), Naïve Bayes Classifier (NB) and Group Method of Data Handling (GMDH). The kappa coefficient was used to measure agreement of classifiers with gold standard decision made by an experienced physician.*

Results: *Our results indicate that the ANN performs better than NB and GMDH in terms of accuracy (95.71%). On the basis of the Kappa coefficient, ANN was also the best 0.96 (0.91-1.00). Additionally, kappa coefficient increased to 0.93 (0.86-1.00) by comparing young physicians' decisions on thyroid cancer therapy before and after using ANN as a decision making tool.*

Conclusion: *Our results suggest that developed classifiers are able to imitate the real decisions of medical expert. Furthermore, classifiers may be utilized to educate inexperienced medical professionals, especially in the absence of strict guidelines' recommendations.*

Key words: *machine learning, radioactive iodine, thyroid cancer*

Introduction

Thyroid cancer is the most frequent endocrine carcinoma and one of the ten most frequent cancers occurring in women [1]. The incidence of well-differentiated thyroid cancer (WDTC) has risen in many European countries over the last three decades (particularly papillary thyroid cancer / (PTC). WDTC itself is largely indolent, whose mortality has remained approximately 0.5 per 100,000 people [2, 3].

Although WDTC has a good prognosis in the vast majority of patients, there are cases who do require radioactive iodine therapy (RAIT) after total

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Received: 01/03/2021; Accepted: 05/04/2021

or near total thyroidectomy. RAIT is administered to: 1) ensure undetectable serum thyroglobulin levels and facilitate surveillance (remnant ablation); 2) destroy any presumed foci of malignant cells to reduce the risk of recurrence as well as to strengthen disease-specific and progression-free survival (adjuvant therapy); 3) and/or treat persistent or recurrent disease to get a better progression-free and overall survival (treatment of known disease) [4,5].

Due to lack of consensus among guidelines, there is no singular agreed-upon method to treat patients suffering from WDTC [3, 4, 6-8]. The recommendations taken from the guidelines vary between one another and advances in medical knowledge and research further complicate the decision making process. To illustrate, the American Thyroid Association (ATA) guidelines gives "consider" recommendation for administration of RAIT in low-and intermediate-risk patients [9]. Therefore, guidelines do not provide recommendations for all potential clinical cases they should cover. Moreover, it has been demonstrated that even low radioactive iodine initial dose may decline patients outcome [10,11]. It is therefore crucial to study prior individual cases and derive their characteristics in order to better learn how to make therapy decision. Consequently, it is still generally left to the physician's best judgment to follow his/her own experience to decide whether postoperative RAIT is necessary or not [9,12]. A skilled physician may more reasonably determine whether a patient should undergo RAIT after surgery or not; nevertheless, it is a complex task for those lacking experience.

As a research area of artificial intelligence, Machine Learning (ML) is a novel method that has biomedical applications in the use of algorithms to classify, predict or estimate [13]. Artificial neural networks (ANN) are information-processing systems capable of learning from experience, and to apply to new cases generalizations derived from previous instances [14]. Based on the Bayes theorem, Naïve Bayes Classifier (NB) is an algorithm that aims to simplify learning based on features being independent and assigned class whereby one probability may not affect another [15]. Identifying non-linear systems' internal structure, Group Method of Data Handling (GMDH) is an inductive self-organizing technique that identifies through extraction from data samples [16].

There are different ML approaches that concerned therapy planning and clinical decision support which were widely used in medicine, especially in radiation oncology [17,18]. The issue regarding iodine treatment in WDTC, has been analyzed in a work of our contributing authors Teodorovic et al [1]. They developed and applied a Bee Colony Optimization metaheuristic and Case-Base Reasoning (CBR-BCO) for the purpose of education for thyroid carcinoma treatment.

This study aimed to develop and compare three ML classifiers based on ANN, NB and GMDH method to gold standard expert medical decision. Machine learning classifiers are here hypothesized to be applicable in the educational process in order to improve the quality of decisions of young physicians that treat WDTC, especially in the absence of strict guidelines' recommendations.

