Laryngology

Thyroid cartilage infiltration in advanced laryngeal cancer: prognostic implications and predictive modelling

Infiltrazione cartilaginea tiroidea nei tumori laringei avanzati: implicazioni prognostiche e analisi predittiva

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SUMMARY

Objective. Detection of laryngeal cartilage invasion is of great importance in staging of laryngeal squamous cell carcinoma (LSCC). The role of prognosticators in locally advanced laryngeal cancer are still widely debated. This study aimed to assess the impact of volume of thyroid cartilage infiltration, as well as other histopathologic variables, on patient survival.

Materials and methods. We retrospectively analysed 74 patients affected by pT4 LSCC and treated with total laryngectomy between 2005 and 2021 at the Department of Otorhinolaryngology – Head and Neck Surgery of the University of Brescia, Italy. We considered as potential prognosticators histological grade, perineural (PNI) and lympho-vascular invasion (LVI), thyroid cartilage infiltration, and pTN staging. Pre-operative CT or MRI were analysed to quantify the volume of cartilage infiltration using 3D Slicer software.

Results. The 1-, 3-, and 5-year disease free survivals (DFS) were 76%, 66%, and 64%, respectively. Using machine learning models, we found that the volume of thyroid cartilage infiltration had high correlation with DFS. Patients with a higher volume (> 670 mm^3) of infiltration had a worse prognosis compared to those with a lower volume.

Conclusions. Our study confirms the essential role of LVI as prognosticator in advanced LSCC and, more innovatively, highlights the volume of thyroid cartilage infiltration as another promising prognostic factor.

KEY WORDS: cartilage infiltration, thyroid cartilage, laryngeal cancer, prognostic factors, machine learning, predictive model

RIASSUNTO

Obiettivo. *La valutazione dell'invasione cartilaginea ha grande importanza nella stadiazione dei carcinomi squamocellulari della laringe (LSCC). Mentre il ruolo dei fattori prognostici nei tumori laringei localmente avanzati è ancora ampiamente discusso, questo studio è finalizzato a valutare l'impatto del volume di infiltrazione della cartilagine tiroidea, oltre che quello di altre variabili istopatologiche, sulla sopravvivenza.*

Materiali e metodi. *Sono stati retrospettivamente analizzati 74 pazienti affetti da pT4 LSCC e trattati con laringectomia totale nel periodo tra il 2005 e il 2021 presso il Reparto di Otorinolaringoiatria e Chirurgia della Testa e del Collo dell'Università degli Studi di Brescia. I parametri considerati come potenziali fattori prognostici sono stati il grading, l'invasione perineurale (PNI) e linfovascolare (LVI), l'infiltrazione della cartilagine tiroidea e la stadiazione pTN. Le immagini CT e MRI pre-operatorie sono state analizzate per quantificare il volume di infiltrazione cartilaginea attraverso il software 3D Slicer.*

Risultati. *La sopravvivenza libera da malattia (DFS) a 1, 3 e 5 anni è stata rispettivamente del 76%, 66% e 64%. Utilizzando modelli di machine learning abbiamo scoperto che il volume di infiltrazione della cartilagine tiroidea aveva un grande impatto sulla DFS. In parti-*

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colare, i pazienti con volume d'infiltrazione maggiore di 670 mm^3 avevano una prognosi peggiore di quelli con volume di infiltrazione inferiore. *Conclusioni. Il nostro studio conferma il ruolo fondamentale della LVI come fattore prognostico nei LSCC avanzati e, in modo più innovativo, identifica il volume di infiltrazione cartilaginea come un'altra variabile impattante la prognosi di questi pazienti.*

PAROLE CHIAVE: *infiltrazione cartilaginea, cartilagine tiroidea, tumore della laringe, fattori prognostici, machine learning, modelli predittivi*

Introduction

Laryngeal squamous cell carcinoma (LSCC) is the second most prevalent malignant neoplasm within the respiratory tract, trailing only pulmonary cancer [1]. Approximately 60% of laryngeal malignancies are diagnosed at an advanced stage due to the non-specific nature of early tumour symptoms. The TNM system is the most widely utilised framework to stage LSCC and provide valuable predictions of survival [2]. The prognostic heterogeneity inherent to laryngeal neoplasms, particularly for those at advanced stages, has been the subject of extensive studies from our group and others aimed at identification of potential predictors [3-10]. Several prognostic factors have been implicated in LSCC, including disease stage, surgical margin status, tumour differentiation, extranodal extension (ENE), and the presence of lympho-vascular (LVI) or perineural invasion (PNI) [11-13]. Early diagnosis is crucial, placing disease stage at the heart of 5-year survival estimation: if it is considered to be around 60% on average, it reaches 78% in early-stage patients, and falls to 34% in cases with metastatic involvement [14,15]. Additionally, histological features such as LVI and PNI represent negative prognostic indicators, underlining the tendency for tumour invasion and its aggressive character. Furthermore, lymph node metastasis, along with the size and quantity of involved lymph nodes (> 4), and ENE can further worsen prognosis [16]. The presence of ENE, for example, dictates more aggressive treatment strategies, necessitating potentially radical neck dissection and adjuvant therapy. Surgical margin status also plays a significant role, influencing both survival rates and the risk of local recurrence and lymph node metastases.

Precise disease staging of LSCC is crucial for an effective therapeutic plan, necessitating both endoscopic and radiologic evaluations, including neck CT or MRI. The former efficiently detects cartilaginous invasions, but may fail to identify minor erosion due to varying degrees of cartilage ossification, potentially confounding the diagnosis[17,18]. MRI is more effective in diagnosis of cartilaginous infiltration, despite occasional difficulties in distinguishing it from peritumoural inflammation [19-21]. Despite the benefits of MRI, CT remains the most frequently employed diagnostic tool due to its widespread availability.

Tumour volumetry, as documented in the literature, serves both as a determinant of optimal treatment strategy and prognostic tool. Hsin et al. [22], in the attempt to evaluate alternatives to surgery aimed at preserving organ function without compromising survival, concluded that for primary tumours with a volume < 15 cm^3 chemo-radiotherapy can obtain survival rates comparable to surgery, while surgical resection remained the most reliable option for lesions with larger volumes. De Andrade et al. [23] criticised the TNM staging system since smaller tumours affecting multiple sites may receive higher staging than larger lesions confined to a single site. This prompted further investigation into the role of maximum tumour volume and more accurate prediction of survival.

Given the ongoing debate surrounding prognostic factors in locally advanced LSCC, this study aims to identify and evaluate the potential prognostic implications of specific histopathological and radiological parameters, with special focus on the influence of the volume of cartilage infiltration, assessed via pre-operative imaging, on survival outcomes. According to the TNM system, full-thickness thyroid cartilage infiltration is of substantial importance, automatically elevating the tumour stage to T4a. Consequently, this study investigates whether the volumetric degree of infiltration can serve as an additional factor in elucidating the different survival rates among patients with equivalent stages.

Materials and methods

Patient selection

We conducted a retrospective, single center study of patients diagnosed with LSCC and treated by total laryngectomy between January 2005 and December 2021 at the Unit of Otorhinolaryngology – Head and Neck Surgery of the University of Brescia, Italy, categorised as pT4a based on post-operative histopathology, and with accessible pre-operative imaging performed at our Institution. Both treatment naïve patients as well as cases with recurrence of previous laryngeal neoplasms were included in the analysis. Patients with incomplete histological data, with less than 12 months of post-operative follow-up, or those lacking accessible survival or oncological outcomes were excluded from the study.

For follow-up and survival data, we utilised electronic medical records (Milos, Health Meeting platform), and contacted patients or their families by phone when necessary. We collected data on demographic and LSCC site, alongside histopathological, radiological, and survival data. The histopathological and radiological parameters considered were grading, PNI, LVI, infiltration of the thyroid cartilage, and pTN staging. The primary endpoint was disease-free survival (DFS), where recurrence was defined by the first clinical or radiological examination documenting it.

Image analysis

The Second Unit of Radiology of the University of Brescia, Italy, provided the pre-operative radiological images used in this study. Two experienced radiologists (M.R. and C.P.), each with a minimum of 4 years of head and neck imaging experience, retrospectively analysed these images. A third radiologist (D.F.), with 28 years of experience, evaluated any doubtful or complex case.