Methods

Data collection

The medical records of 210 patients who had undergone a total thyroidectomy and central lymph node dissection at the Institute for Oncology and Radiology of Serbia (IORS) between 2015 and 2018 were retrospectively reviewed. A sentinel lymph node (SLN) biopsy in the lateral neck compartment was performed on those patients who showed clinically negative lymph nodes to decide upon the necessity for modified radical neck dissection (MRND) [19]. A MRND was also carried out for those patients who showed any clinically palpable and/or suspicious preoperative imaging appearance of the lateral lymph nodes as well as for patients in whom fine-needle aspiration biopsy or surgical biopsy of the neck lymph nodes proved the presence of thyroid carcinoma metastasis. These procedures were all performed according to the single Institution's experience. The IORS's multidisciplinary tumor board decided as to whether patients were to be candidates for radioactive iodine (RAI) ablation or RAI adjuvant therapy and/or thyroid-stimulating hormone suppression therapy. If it was decided that there will be a continuation of the I131 therapy, the patients were administered it in the centers where it was available.

All the collected patient data were then reevaluated according to the 8^{th} tumor, node, metastasis (TNM) classification of malignant tumors [20]. Eligible patients were histologically confirmed to have papillary thyroid cancer (classic or follicular variant histologic subtype), under tumor stage T1a–T4a with or without lymph node involvement. No case showed any distant metastasis. In accordance with the above-noted classification system and taking into consideration recommendations from recently published articles and thyroid cancer management guidelines, decisions on optimally administered I-131 activity were reassessed by a nuclear medicine specialist with more than 30 years of experience [3, 6, 8, 21-29].

Developing of ML classifiers

In this paper, three ML algorithms were applied to find out classification patterns from the available data: Artificial Neural Network, Naïve Bayes Classifier and Group Method of Data Handling.

Every patient in the study was defined by the following demographic and histopathology characteristics of tumors: age, gender, tumor size, presence/absence of extra thyroidal extension, degree of lymph nodal involvement and multifocality. The importance of the aforementioned attributes was confirmed in several studies [23-29]. These characteristics represented the input (independent variables) and their descriptors are shown in Table 1. The target output (dependent variable) was the appropriate treatment decision defined as: (0) patients not to be treated by radioactive iodine therapy; (1) patients to be treated by radioactive iodine therapy and to receive a dose of 1.85 GBq; (2) patients to be treated by radioactive iodine and to receive a dose of 3.7 GBq; (3) patients to be treated by radioactive iodine therapy after the surgery and to receive a dose of 5.55 GBq.

All the patients were then randomly divided into two sets. Training set which has around 70% of all patients (150 patients) was used to develop classifiers. After training the data the developed models were evaluated using the test data set consistent from the remaining 30% of patients (70 patients). Additionally, different configurations of the ANN were tried in order to obtain the best possible results. The flowchart of the study design is shown in Figure 1.

Software and statistical analysis

For the GMDH method, the GMDH Shell DS 3.8.9 software was used; for the artificial neural networks, software Weka 3.8.4 was used. Furthermore, the software for the Naïve Bayes classifier was developed in Java programming language (in NetBeans IDE 8.2 development environment).

Statistical analyses were performed using the IBM SPSS 22 software (IBM Corporation, Armonk, NY, USA). Descriptive statistics was used to summarize data about patients and tumor characteristics and their results were presented as numbers and frequencies (%). A weighted kappa coefficient with 95% confidence interval (CI) was

Table 1. The characteristics of patients and the tumors as well as their descriptors

Characteristics	*Total n (%)*	*Type*
Sex		Categorical
Male	50 (23.81)	1
Female	160 (76.19)	2
Age		Categorical
<55	143 (68.09)	1
≥55	67 (31.91)	2
T stage		Categorical
T1a	108 (51.43)	1
T1b	52 (24.77)	2
T2	29 (13.81)	3
T3a	5 (2.38)	4
T3b	11 (5.23)	5
T4a	5 (2.38)	6
Multifocality		Categorical
No	109 (51.90)	1
Yes	101 (48.10)	2
Extrathyroidal extension (ETE)		Categorical
No	153 (72.86)	0
Minimal/Microscopic	42 (20)	1
Gross	15 (7.14)	2
Lymph node involvement		Categorical
N0	84 (40)	1
N1a	46 (21.90)	2
N1b	9 (4.29)	3
N1a + N1b	71 (33.81)	4