The radiological analysis aimed to quantify the thyroid cartilage neoplastic infiltration. For this purpose, we used an open-source software, 3D Slicer [24], which processes images with graphic segmentation tools. The radiologists manually outlined the area of infiltrated cartilage on each section where the lesion was visible to determine the volume of infiltration. The software then calculated a numerical value for infiltration volume, expressed in mm^3. Segmentation was carried out on the venous phase of CT scans (performed 90 seconds post-contrast injection and reconstructed in the axial plane with a thickness of 2-3 mm), or T2-weighted MRI scans (axial plane, 3 mm thickness).

Statistical analysis

We compiled all data in an Excel spreadsheet and processed it using the Python-based Dataspell programme [25] and its associated statistical packages, with DFS as the primary outcome. Event incidence was computed using the Kaplan-Meier method and compared using the log-rank test. A p-value of < 0.05 was considered statistically significant.

Furthermore, we conducted multivariate Cox regression with a proportional hazards model, treating histopathological and radiological factors as covariates. To verify the predictive capacity of statistical models and the features considered in a non-parametric manner, we employed various machine learning (ML) algorithms. Before data processing, we performed feature scaling for normalisation to assess the role of thyroid cartilage infiltration in prognostic stratification. This integration of ML models into traditional statistics allowed for a more nuanced exploration of cartilage infiltration's prognostic implications. The models employed were Logistic Regression, K Nearest Neighbor, Support Vector Machines (Linear and RBF Classifiers), Gaussian Naive Bayes, Decision Tree Classifier, and Random Forest Classifier.

Table I. Patient characteristics.

Characteristic	N
Patients, no.	74
Age, years (mean)	69
Gender, no.	
Male	69
Female	5
Pre-operative imaging:	
CT or MR	71
CT and MR	3
pTN	
T4a	74
N0	47
N1	5
N2b	3
N3b	18
PNI-LVI	
PNI-	38
PNI+	36
LVI-	34
LVI+	40

Results

Patient characteristics

Our selection criteria resulted in a cohort of 74 patients, comprising 5 women (6.7%) and 69 men (93.3%). The mean age at diagnosis was 69 years (range, 38-93). All patients underwent pre-operative CT and/or MRI imaging (3 patients had both examinations and, in these cases, MRI was preferentially analysed due to the equivalent image quality). The analysis showed that over half of patients had a cartilage infiltration volume < 500 mm^3. All patients underwent total laryngectomy (TL) (20 salvage and 54 primary TL), with post-operative histopathological exam revealing always a pT4 category. For pN category, except for 1 patient (1.3%) who did not undergo neck dissections since already performed before for another tumour, 63.5% were classified as pN0, 6.8% as pN1, 4.1% as pN2b, and 24.3% as pN3b. Table I summarises the patient characteristics.

Follow-up and oncological outcomes

Patients underwent mean follow-up of 44 months (median, 32; range, 2-55). The 1-, 3-, and 5-year DFS was 76%, 66%, and 64%, respectively. Most events occurred within the initial 20 months, with no events recorded after 80 months (Fig. 1). DFS was further analysed in relation to each histopathological factor.

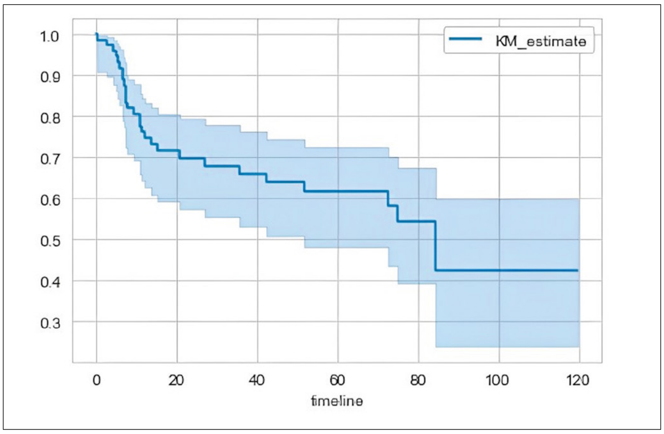

Figure 1. DFS (disease free survival).

Influence of histopathological factors on DFS

LVI was notably influential on DFS, leading to a marked difference in 5-year DFS rates between LVI positive (54%) and negative (80%) patients (Fig. 2). This substantial divergence confirms the prognostic importance of LVI (p-value < 0.05).

PNI had a significant impact on DFS as well, resulting in a lower 5-year DFS of 43% in patients with PNI compared to 78% in patients without (Fig. 3). This contrast further underlines the importance of PNI in prognostic evaluation (p-value < 0.05).

In terms of lymph node involvement, a consistent DFS pattern was observed between patients with pN+ and those pN0 for the initial 10 months, which significantly diverged later (Fig 4). The 5-year DFS was notably lower at 47% in patients with pN+ compared to 70% in those pN0 (p-value < 0.05).

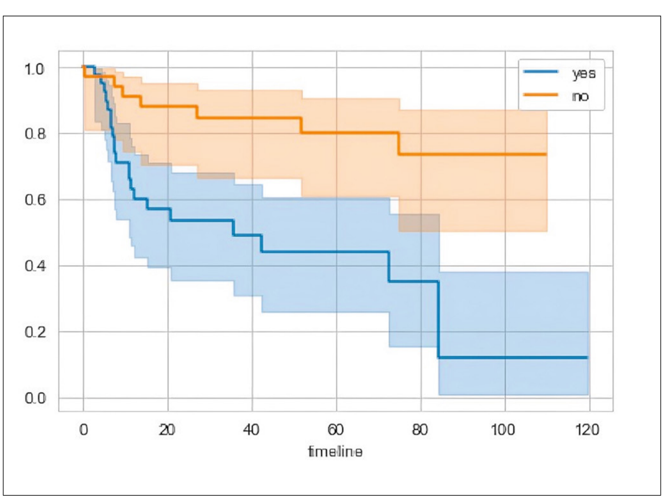

Figure 2. DFS and lympho-vascular invasion (LVI).

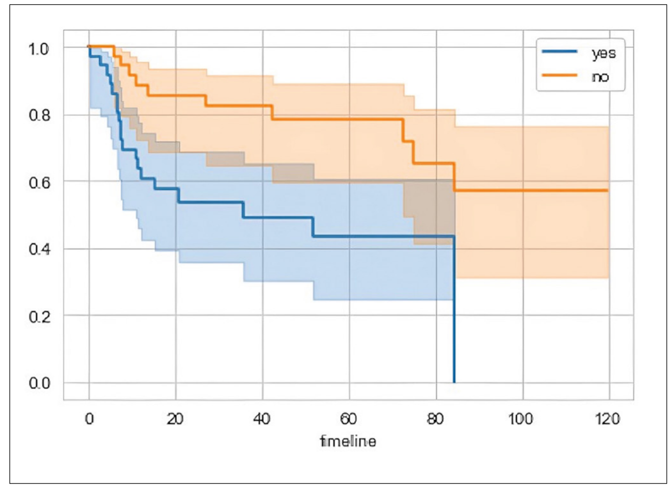

Figure 3. DFS and perineural invasion (PNI).

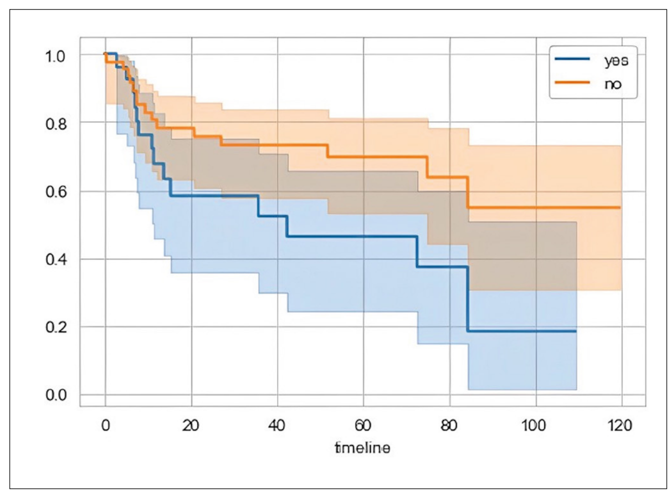

Figure 4. DFS and lymph nodes involvement.

Regarding volume of cartilage infiltration, patients with volumes exceeding the 75th percentile (670 mm^3) exhibited significantly poorer DFS, especially beyond 7 months (Fig. 5). This correlation, although suggestive of a statistical trend (p-value 0.08), was not conclusively significant.