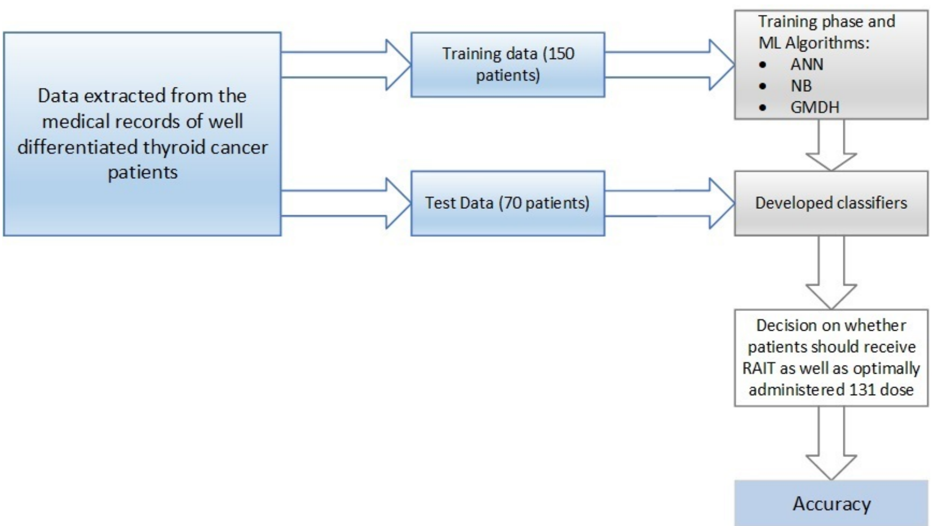

Figure 1. The flowchart of the study design.
ANN: Artificial neural network, NB: Naïve Bayes classifier, GMDH: Group method of data handling

used to assess the agreement of the models result with the gold standard represented by physician's decisions.

Acceptance of the developed software

In order to preliminarily test the acceptance of the best developed classifier by potential users, three groups of 10 patients (30 patients in total) were randomly created from the testing group and were presented to four young nuclear medicine physicians, located in four separate hospitals.

The data from the first group of 10 patients were shown to physicians who were then asked to propose the best therapy treatment for each patient. They could choose from the following options: (a) whether the patient should undergo radioactive iodine therapy after surgery; and if so, they were then asked to (b) propose the I-131 iodine dose that should be administered. After making their decisions, the physicians were then asked to compare them with the decisions made by classifier. The physicians were given enough time to study the classifier's proposed answers. After that, a second and third ten-patient-group were shown to the physicians and the entire procedure was repeated in the same manner. This was the learning phase.

Table 2. Accuracy of the classifiers within the test group

	ANN[1]	*NB*[2]	*GMDH*[3]
Correctly classified instances	67	65	63
Incorrectly classified instances	3	5	7
Percent of correctly classified instances	95.71%	92.86%	90%

[1]Artificial Neural Network, [2]Naïve Bayes, [3]Group Method of Data Handling

After the learning phase was completed, a second phase was initiated in which the same patients used in the learning process were re-randomized into two newly-generated groups. The physicians' responses were then reviewed to check if their performance had improved. We used the weighted kappa coefficient to measure the agreement of the inexperienced physicians' decision with the gold standard before and after using classifier as a decision support.

Results

Data description

At the time of diagnosis, the majority of patients (68.09%) were under the age of 55. Patients were predominantly female. Table 1 lays out the characteristics of the 210 patients and the tumors' clinicopathological characteristics. The majority of WDTC cases (108/51.9%) were diagnosed under the T1a stage. Lymph node metastases were present in 126 patients. 153 patients presented no extrathyroidal extension and 109 patients (51.09%) were unilateral.

Performance of the classifiers in radioactive iodine treatment planning

Comparing all algorithms, it was concluded that the ANN was proven to be the most successful ML classifier, with 67 identical decisions as physicians (approximately 96% of cases in the test group). This was followed by Naïve Bayes with 65 identical decisions (93%). The GMDH method yielded the lowest results with the 63 identical decisions (90% of accuracy). The obtained results are shown in Table 2.