Insights from Cox proportional hazards model and hazard ratio

The Cox proportional hazards model identified LVI as an independent risk factor for prognosis in patients with locally advanced LSCC (p-value 0.01).

PNI and cartilage infiltration volume exceeding the 75th percentile showed a trend towards negatively affecting prognosis, although it was not statistically significant (p-value 0.11).

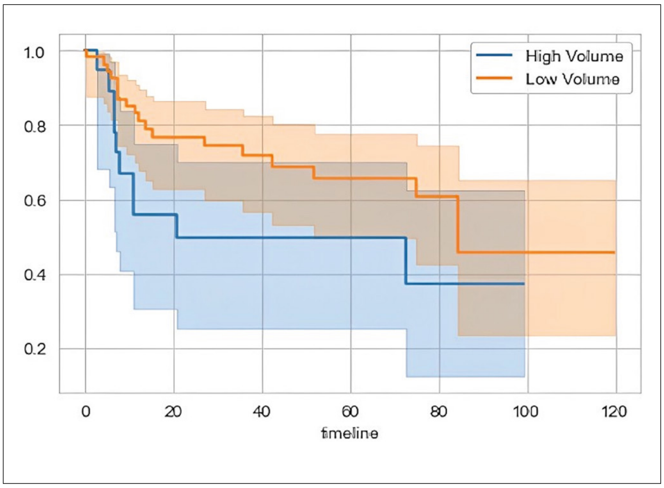

Figure 5. DFS and cartilage infiltration volume.

Investigations using ML models

The Decision Tree Classifier and the Random Forest Classifier showed superior predictive performance (Tab. II). They identified the Maximum Diameter and volume as the most substantial features impacting DFS, with respective importance of 34.6% and 28%. These two variables exhibited a strong positive correlation (correlation coefficient: 0.7784, p-value < 0.0001).

Discussion

Our investigation into histopathological variables, including LVI, PNI, and pN status, yielded confirmatory insights about their influence on DFS. In particular, the Kaplan-Meier analysis at 1, 3, and 5 years confirmed a robust prognostic impact.

LVI was substantiated as an independent prognostic factor through a multivariate analysis using the Cox model. Notably, this result diverges from the conclusions drawn by Santos et al. [26], who, while acknowledging the importance of LVI as a prognostic factor, did not find it as independently predictive [27]. However, it is important to note that the patient population in their study included those with both pT3 and pT4 tumours.

While PNI demonstrated a considerable effect on DFS, it did not emerge as an independent risk factor in the Cox model. This outcome is consistent with a recent study[12] that employed a Matched-Pair Analysis methodology, underlining the complex nature of LSCC prognosis.

The role of LVI and PNI in prognosis has also been recognised by the American Joint Committee on Cancer (AJCC) [28]. They suggested, in fact, that these factors are indicators for adjuvant therapy to enhance loco-regional control, even though they do not alter the TNM staging.

Lymph node involvement is a widely recognised prognosticator in LSCC. Our evaluation of this factor, however, was dichotomous due to the sparse distribution across the N categories. While it affected DFS, it was not identified as an independent risk factor in the multivariate analysis.

The key innovation in our study is that, in addition to traditional variables, we utilised ML algorithms to interpret pre-operative radiological data. In particular, we divided patients into volumetric categories based on cartilage infiltration, above and below the 75th percentile.

When assessing it with conventional statistics, volumetric cartilage invasion failed to reach statistical significance (p-value: 0.08). Therefore, to further enhance our analysis, we applied ML techniques for non-parametric statistics considering the abovementioned variables (LVI, PNI, pN+, and cartilaginous infiltration volume). Data normalisation through feature scaling was performed before integrating the variables into various ML algorithms. The dataset was split into a training and a validation set, with an accuracy calculation for each algorithm.

The Decision Tree Classifier and Random Forest Classifier, two of the seven algorithms applied, demonstrated superior predictive ability. The Decision Tree Classifier is an algorithm that mimics the structure of a tree and is based on inductive learning. Each "Decision Node" consists of a test on a particular variable, based on which the flow takes one direction rather than another. The so-called "Decision Nodes" are the inputs that are provided to the algorithm, while the "Leaf Nodes" are the returned outputs. The Random Forest Classifier combines several Decision Tree Classifiers by introducing a random component. In the first phase, the different "trees" that make up the "forest" are built by randomly associating the different observations (note that individual observations can be used multiple times). In the second phase, several variables are associated with each observation, also randomly, and one of these emerges as the most important. By repeating this process multiple times, a more or less numerous series of Decision

Table II. Evaluation of models in terms of accuracy for the training and validation sets.

	Training set	Validation set
Logistic Regression	71.2%	86.7%
K-nearest Neighbours	71.2%	86.7%
Linear Classifier	67.8%	66.7%
RBF Classifier	79.7%	73.3%
Gaussian Naive Bayes	67.8%	73.3%
Decision Tree Classifier	96.6%	86.7%
Random Forest Classifier	91.5%	93.3%

Tree Classifiers are built and create a Random Forest Classifier. A new observation is handled in the following way: each Decision Tree gives its own response; a majority evaluation is made to use the predictive ability of the algorithm. These algorithms placed thyroid cartilage infiltration as the top-ranked feature, affirming its non-linear impact on survival. It is pertinent to note that radiological assessment of thyroid cartilage infiltration is currently limited by the less-than-optimal sensitivity and specificity of CT and MRI. However, recent advancements in radiomics highlight the potential of ML algorithms to predict and quantify cartilage invasion with higher accuracy compared to traditional radiologist interpretation. In fact, a recent review [29] evaluating possible applications of radiomics for laryngeal tumours suggested that cartilage infiltration may be a variable worthy of attention. In our study, through the support of ML algorithms analysing radiological parameters, it was confirmed that thyroid cartilage infiltration has a significant, although non-linear, impact on survival. However, in terms of future perspectives, the literature provides an interesting insight: a recent radiomics study [30] compared the pathologic report to a radiologist evaluation and a ML algorithm which predicted the possibility of cartilage invasion; the latter was found to have greater accuracy, highlighting the potential of this type of approach.

The retrospective nature and the type of the present study analysis gives rise to intrinsic limitations: specifically, CT/MRI annotation for volumetric cartilage involvement was manually performed and intrinsically subjective. Furthermore, even with high quality radiologic imaging, it is not always possible to precisely detect and delineate cartilage infiltration.

Conclusions

In the continuously evolving domain of oncology, initial diagnostic staging serves as a preliminary risk stratification tool to guide the evaluation of potential therapeutic options. Nevertheless, as modern medicine shifts toward personalised and targeted treatment strategies, conventional stage-based evaluation can oversimplify the intricate landscape of oncological diseases. Thus, unraveling the heterogeneity of prognostic indicators within each stage becomes crucial to improve predictive precision and personalised patient care.

Our study underlines the importance of such nuanced factors, highlighting the essential role of LVI in the prognosis of locally advanced LSCC. More innovatively, we identified the volume of thyroid cartilage infiltration as a promising prognostic determinant. This element possesses a unique dimension of utility, as it can be non-invasively assessed pre-operatively, offering critical insight into therapeutic decision-making at the inception of the treatment journey.

ML, as seen herein, holds considerable promise in augmenting traditional analysis, especially in large-scale studies for deriving diagnostic, prognostic, and therapeutic response data. The focal point of its application remains the appraisal of anatomical complexity, particularly in LSCC, and the inherent intra-tumoural variability, which are both key to optimising oncological outcomes while minimising functional compromise.

However, it is essential to emphasise the importance of a well-structured training period, even though it may be significantly accelerated compared to the conventional learning curve of a clinician. The goal remains to enable a responsible and informed application of artificial intelligence in clinical decision-making, creating a symbiosis of human expertise and algorithmic precision to improve patient outcomes.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

CM, AP, FEN contributed to data collection and analysis; MR, CP, DF retrospectively analyzed radiological images; AP performed statistical analysis integrated with machine learning models; CM, AP, CP performed manuscript preparation; AP, CP performed final edits and revisions; CM, AP, DL, FDB, MR, CP, DF, FEN, CP contributed conceptually to the article and approved the submitted version.

Ethical consideration

This study was approved by the Institutional Ethic Committee (CE Spedali Civili, Brescia) (protocol number: 4554). The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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