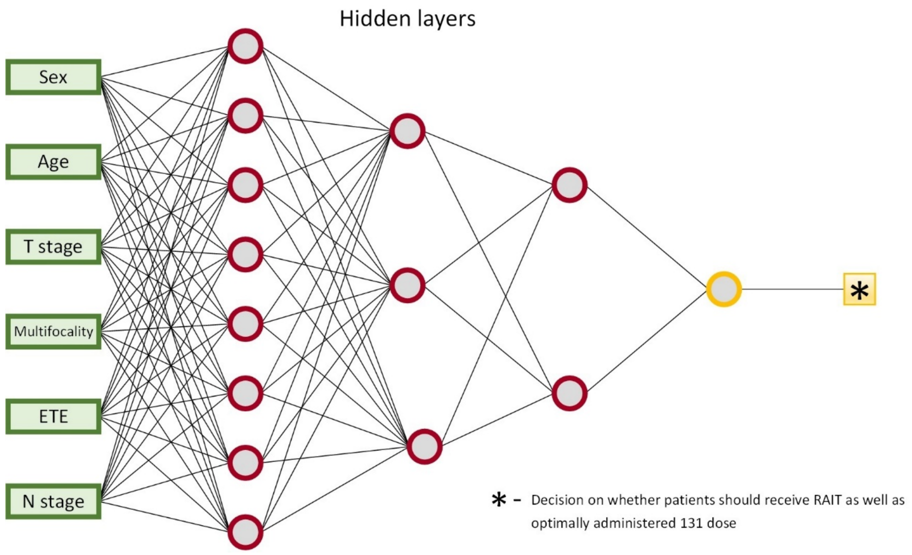

Figure 2. Graphical presentation of the Artificial Neural Network with best performance
ETE: Extrathyroidal extension, N: Regional lymph nodes

Furthermore, we compared the different ANN configurations and concluded that the best results were achieved in the case of ANN that has the three hidden layers. The first layer had eight neurons, the second layer had three and the third layer two neurons (Figure 2).

On the basis of the kappa coefficient, all models were in very good agreement with the physicians' original decision, as shown in Table 3. The Artificial Neural Network was the most successful. Its Kappa coefficient value was 0.96. It follows the Naïve Bayes with a value of 0.92. The GMDH method had the lowest concurrence at a value of 0.89. The graphical illustration of the physician's and classifiers agreement is given in Figure 3.

Table 3. Weighted Kappa coefficient for proposed classifiers

Machine Learning Classifiers	*Weighted Kappa Coefficient with 95% confidence interval*
Artificial Neural Network (ANN)	0.96 (0.91-1.00)
Naïve Bayes (NB)	0.92 (0.84-0.99)
Group Method of Data Handling (GMDH)	0.89 (0.79-0.98)

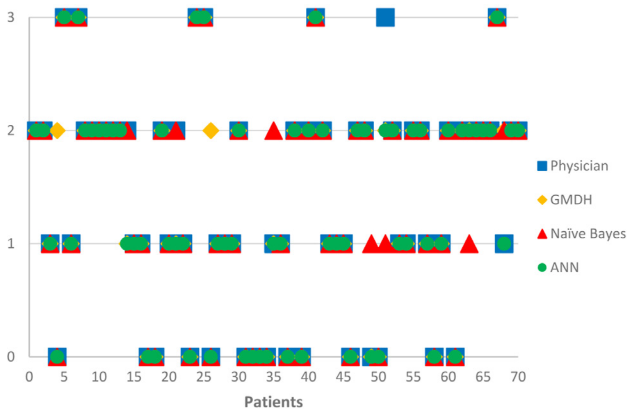

Figure 3. Agreement between the classifiers' and gold standard (physician's decision) regarding radioactive iodine treatment.
GMDH: Group method of data handling, NB: Naïve Bayes classifier, ANN: Artificial neural network

Acceptance of the developed software

As previously stated in the Methods section, the young physicians used the best developed classifier, which in this case was the ANN as a decision aid during the learning phase. The kappa coefficient was 0.70 (0.56-0.84) when the first group of patients was presented to young physicians before using ANN as a decision support system. After the learning phase kappa coefficient was 0.93 (0.86-1.00) which suggests that the ANN classifier is useful for educational purposes (Figure 4).

Discussion

The present study developed and compared three classifiers which serve to instruct inexperienced physicians when deciding on possible RAIT administration. In order to find the best classifier available to correspond to the experienced physician's decision, the authors compared three ML systems. While all three developed models were shown to be highly accurate, the artificial neural network was the most successful, due to its ability to imitate decisions of the medical expert. Additionally, it has been shown that ANN could guide inexperienced physicians in making decisions about RAIT treatment.

All models showed high accuracy when asked whether RAIT should be administered or not. The only occurring errors concerned the dose of I131 that should be given. Although the ANN demonstrated the highest accuracy, it did not deliver

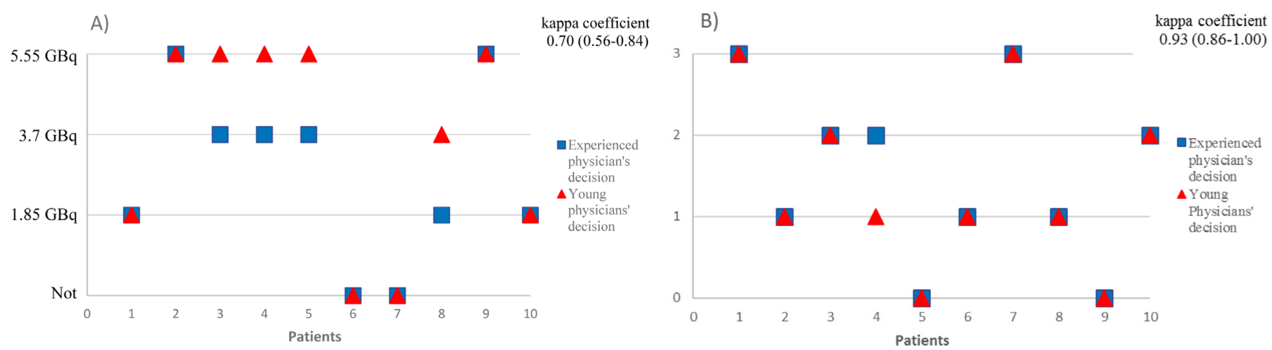

Figure 4. Comparison between young physician's decision and gold standard represented by experienced physician's decision: **A:** before the learning phase without Artificial Neural Network classifier's aid. **B:** after the learning phase where Artificial Neural Network classifier was used as a decision aid tool.

the best decision on doses for 3 patients. Through the analysis of these cases, it was found that the patients with these combinations of input variables were not included into the training group. Consequently, the network was unable to recognize these three patients.

As mentioned earlier, there is no clear concurrence on RAIT among guidelines [3, 4, 6-8]. Even if the most cited ATA 2015 guideline does generally advise against I-131 therapy, data reported in the last decade is in favor of postoperative RAIT in WDTC [22]. Recommendations on dosage are another issue as they are still generalized and not always able to provide clear guidance for all potential cases. The final decision is made by practicing physicians in the field, based on their education and experience [9]. All this may confuse the young physician when deciding on treatment. Therefore, we aimed to create a model based on real life practice, which contains information from the past clinical cases and by which physicians can learn from. Similar studies were purposed for treatment decisions in diabetes type-2 patients when there was no clear recommendation within the existing guidelines [12,30]. Their results showed that gaps within the guidelines were able to be filled by applying ML models with rules learnt from experienced physicians' decisions.

To the best of our knowledge, this research represents one of the first attempts to apply ANN, Naïve Bayes Classifier, and GMDH in WDTC therapy. The issues analyzed within the scope of our research have been addressed in a work of our contributing authors where CBR-BCO model was used. They found that this model could be used for educational purposes since its decisions were in agreement with those of nuclear medicine physicians [1], as we have also seen in our study. Additionally, we have extended our research by testing the best performing classifier (ANN) on four inexperienced nuclear medicine physicians. Our results indicated that the likelihood of an error being made when deciding on I131 therapy decreases with repeated use of the ANN classifier. Consequently, studying ANN decisions is useful in the decision making process, since its recommendations are based on the characteristics of real patients data taken from practice.

Although there has been limited research into ML algorithms use for thyroid cancer treatment, the recommended models have been widely used for classification in other fields of cancer research. They have demonstrated potential to assist physicians in improving their decision making process. Similar to our study, other research has also utilized ML algorithms and compared them with one another, in order to find one to classify patients in the most effective manner [31-35].

This study has its limitations. The most important one is the degree of surgical resection. All the patients included into the study underwent a total thyroidectomy with a central dissection and SLN biopsy and/or MRND for the lateral neck lymph nodes [19]. This approach may not be the standard of care in other healthcare institutions whose treatment standards may vary. It also should be noted that this was a retrospective study and due to the limitations of the random selection, some patients who presented with rare combinations of input parameters were not included in the training group which may hinder the neural networks ability to learn from the given data set.

The main focus of our study was to build classifiers to help young, inexperienced physicians to check their knowledge. To this aim, the authors developed and compared three classifiers: Artificial Neural Networks, Naive Bayes and the Group Method of Data Handling. We have demonstrated that the proposed classifiers are able to imitate real decisions of experienced physicians on radioactive iodine therapy for thyroid cancer patients. The most accurate was the ANN. A further multicentric study is necessary to evaluate the diagnostic accuracy of classifiers in larger data of WDTC patients including those with distant metastases. In addition, physicians specialized in other fields should also be involved as WDTC demands a multidisciplinary approach.

Acknowledgement

This research was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (grant No. III41031) for institutional funding. The study was approved by the Ethics Committee of the Institute for Oncology and Radiology of Serbia and conducted with the understanding and consent of all subjects involved. The Ethics Committee stated that the rights, safety, physical and mental integrity of the subjects participating in this clinical trial are completely protected.

Conflict of interests

The authors declare no conflict of interests.

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